Unification of Reaction Metrics II: Evaluation of Named Organic Reactions and Application to Reaction Discovery

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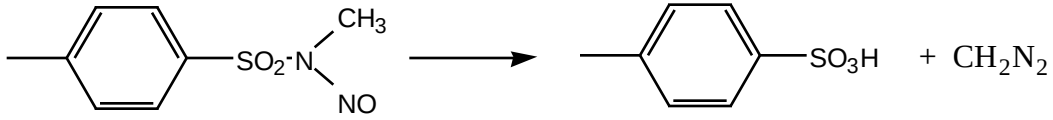
Supplementary Material

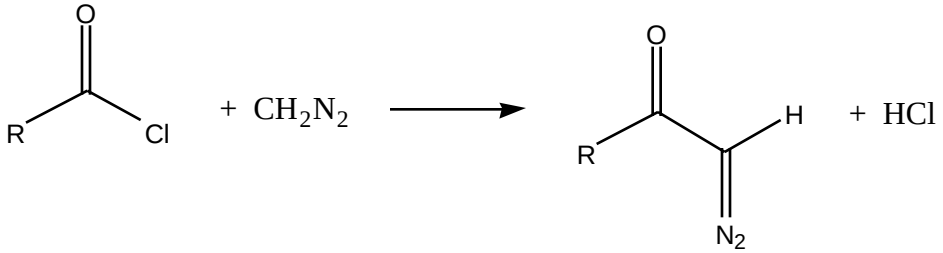
Table D9. Categorization of Named Sequences by Minimum Atom Economy and Maximum Environmental Impact Factor
(Reactions are listed alphabetically.)

Arndt-Eistert reaction

Arndt, F.; Eistert, B., *Chem. Ber*. **1935**, 68, 200

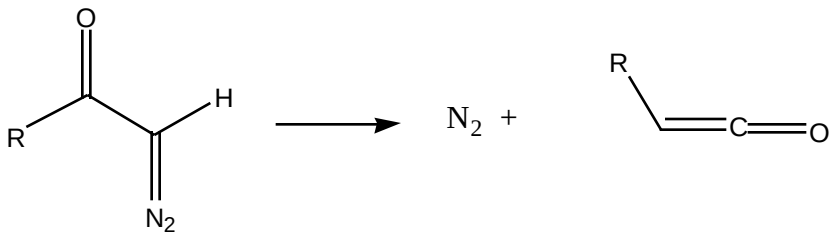
(1) 

214 172 42

(2) 

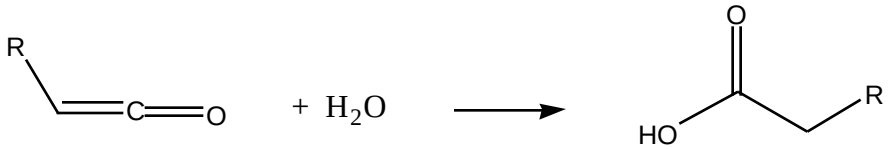
x + 63.45 42 x + 69 36.45

(3)



x + 69 28 x + 41

(4)



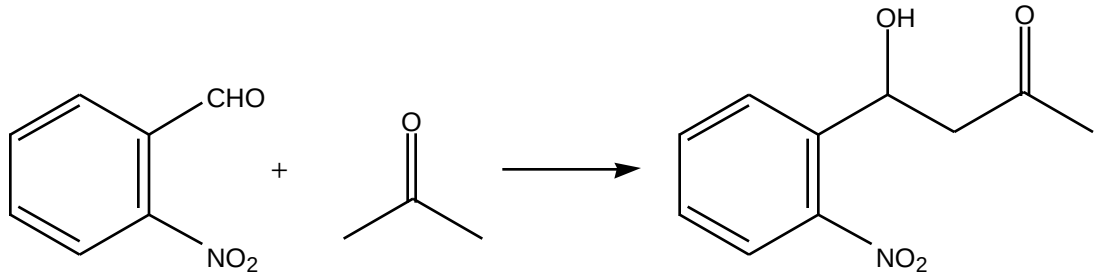
x + 41 18 x + 59

R = x

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	4.10	0.20	4.10	0.20
2	36.45/[x + 69]	[x + 69]/[x + 105.45]	0.52	0.66
3	28/[x + 41]	[x + 41]/[x + 69]	0.67	0.60
4	0	1	0	1
Overall	236.45/[x + 59]	[x + 59]/[x + 295.45]	**3.94**	**0.20**

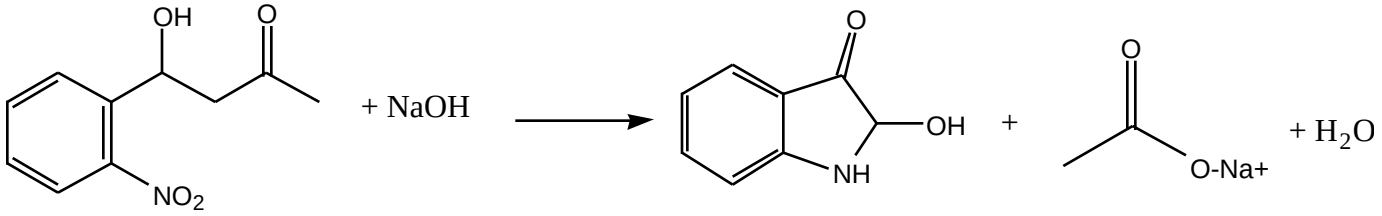
Baeyer-Drewson synthesis of indigo
Baeyer, A.; Drewson, V. *Chem. Ber.* **1882**, 15, 2856

(1)



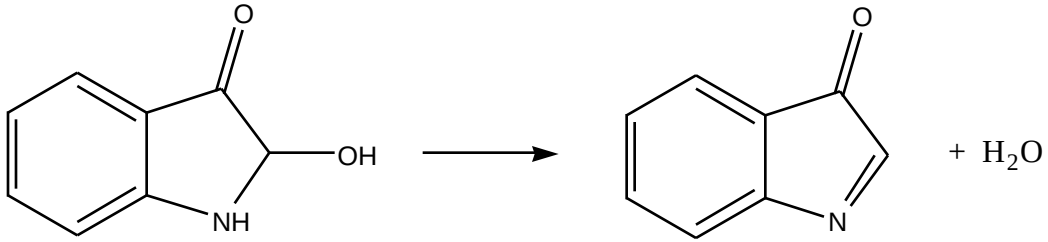
151 58 209

(2)

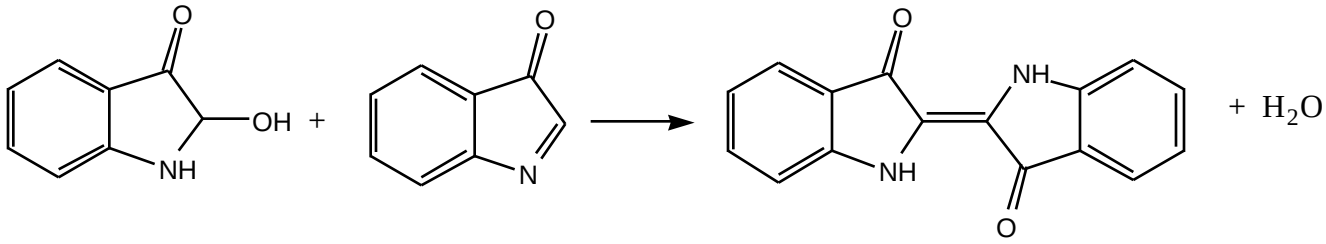


209 40 149 82 18

(3)



149 131 18

(4) 

149 131 262 18

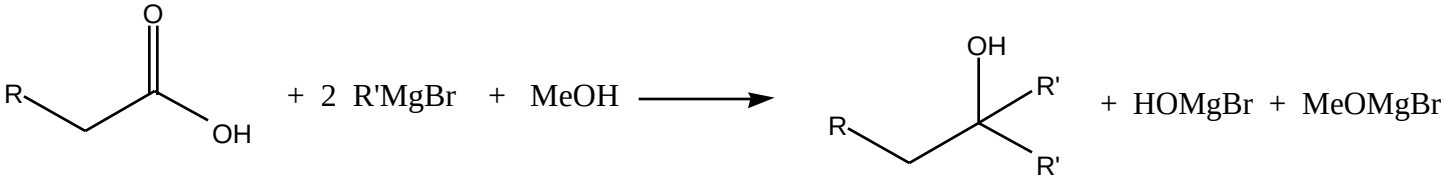
Step	E	AE
1	0	1
2	0.67	0.60
3	0.14	0.88
4	0.069	0.94

Overall E = [2(82 + 18) + 18 + 18]/262 = 0.90; AE = 0.53

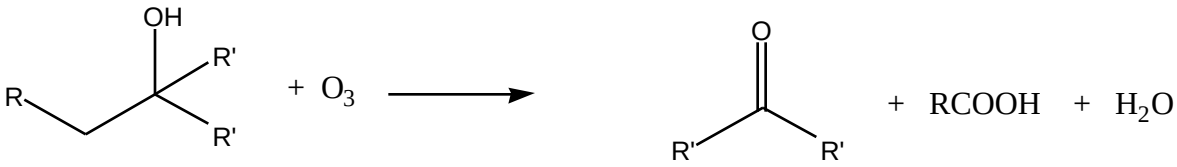
Barbier-Wieland Reaction

Wieland, H., *Chem. Ber*. **1912**, 45, 484

Barbier, P.; Locquin, R., *Compt. Rend*. **1913**, 156, 1443

(1) 

x + 59 2(y + 104.2) 32 x + 2y + 43 121.2 135.2

(2) 

x + 2y + 43 48 2y + 28 x + 45 18

R = x; R' = y

Ketone as target product: R' = Me

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	256.4/[x + 2y + 43]	[x + 2y + 43]/[x + 2y + 299.4]	256.4/[x + 73]	[x + 73]/[x + 329.4]
2	[x + 63]/[2y + 28]	[2y + 28]/[2y + x + 91]	[x + 63]/58	58/[x + 121]
Overall	[x + 319.4]/[2y + 28]	[2y + 28]/[x + 2y + 347.4]	**[x + 319.4]/58**	**58/[x + 377.4]**

X	**E(max)**	**AE(min)**
H	5.52	0.15
Me	5.77	0.15
Et	6.01	0.14

Carboxylic acid as target product: R = H

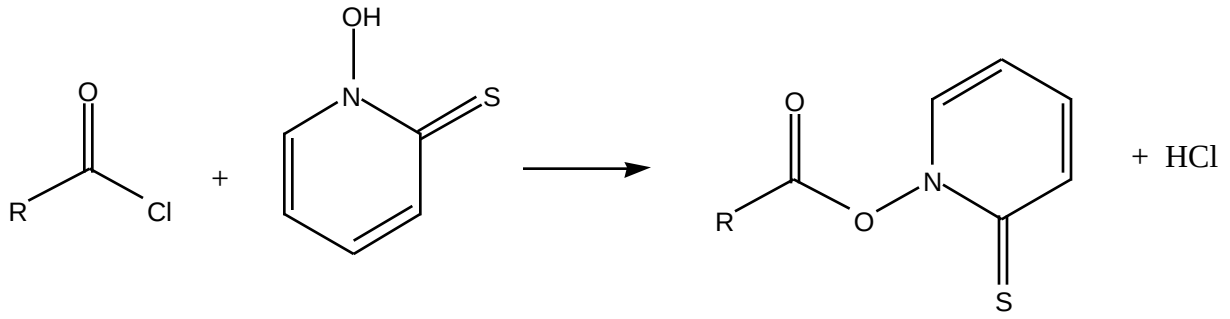
Step	**E**	**AE**	**E(max)**	**AE(min)**
1	256.4/[x + 2y + 43]	[x + 2y + 43]/[x + 2y + 299.4]	256.4/[x + 73]	[x + 73]/[x + 329.4]
2	[2y + 46]/[x + 45]	[x + 45]/[2y + x + 91]	[2y + 46]/46	46/[2y + 92]
Overall	[2y + 302.4]/[x + 45]	[x + 45]/[x + 2y + 347.4]	**[2y + 302.4]/46**	**46/[2y + 348.4]**

Y	**E(max)**	**AE(min)**
Me	6.62	0.13
Et	7.83	0.11
Ph	9.92	0.09

Barton decarboxylation

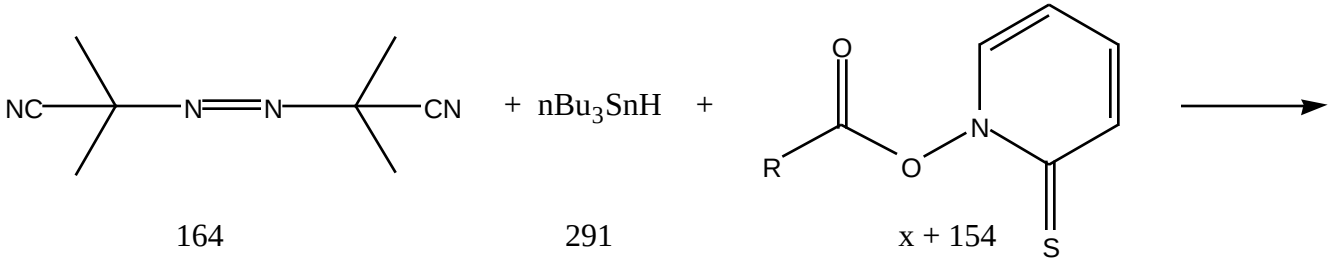
Barton, D.H.R.; Crich, D.; Motherwell, W.B. *Chem. Commun.* **1983**, 939

(1)

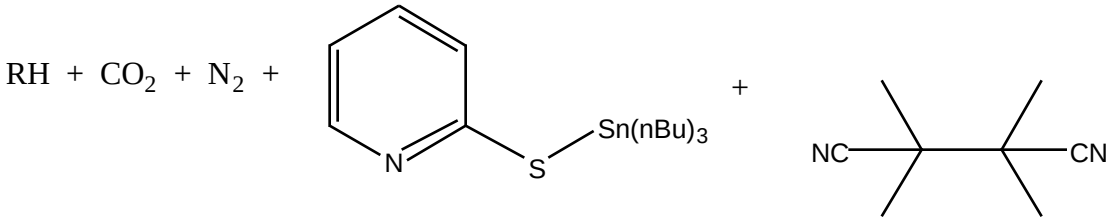


x + 63.45 127 x + 154 36.45

(2)



164 291 x + 154



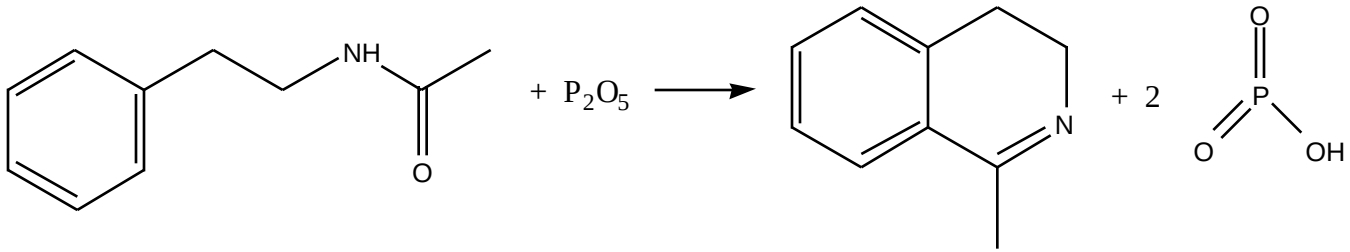
x + 1 44 28 400 136

R = x

Step	**E**	**AE**	**E(max)**	**AE(min)**	
1	36.45/[x + 154]	[x + 154]/[x + 190.45]	0.22	0.82	(R = Me)
2	608/[x + 1]	[x + 1]/[x + 609]	38	0.026	
Overall	644.45/[x + 1]	[x + 1]/[x + 645.45]	**40.28**	**0.024**	

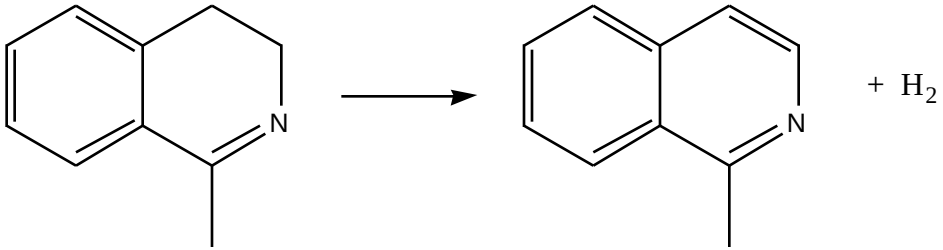
Bischler-Napieralski synthesis
Bischler, A.; Napieralski, B., *Chem. Ber*. **1893**, 26, 1903

(1)



163 142 145 160

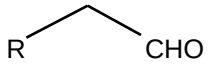
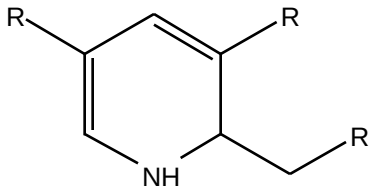
(2)



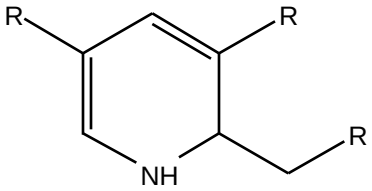
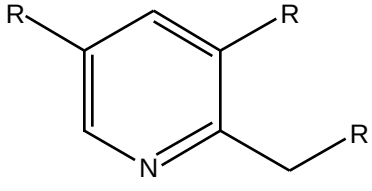
145 143 2

Step	**E**	**AE**
1	1.10	0.48
2	0.014	0.99
Overall	**1.13**	**0.47**

Chichibabin pyridine synthesis
Chichibabin, A.E. *J. Russ. Phys. Chem. Soc.* **1906**, 37, 1229

(1) 3  + 2 NH_3 →  + 2 H_2O + NH_4OH

3(x + 43) 34 3x + 92 36 35

(2)  + 0.5 O_2 →  + H_2O

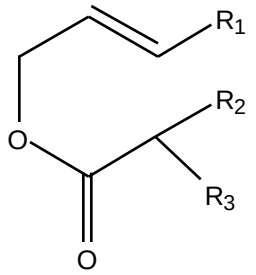
3x + 92 16 3x + 90 18

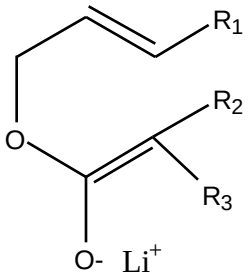
R = x

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	71/[3x + 92]	[3x + 92]/[3x + 163]	0.75	0.57
2	18/[3x + 90]	[3x + 90]/[3x + 108]	0.19	0.84
Overall	89/[3x + 90]	[3x + 90]/[3x + 179]	**0.96**	**0.51**

Claisen-Ireland rearrangement

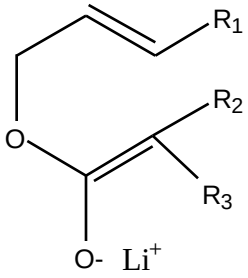
Ireland, R.E.; Mueller, R.H., *J. Am. Chem. Soc*. **1972**, 94, 5897
Ireland, R.E.; Willard, A.K., *Tetrahedron Lett.* **1975**, 3975

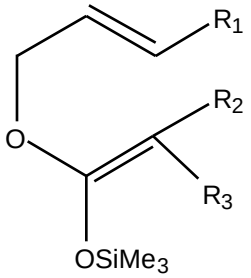
(1) 

+ LiN(*i*Pr)(Cy) → 

+ HN(*i*Pr)(Cy)

x + y + z + 97 147 x + y + z + 103 141

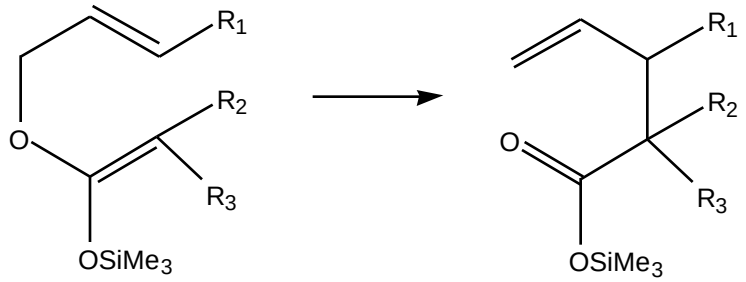
(2) 

+ Me_3SiCl → 

+ LiCl

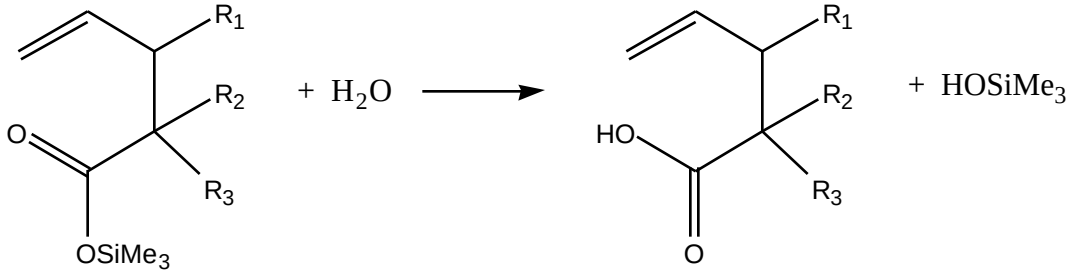
x + y + z + 103 108.45 x + y + z + 169 42.45

(3)



x + y + z + 169 x + y + z + 169

(4)

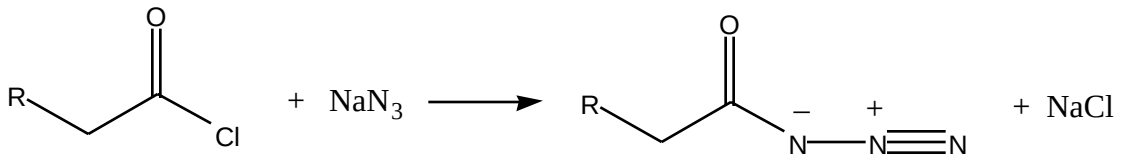


x + y + z + 169 18 x + y + z + 97 90

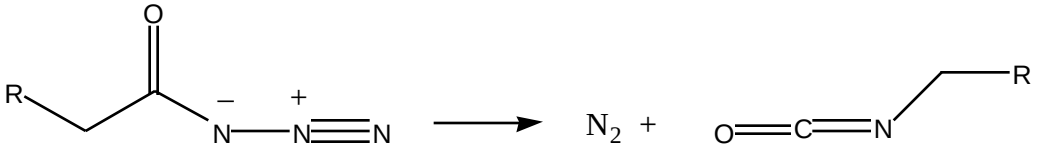
R1 = x; R2 = y; R3 = z

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	141/[x + y + z + 103]	[x + y + z + 103]/[x + y + z + 244]	1.33	0.43
2	42.45/[x + y + z + 169]	[x + y + z + 169]/[x + y + z + 211.45]	0.25	0.80
3	0	1	0	1
4	90/[x + y + z + 97]	[x + y + z + 97]/[x + y + z + 187]	0.90	0.53
Overall	273.45/[x + y + z + 97]	[x + y + z + 97]/[x + y + z + 370.45]	**2.73**	**0.27**

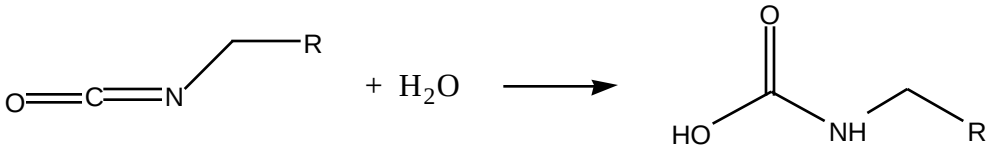
Curtius Reaction (rearrangement)
Curtius, T., *Chem. Ber*. **1890**, 23, 3023

(1) 

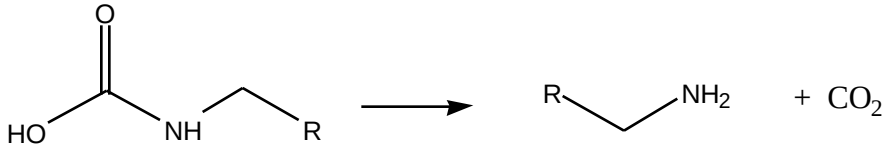
x + 77.45 65 x + 84 58.45

(2) 

x + 84 28 x + 56

(3) 

x + 56 18 x + 74

(4) 

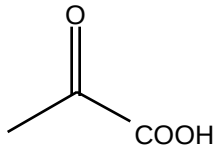
x + 74 x + 30 44

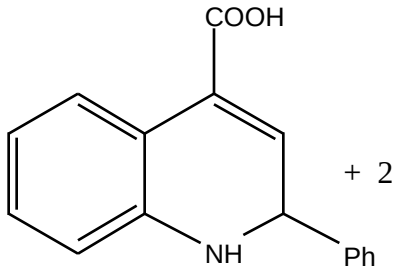
R = x

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	58.45/[x + 84]	[x + 84]/[x + 142.45]	0.69	0.59
2	28/[x + 56]	[x + 56]/[x + 84]	0.49	0.67
3	0	1	0	1

4	44/[x + 30]	[x + 30]/[x + 74]	1.42	0.41
Overall	130.45/[x + 30]	[x + 30]/[x + 160.45]	**4.35**	**0.19**

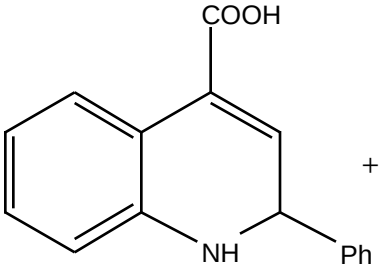
Doebner reaction
Doebner, O. *Ann. Chem.* **1887**, 242, 256

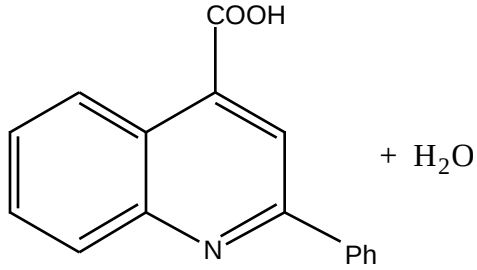
(1) $PhNH_2$ + PhCHO + 



+ 2 H_2O

93 106 88 251 36

(2) 

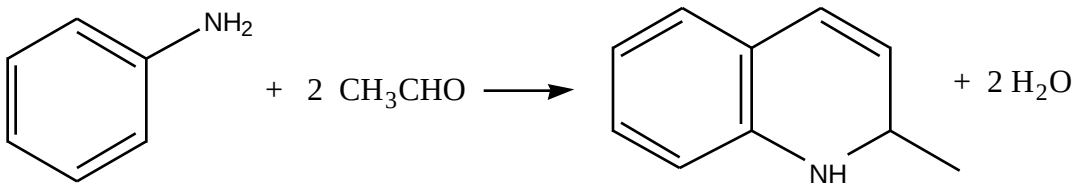
+ 0.5 O_2 

+ H_2O

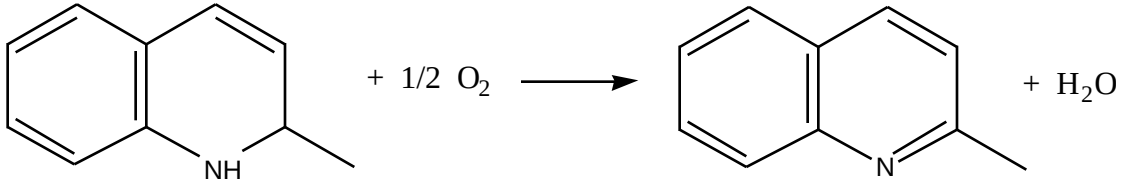
251 16 249 18

Step	**E**	**AE**
1	0.14	0.87
2	0.072	0.93
Overall	**0.22**	**0.82**

Doebner-Miller reaction
Doebner, O.; von Miller, W., *Chem. Ber*. **1883**, 16, 2464

(1) 

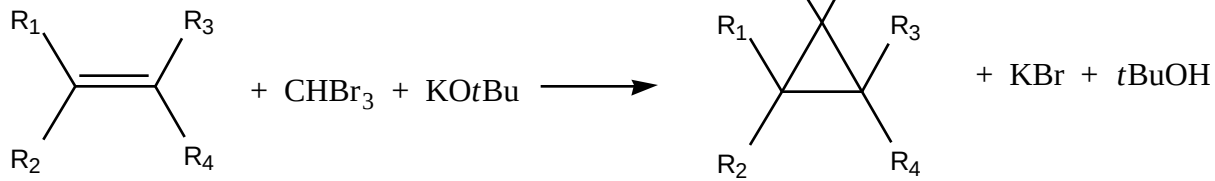
93 88 145 36

(2) 

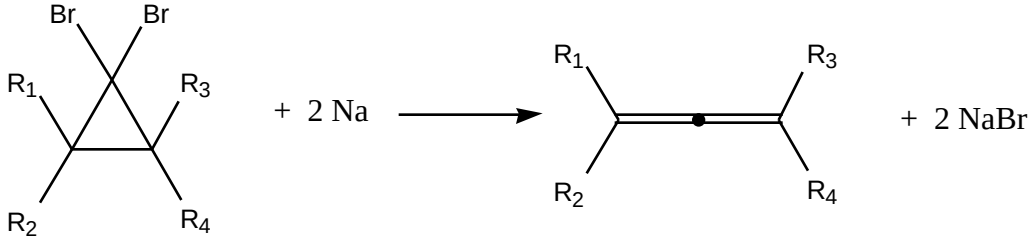
145 16 143 18

Step	**E**	**AE**
1	0.25	0.80
2	0.13	0.89
Overall	**0.38**	**0.73**

Doering-LaFlamme allene synthesis
Doering, W. v. E.; LaFlamme, P.M. *Tetrahedron* **1958**, 2, 75

(1) 

x + 24 252.7 112 x + 195.8 118.9 74

(2) 

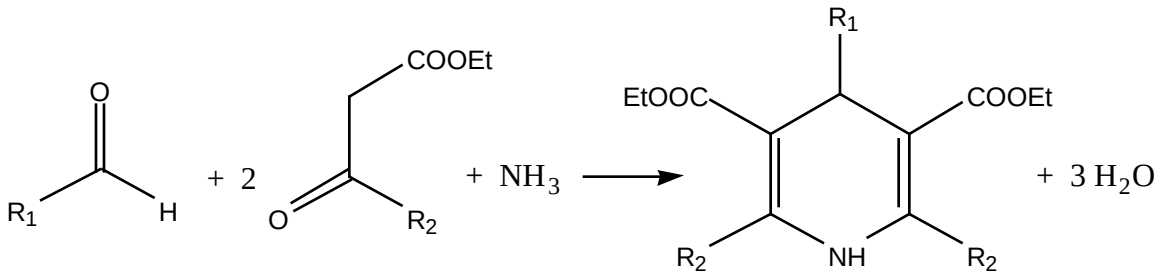
x + 195.8 46 x + 36 205.8

R1 + R2 + R3 + R4 = x

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	192.9/[x + 195.8]	[x + 195.8]/[x + 388.7]	0.97	0.51
2	205.8/[x + 36]	[x + 36]/[x + 241.8]	5.15	0.16
Overall	398.7/[x + 36]	[x + 36]/[x + 434.7]	**9.97**	**0.091**

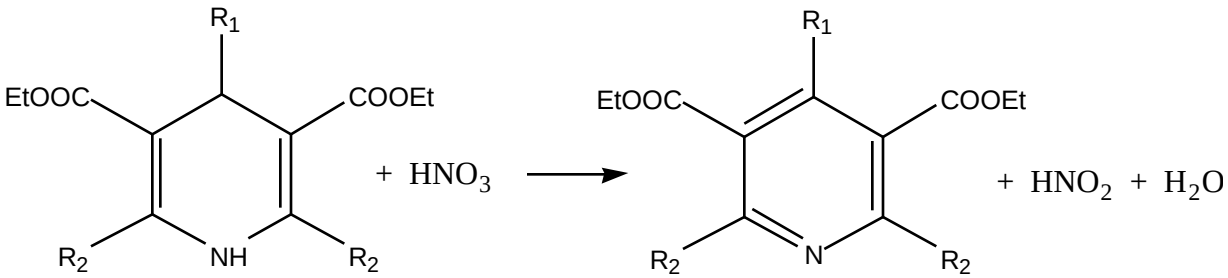
Hantzsch synthesis of pyridines
Hantzsch, A. *Ann. Chem.* **1882**, 215, 1

(1)

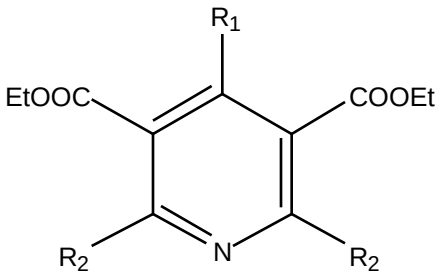


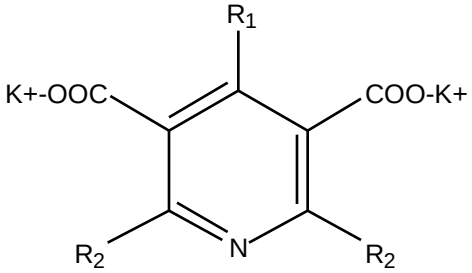
x + 29 2(y + 115) 17 2y + x + 222 54

(2)



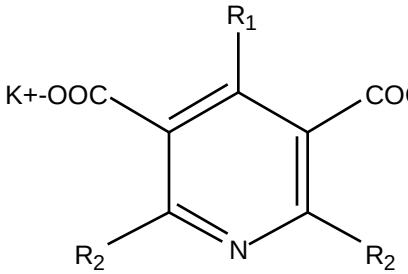
2y + x + 222 63 2y + x + 220 47 18

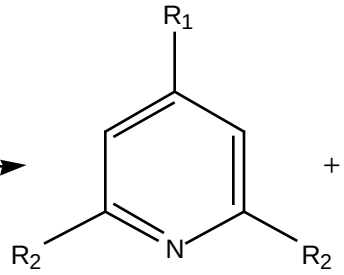
(3) 

+ 2 KOH ⟶ 

+ 2 EtOH

2y + x + 220 112 2y + x + 240 92

(4) 

+ 2 H_2O ⟶ 

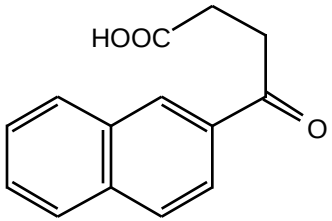
+ 2 CO_2 + 2 KOH

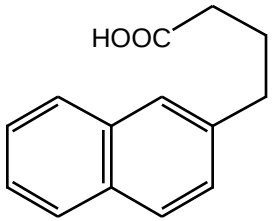
2y + x + 240 36 2y + x + 76 88 112

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	54/[x + 2y + 222]	[x + 2y + 222]/[x + 2y + 276]	0.24	0.81
2	65/[x + 2y + 220]	[x + 2y + 220]/[x + 2y + 285]	0.29	0.77
3	92/[x + 2y + 240]	[x + 2y + 240]/[x + 2y + 332]	0.38	0.73
4	200/[x + 2y + 76]	[x + 2y + 76]/[x + 2y + 276]	2.53	0.28
Overall	263/[x + 2y + 76]	[x + 2y + 76]/[x + 2y + 339]	**3.33**	**0.23**

Haworth phenanthrene synthesis

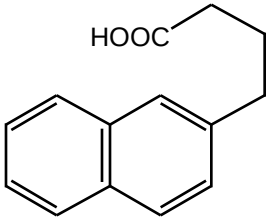
Haworth, R.D. *J. Chem. Soc.* **1932**, 1125; 2717
Haworth, R.D.; Letsky, B.M.; Mavin, C.R. *J. Chem. Soc.* **1932**, 1784
Haworth, R.D.; Bolam, F.M. *J. Chem. Soc.* **1932**, 2248
Haworth, R.D.; Mavin, C.R. *J. Chem. Soc.* **1932**, 2720
Haworth, R.D.; Mavin, C.R.; Sheldrick, G. *J. Chem. Soc.* **1934**, 454

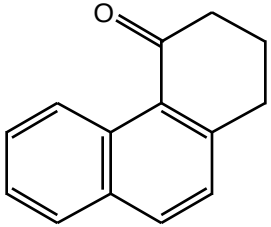
(1) 

+ 4 HCl + 2 Zn ⟶ 

+ 2 $ZnCl_2$ + H_2O

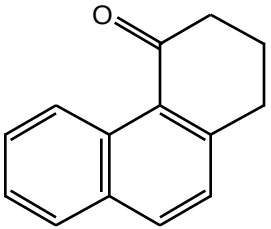
228 145.8 130.8 214 272.6 18

(2) 

⟶ 

+ H_2O

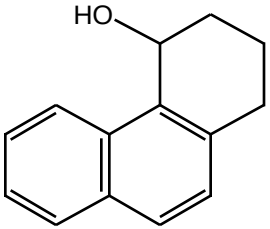
214 196 18

(3) 

9.5 11.5 13.5

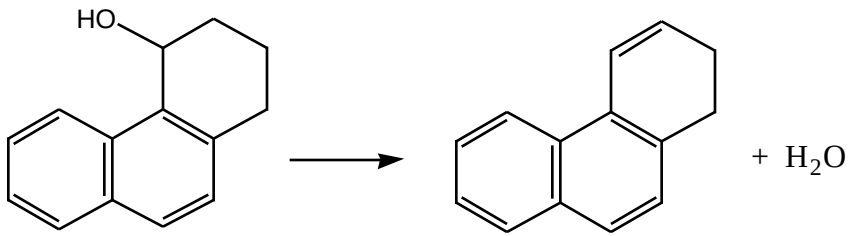
+ 1/4 $LiAlH_4$ + 1/4 EtOH + 3/4 H_2O ⟶

196

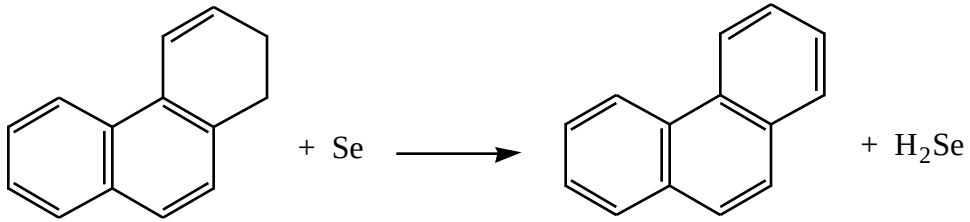


+ 1/4 $Al(OH)_3$ + 1/4 LiOEt

198 19.5 13

(4) 

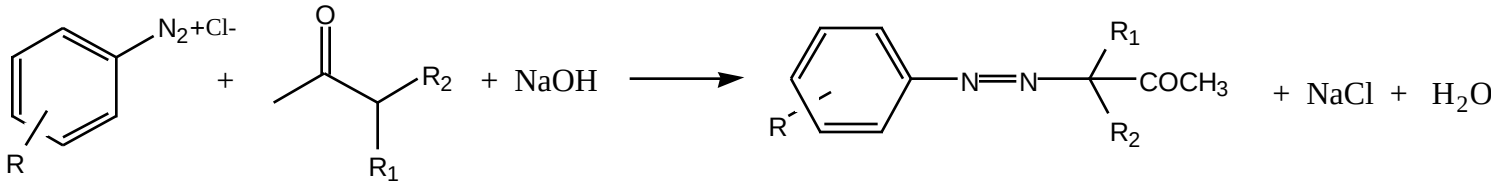
198 180 18

(5) 

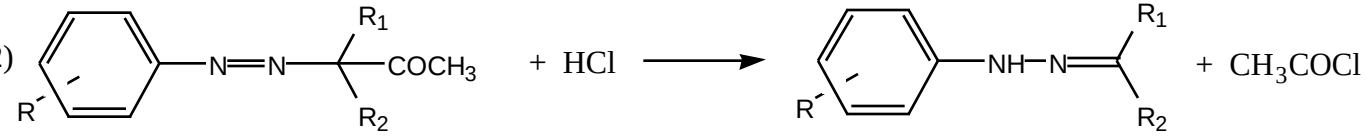
180 79 178 81

Step	**E**	**AE**
1	1.36	0.42
2	0.092	0.92
3	0.16	0.86
4	0.10	0.91
5	0.46	0.69
Overall	**2.47**	**0.29**

Japp-Klingemann reaction
Japp, F.R.; Klingemann, F., *Ann. Chem*. **1888**, 247, 190

(1) 

x + 135.45 y + z + 56 40 x + y + z + 155 58.45 18

(2) 

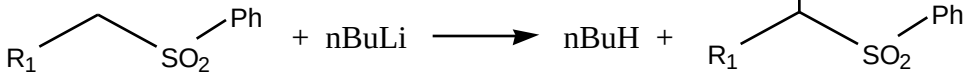
x + y + z + 155 36.45 x + y + z + 113 78.45

R = x (sum of substituents); R1 = y; R2 = z

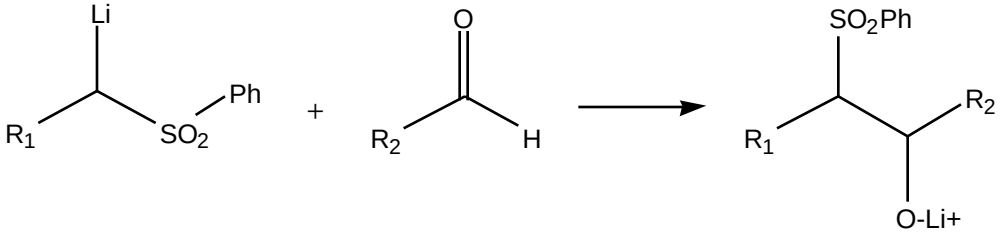
Step	**E**	**AE**	**E(max)**	**AE(min)**
1	76.45/[x + y + z + 155]	[x + y + z + 155]/[x + y + z + 231.45]	0.47	0.68
2	78.45/[x + y + z + 113]	[x + y + z + 113]/[x + y + z + 191.45]	0.65	0.60
Overall	154.9/[x + y + z + 113]	[x + y + z + 113]/[x + y + z + 267.9]	**1.29**	**0.44**

Julia olefination

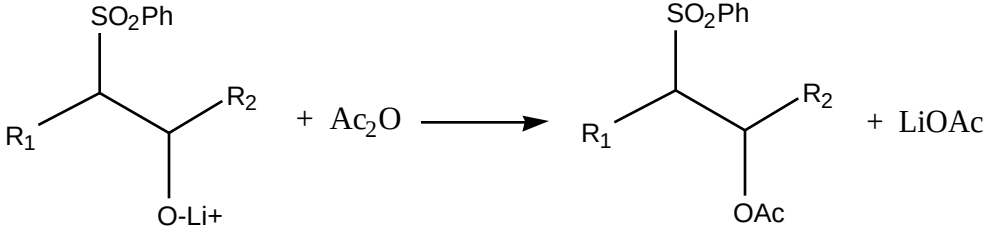
Julia, M.; Paris, J.M., *Tetrahedron Lett.* **1973**, 4933

(1) 

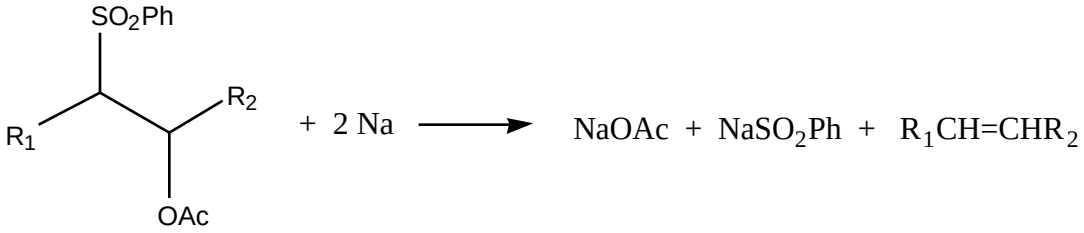
x + 155 64 58 x + 161

(2) 

x + 161 y + 29 x + y + 190

(3) 

x + y + 190 102 x + y + 226 66

(4) 

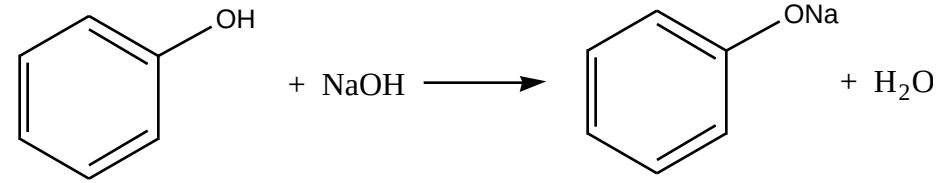
x + y + 226 46 82 164 x + y + 26

R1 = x; R2 = y

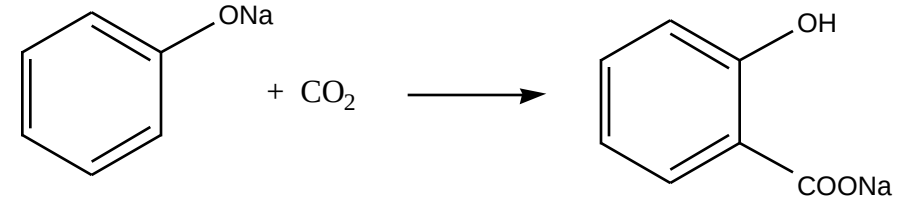
Step	**E**	**AE**	**E(max)**	**AE(min)**
1	58/[x + 161]	[x + 161]/[x + 219]	0.36	0.74
2	0	1	0	1
3	66/[x + y + 226]	[x + y + 226]/[x + y + 292]	0.29	0.78
4	246/[x + y + 26]	[x + y + 26]/[x + y + 272]	8.79	0.10
Overall	370/[x + y + 26]	[x + y + 26]/[x + y + 396]	**13.21**	**0.070**

Kolbe synthesis of aspirin

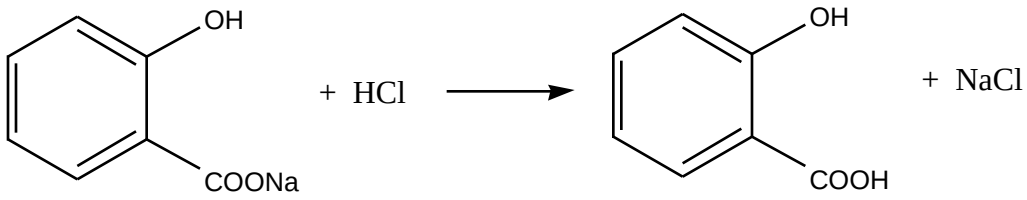
Kolbe, A. *Ann. Chem.* **1860**, 113, 125
Kolbe, A. *J. Prakt. Chem.* **1874**, 118(10), 89
Kolbe, A. *J. Prakt. Chem*. **1875**, 119(11), 9; 213
Kolbe, A. *J. Prakt. Chem*. **1875**, 120(12),151;161

(1) 

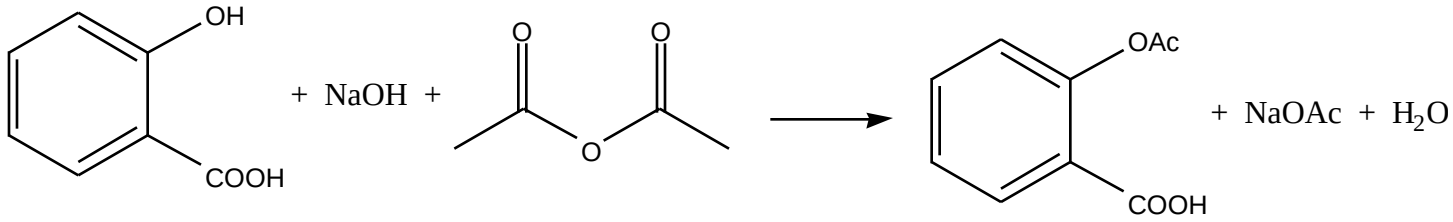
94 40 116 18

(2) 

116 44 160

(3) 

160 36.45 138 58.45

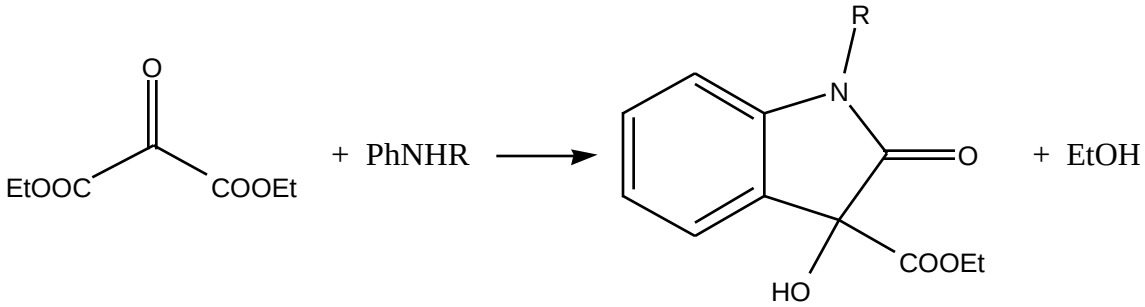
(4) 

138 40 102 180 82 18

Step	**E**	**AE**
1	0.16	0.87
2	0	1
3	0.42	0.70
4	0.56	0.64
Overall	**0.98**	**0.50**

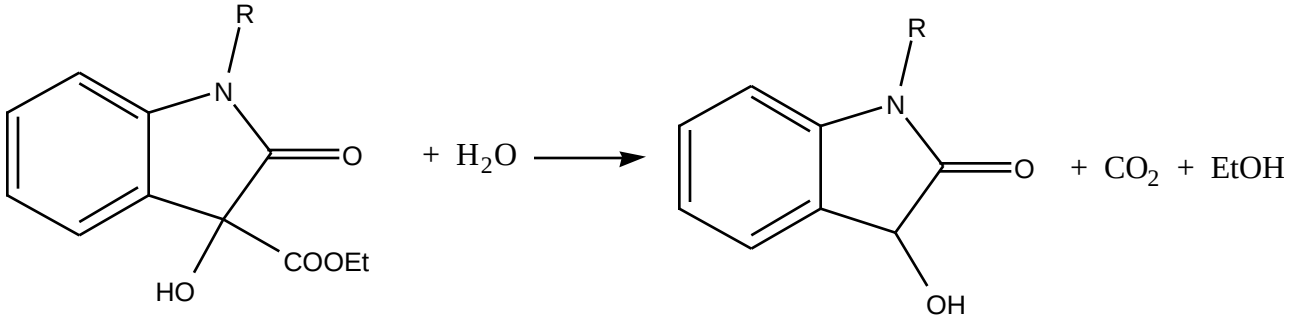
Martinet dioxindole synthesis
Guyot, A.; Martinet, J. *Compt. Rend.* **1913**, 156, 1625

(1)



174 x + 92 x + 220 46

(2)



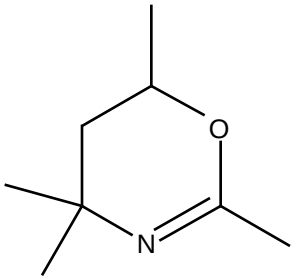
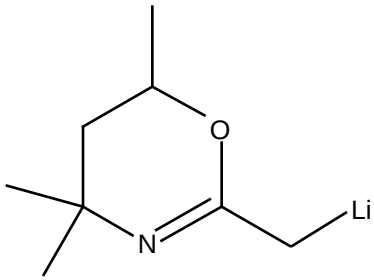
x + 220 18 x + 148 44 46

R = x

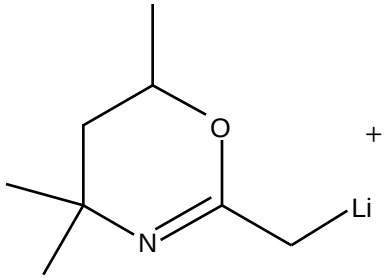
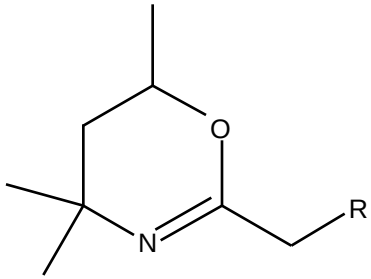
Step	**E**	**AE**	**E(max)**	**AE(min)**
1	46/[x + 220]	[x + 220]/[x + 266]	0.21	0.83
2	90/[x + 148]	[x + 148]/[x + 238]	0.60	0.62
Overall	136/[x + 148]	[x + 148]/[x + 284]	**0.91**	**0.52**

Meyers aldehyde synthesis

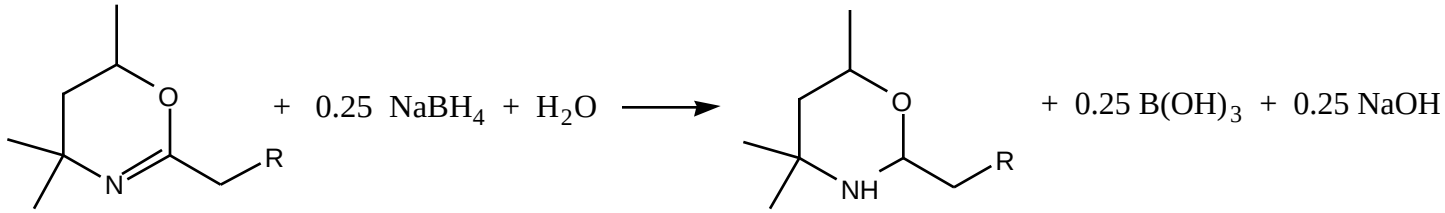
Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Politzer, I.R. *J. Am. Chem. Soc.* **1969**, 91, 763
Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Politzer, I.R.; Malone, G.R.; Kovelesky, A.C.; Nolen, R.L.; Portnoy, R.C. *J. Org. Chem.* **1973**, 38, 36

(1)  + nBuLi →  + nBuH

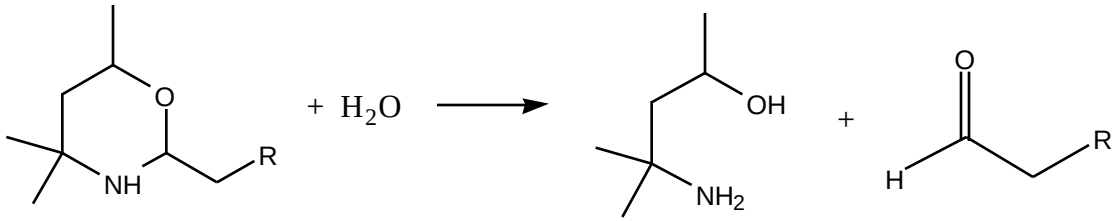
141 64 147 58

(2)  + RX →  + LiX

147 x + r 140 + r x + 7

(3) 

140 + r 9.5 18 142 + r 15.5 10

(4) 

142 + r 18 117 r + 43

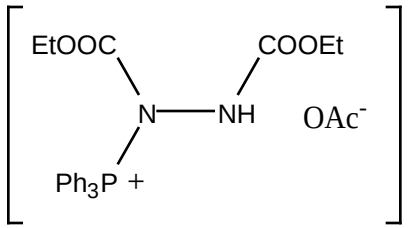
R = r; X = x (halide)

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	0.39	0.72	0.39	0.72
2	[x + 7]/[r + 140]	[r + 140]/[x + r + 147]	[x + 7]/[x + 148]	141/[x + 147]
3	25.5/[r + 142]	[r + 142]/[r + 167.5]	0.18	0.85
4	117/[r + 43]	[r + 43]/[r + 160]	2.66	0.27
Overall	[x + 207.5]/[r + 43]	[r + 43]/[x + r + 250.5]	**[x + 201.5]/44**	**44/[x + 250.5]**

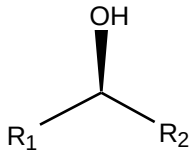
X	**E(max)**	**AE(min)**
Cl	5.39	0.16
Br	6.40	0.14
I	7.47	0.12

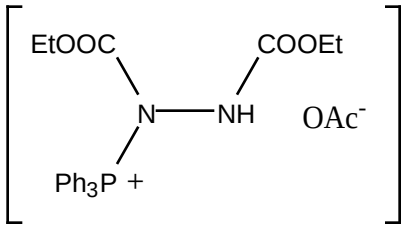
Mitsunobu reaction

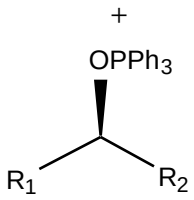
Mitsunobu, O., *Bull. Chem. Soc. Jpn.* **1967**, 40, 4235
Mitsunobu, O., *Tetrahedron* **1970**, 26, 5731

(1) EtOOC-N=N-COOEt + PPh_3 + HOAc ⟶ 

174 262 60 496

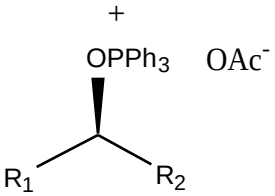
(2) 

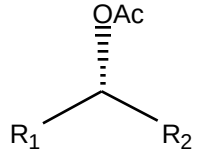
+ 

⟶ 

+ EtOOC-NHNH-COOEt

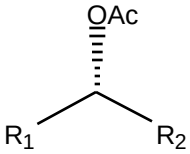
x + y + 30 496 x + y + 350 176

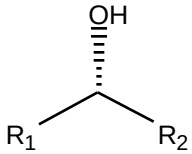
(3) 

⟶ 

+ $O=PPh_3$

x + y + 350 x + y + 72 278

(4) 

+ H_2O ⟶ 

+ HOAc

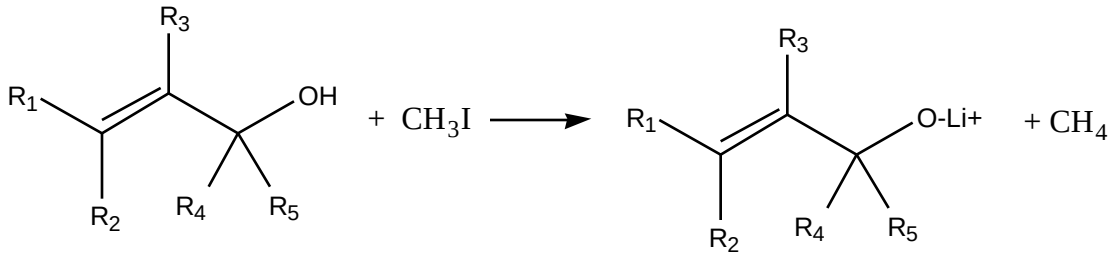
x + y + 72 18 x + y + 30 60

R1 = x; R2 = y

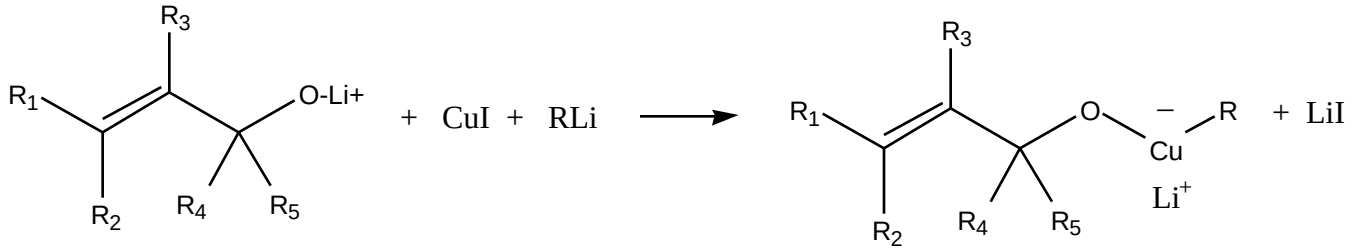
Step	**E**	**AE**	**E(max)**	**AE(min)**
1	0	1	0	1
2	176/[x + y + 350]	[x + y + 350]/[x + y + 526]	0.50	0.67
3	278/[x + y + 72]	[x + y + 72]/[x + y + 350]	3.76	0.21
4	60/[x + y + 30]	[x + y + 30]/[x + y + 90]	1.88	0.35
Overall	454/[x + y + 30]	[x + y + 30]/[x + y + 484]	**14.19**	**0.066 (HOAc reclaimed)**
Overall	514/[x + y + 30]	[x + y + 30]/[x + y + 544]	**16.06**	**0.059 (HOAc counted as waste)**

Murahashi reaction

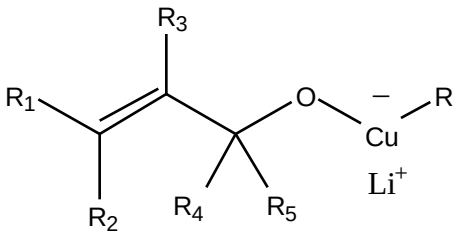
Tanigawa, Y.; Ohta, H.; Sonoda, A.; Murahashi, S.I. *J. Am. Chem. Soc.* **1978**, 100, 4610
Tanigawa, Y.; Kanamaru, H.; Sonoda, A.; Murahashi, S.I., *J. Am. Chem. Soc.* **1977**, 99, 2361

(1) 

r + 53 22 r + 59 16

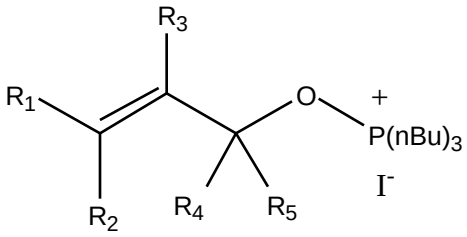
(2) 

r + 59 190.5 x + 7 r + x + 122.5 134

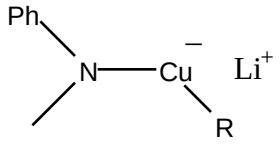
(3) 

+ $[(nBu)_3PN(CH_3)(Ph)]^+ I^-$ ⟶

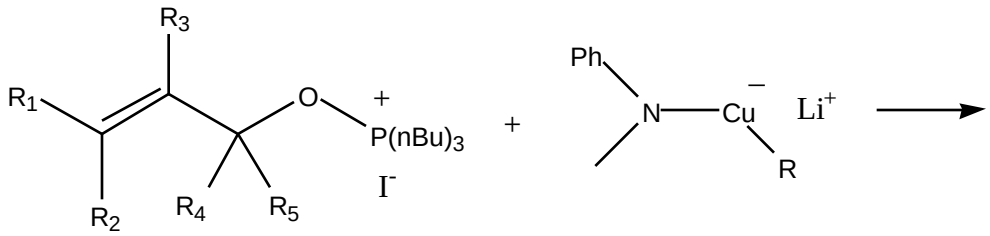
r + x + 122.5 435



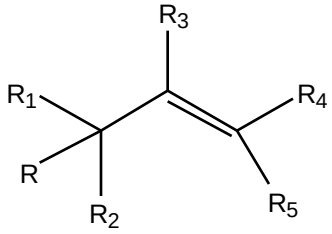
+



r + 381 x + 176.5

(4) 

r + 381 x + 176.5



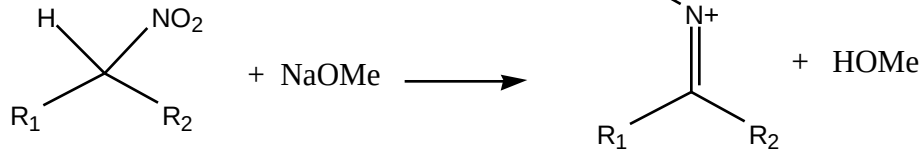
+ $(nBu)_3P=O$ + LiI + Cu^+ $[CH_3NPh]^-$

r + x + 36 218 134 169.5

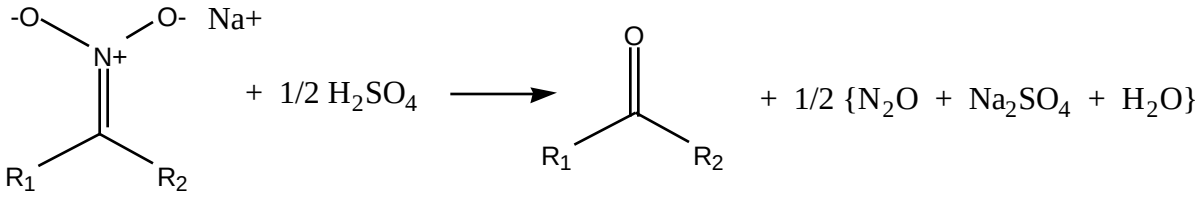
r = R1 + R2 + R3 + R4 + R5; R = x

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	16/[r + 69]	[r + 69]/[r + 85]	0.22	0.82
2	134/[r + x + 122.5]	[r + x + 122.5]/[r + x + 256.5]	1.04	0.49
3	[x + 176.5]/[r + 381]	[r + 381]/[x + r + 557.5]	0.46	0.68
4	521.5/[r + x + 36]	[r + x + 36]/[r + x + 557.5]	12.42	0.075
Overall	671.5/[r + x + 36]	[r + x + 36]/[r + x + 707.5]	**17.67**	**0.054**

Nef reaction
Nef, J.U., *Ann. Chem*. **1894**, 280, 263

(1) 

x + y + 59 54 x + y + 81 32

(2) 

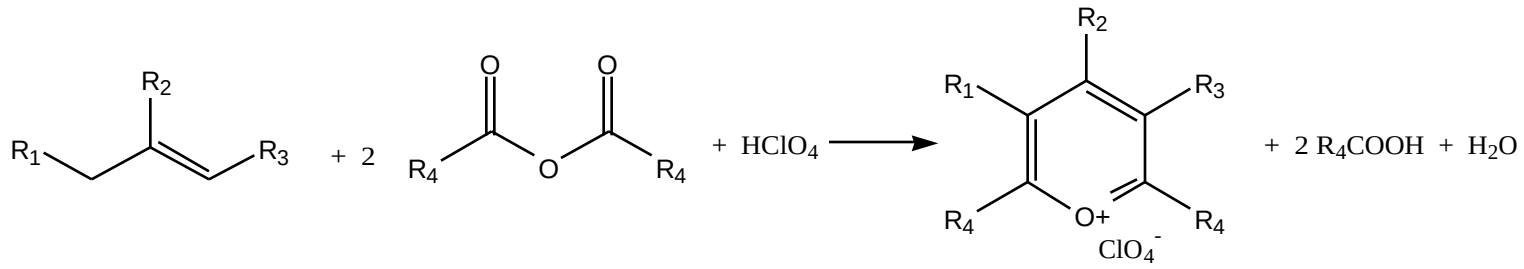
x + y + 81 49 x + y + 28 102

R1 = x; R2 = y

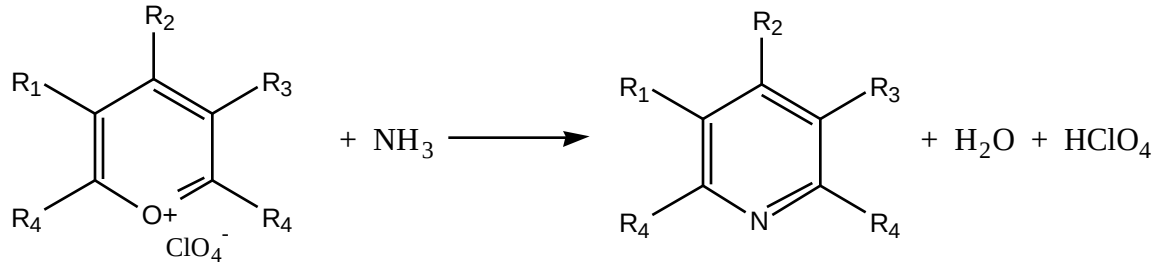
Step	**E**	**AE**	**E(max)**	**AE(min)**
1	32/[x + y + 81]	[x + y + 81]/[x + y + 113]	0.39	0.72
2	102/[x + y + 28]	[x + y + 28]/[x + y + 130]	3.4	0.23
Overall	134/[x + y + 28]	[x + y + 28]/[x + y + 162]	**4.47**	**0.18**

Nenitzescu-Praill synthesis of substituted pyridines via pyrylium salts

Balaban, A.T.; Nenitzescu, C.D. *Ann. Chem.* **1959**, 625, 74
Balaban, A.T.; Nenitzescu, C.D. *J. Chem. Soc.* **1961**, 3553; 3561; 3564
Praill, P.F.G.; Whitear, A.L. *J. Chem. Soc.* **1961**, 3573
Praill, P.F.G.; Whitear, A.L. *Proc. Chem. Soc.* **1961**, 312

(1) 

x + y + z + 39 4 w + 144 100.45 x + y + z + 2w + 175.45 2w + 90 18

(2) 

x + y + z + 2w + 175.45 17 x + y + z + 2w + 74 18 100.45

R1 = x; R2 = y; R3 = z; R4 = w

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	[2w + 108]/[x + y + z + 2w + 175.45]	[x + y + z + 2w + 175.45]/[x + y + z + 4w + 283.45]	0.66	0.60
2	118.45/[x + y + z + 2w + 74]	[x + y + z + 2w + 74]/[x + y + z + 2w + 192.45]	1.11	0.47
Overall				
	[2w + 226.45]/[x + y + z + 2w + 74]	[x + y + z + 2w + 74]/[x + y + z + 2w + 300.45]	**2.40**	**0.29**

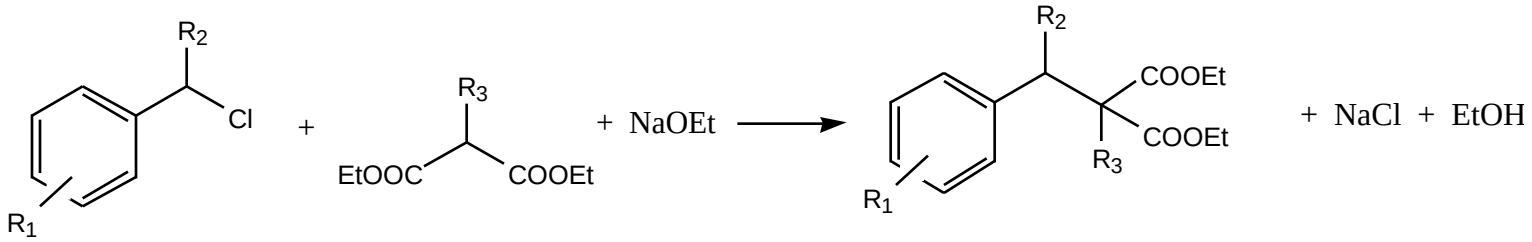
R4 = Me, R1 = R2 = R3 = H

Pfau-Plattner synthesis of azulenes

Pfau, A. St.; Plattner, P.A. *Helv. Chim. Acta* **1939**, 22, 202
Plattner, P.A.; Wyss, J. *Helv. Chim. Acta* **1940**, 23, 907
Plattner, P.A.; Wyss, J. *Helv. Chim. Acta* **1941**, 24, 483

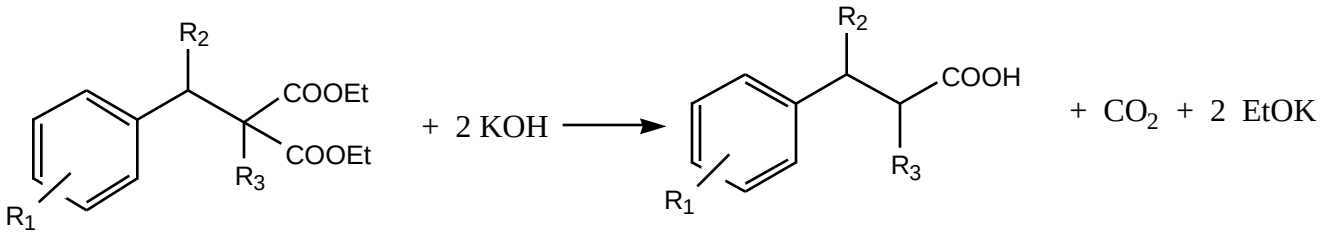
Plattner, P.A.; Roniger, H. *Helv. Chim. Acta* **1942**, 25, 590

(1)

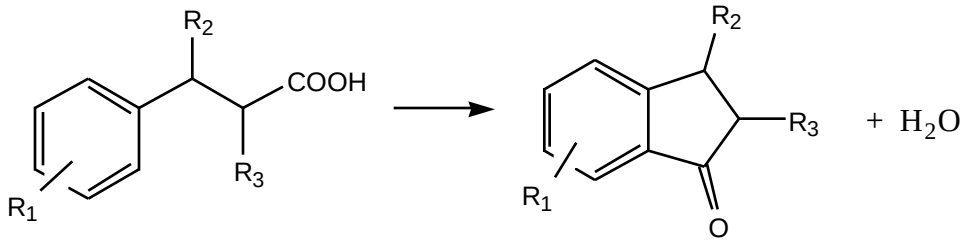


x + y + 120.45 z + 159 68 x + y + z + 243 58.45 46

(2)

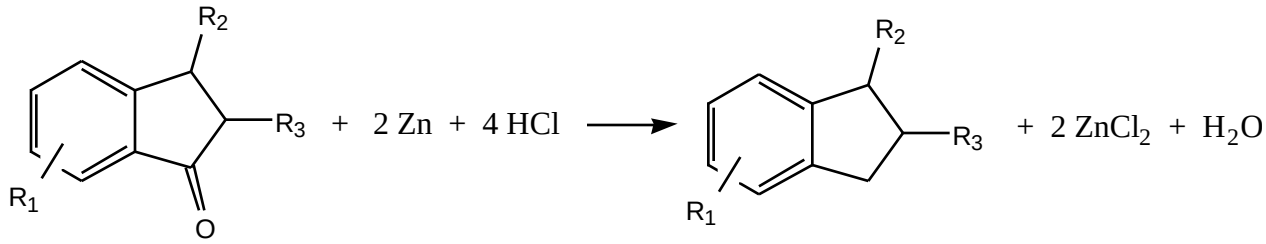


x + y + z + 243 112 x + y + z + 143 44 168

(3) 

+ H_2O

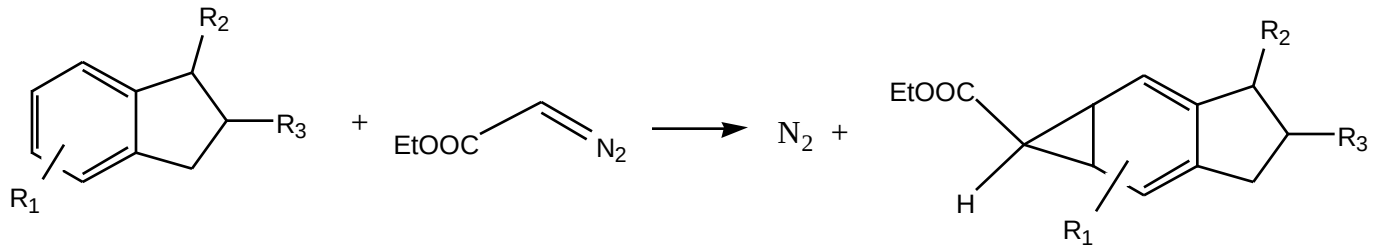
x + y + z + 143 x + y + z + 125 18

(4) 

+ 2 Zn + 4 HCl + 2 $ZnCl_2$ + H_2O

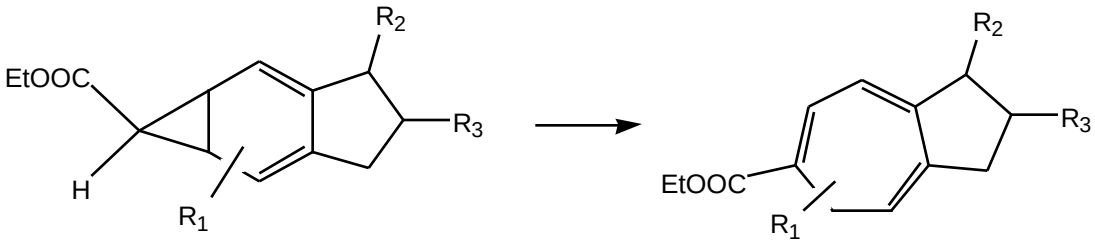
x + y + z + 125 130.8 145.8 x + y + z + 111 272.6 18

(5)

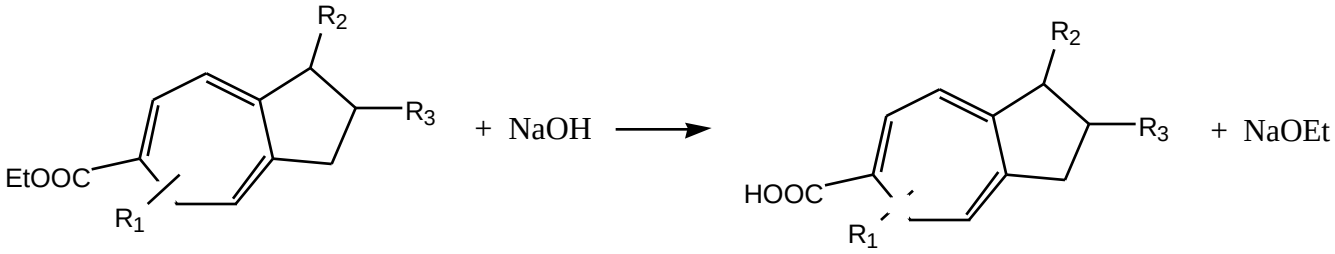


x + y + z + 111 114 28 x + y + z + 197

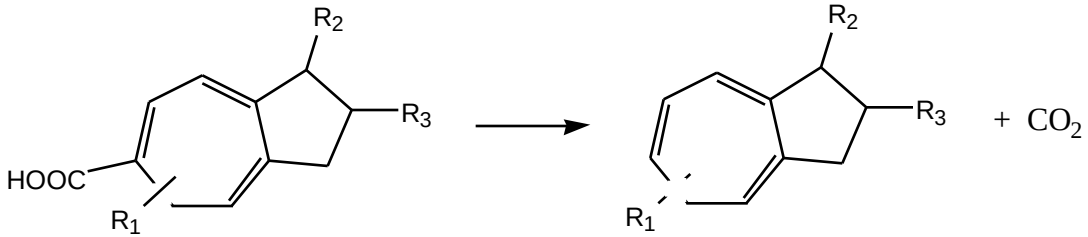
(6)



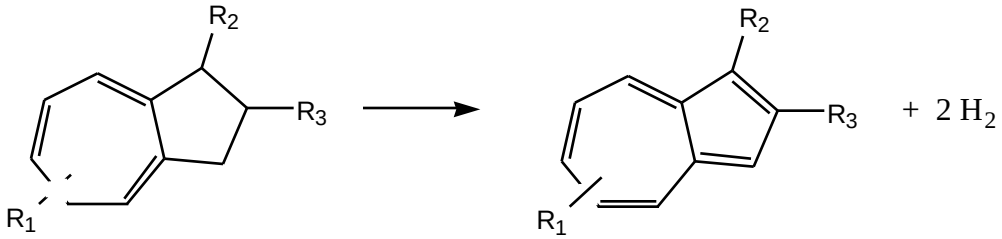
x + y + z + 197 x + y + z + 197

(7) 

x + y + z + 197 40 x + y + z + 169 68

(8) 

x + y + z + 169 x + y + z + 125 44

(9) 

x + y + z + 125 x + y + z + 121 4

R1 = x (sum of substituents); R2 = y; R3 = z

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	104.45/[x + y + z + 243]	[x + y + z + 243]/[x + y + z + 347.45]	0.42	0.70
2	212/[x + y + z + 143]	[x + y + z + 143]/[x + y + z + 355]	1.45	0.41
3	18/[x + y + z + 125]	[x + y + z + 125]/[x + y + z + 143]	0.14	0.88

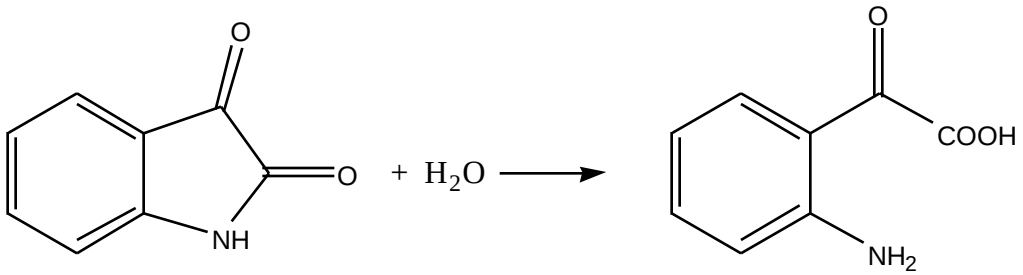
4	290.6/[x + y + z + 111]	[x + y + z + 111]/[x + y + z + 401.6]	2.55	0.28
5	28/[x + y + z + 197]	[x + y + z + 197]/[x + y + z + 225]	0.14	0.88
6	0	1	0	1
7	68/[x + y + z + 169]	[x + y + z + 169]/[x + y + z + 237]	0.40	0.72
8	44/[x + y + z + 125]	[x + y + z + 125]/[x + y + z + 169]	0.34	0.74
9	4/[x + y + z + 121]	[x + y + z + 121]/[x + y + z + 125]	0.032	0.97
Overall	769.05/[x + y + z + 121]	[x + y + z + 121]/[x + y + z + 890.05]	**6.20**	**0.14**

Pfitzinger reaction

Pfitzinger, W. *J. Prakt. Chem.* **1886**, 33[2], 100

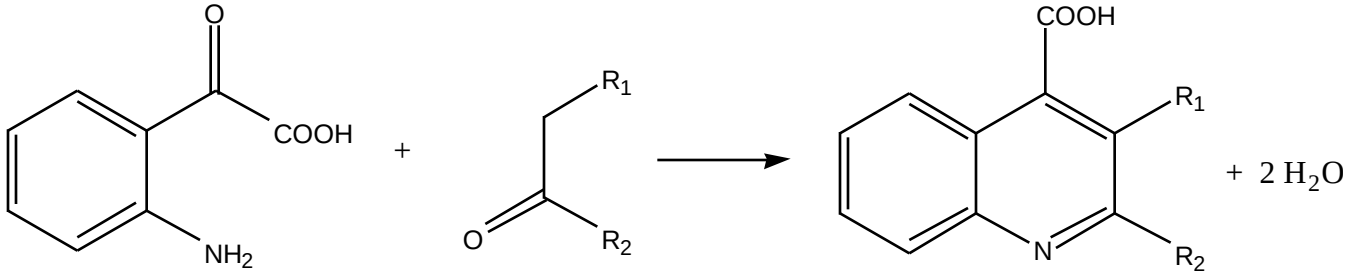
Pfitzinger, W. *J. Prakt. Chem.* **1888**, 38, 582

(1)

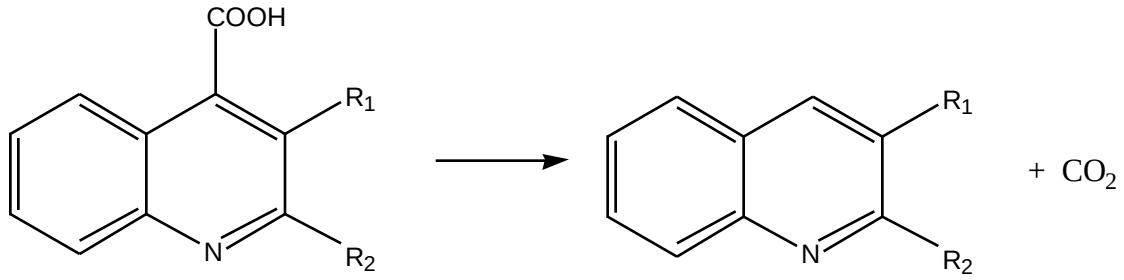


147 18 165

(2)



165 x + y + 42 x + y + 171 36

(3) 

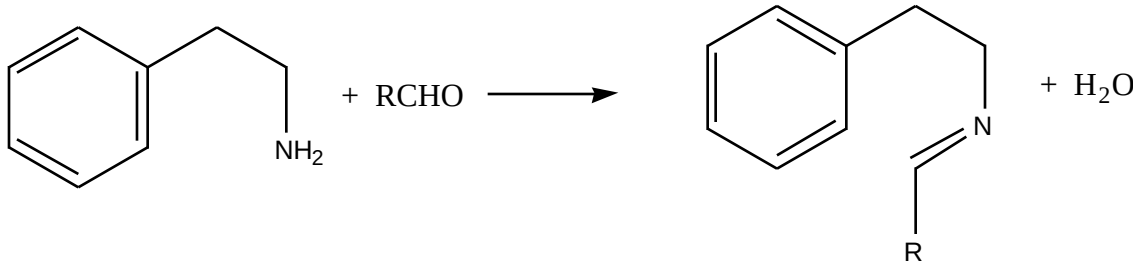
+ CO_2

x + y + 171 x + y + 127 44

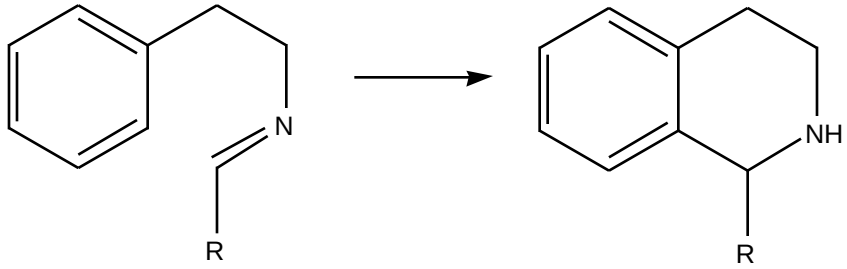
R1 = x; R2 = y

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	0	1	0	1
2	36/[x + y + 171]	[x + y + 171]/[x + y + 207]	0.21	0.83
3	44/[x + y + 127]	[x + y + 127]/[x + y + 171]	0.34	0.75
Overall	62/[x + y + 127]	[x + y + 127]/[x + y + 189]	**0.48**	**0.68**

Pictet-Spengler isoquinoline synthesis
Pictet, A.; Spengler, T. *Chem. Ber.* **1911**, 44, 2030

(1) 

121 x + 29 x + 132 18

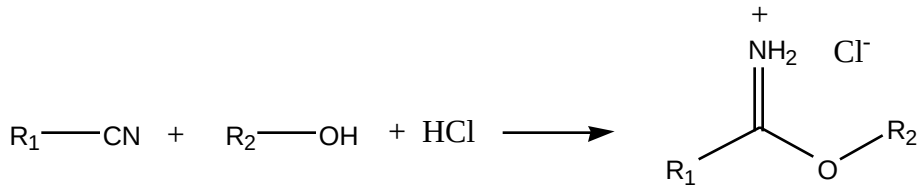
(2) 

x + 132 x + 132

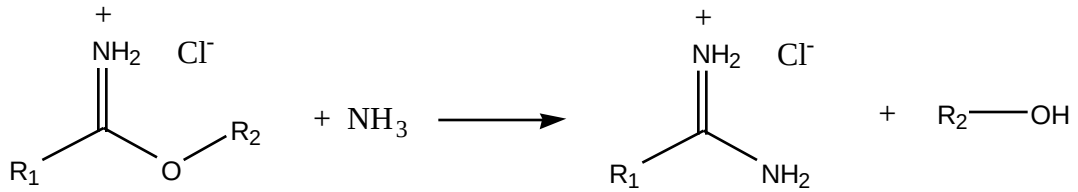
R = x

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	18/[x + 132]	[x + 132]/[x + 150]	0.14	0.88
2	0	1	0	1
Overall	18/[x + 132]	[x + 132]/[x + 150]	**0.14**	**0.88**

Pinner synthesis
Pinner, A.; Klein, F. *Chem. Ber.* **1877**, 10, 1889

(1) 

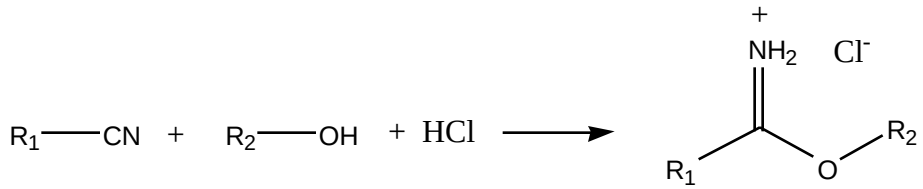
x + 26 y + 17 36.45 x + y + 79.45

(2) 

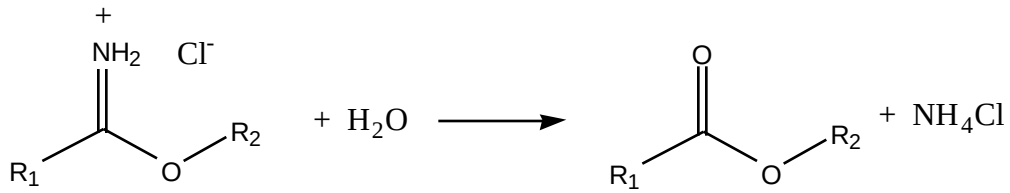
x + y + 79.45 17 x + 79.45 y + 17

R1 = x ; R2 = y

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	0	1	0	1
2	[y + 17]/[x + 79.45]	[x + 79.45]/[x + y + 96.45]	0.22	0.82
Overall	[y + 17]/[x + 79.45]	[x + 79.45]/[x + y + 96.45]	**0.22**	**0.82**

(1) 

x + 26 y + 17 36.45 x + y + 79.45

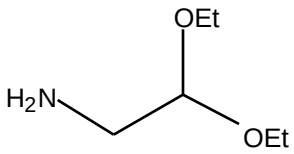
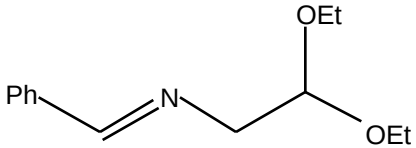
(2) 

x + y + 79.45 18 x + y + 44 53.45

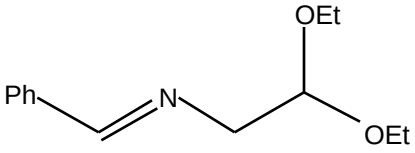
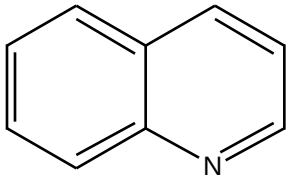
Step	**E**	**AE**	**E(max)**	**AE(min)**
1	0	1	0	1
2	53.45/[x + y + 44]	[x + y + 44]/[x + y + 97.45]	1.16	0.46
Overall	53.45/[x + y + 44]	[x + y + 44]/[x + y + 97.45]	**1.16**	**0.46**

Pomeranz-Fritsch reaction

Pomeranz, C. *Monatsch. Chem.* **1893**, 14, 116
Fritsch, P. *Chem. Ber.* **1893**, 26, 419

(1) PhCHO +  →  + H_2O

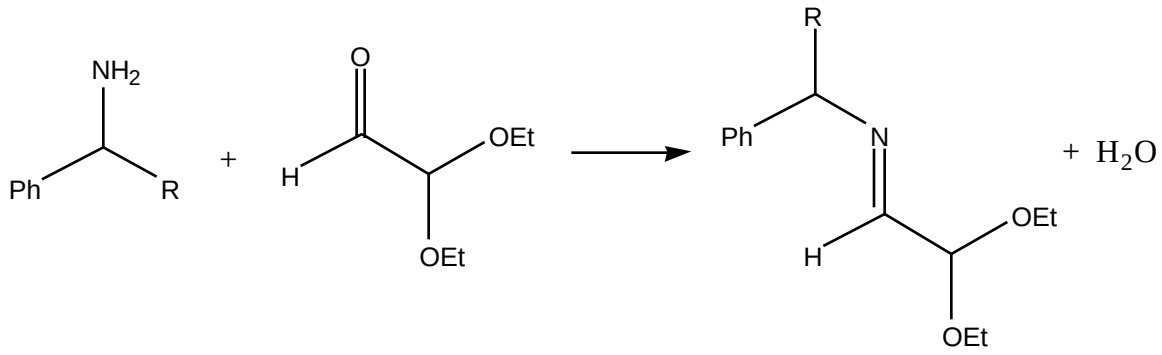
106 133 221 18

(2)  →  + 2 EtOH

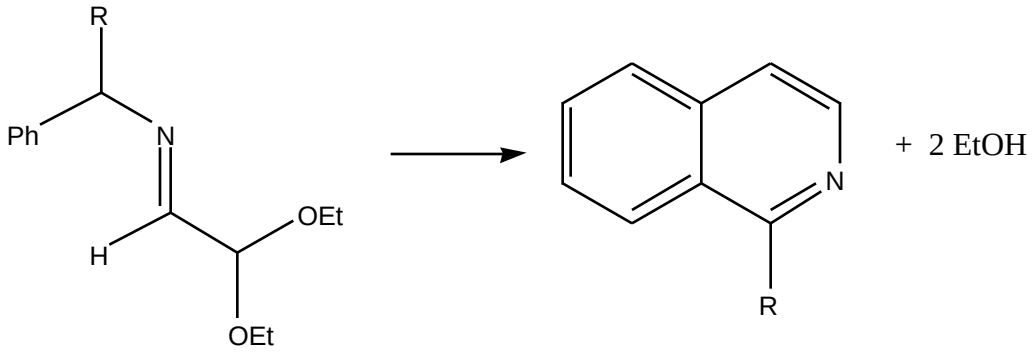
221 129 92

Step	**E**	**AE**
1	0.081	0.92
2	0.71	0.58
Overall	**0.85**	**0.54**

Schlittler-Mueller modification
Schlittler, E.; Mueller, J. *Helv. Chim. Acta* **1948**, 31, 914; 1119

(1) 

x + 106 132 x + 220 18

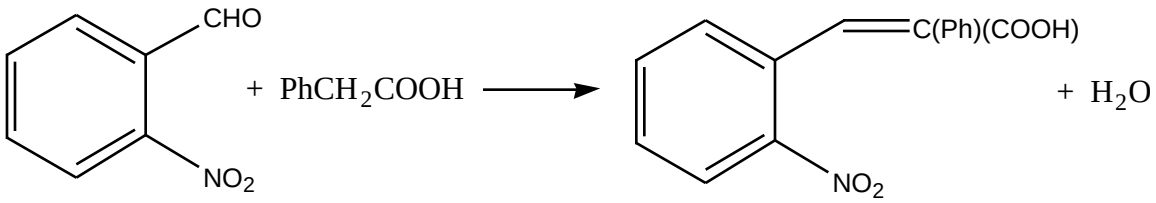
(2) 

x + 220 x + 128 92

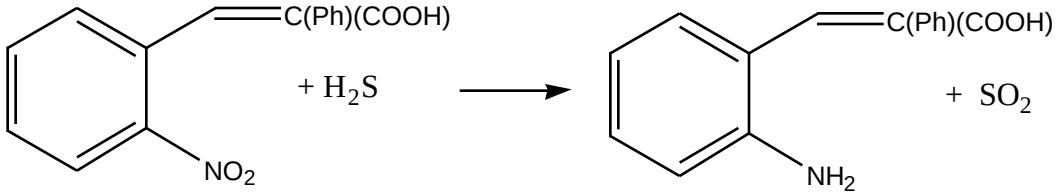
R = x

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	18/[x + 220]	[x + 220]/[x + 238]	0.081	0.92
2	92/[x + 128]	[x + 128]/[x + 220]	0.71	0.58
Overall	110/[x + 128]	[x + 128]/[x + 238]	**0.85**	**0.54**

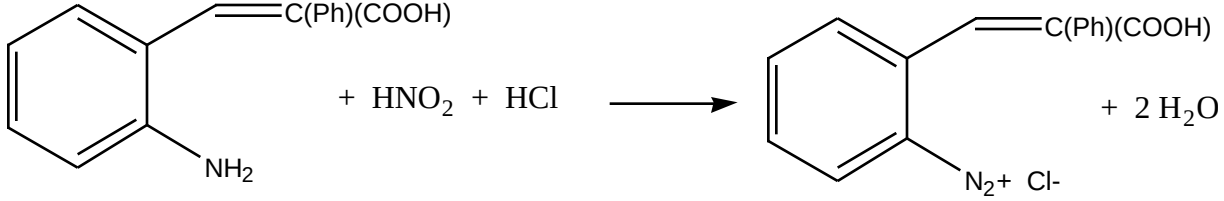
Pschorr reaction
Pschorr, R. *Chem. Ber.* **1896**, 29, 496

(1) 

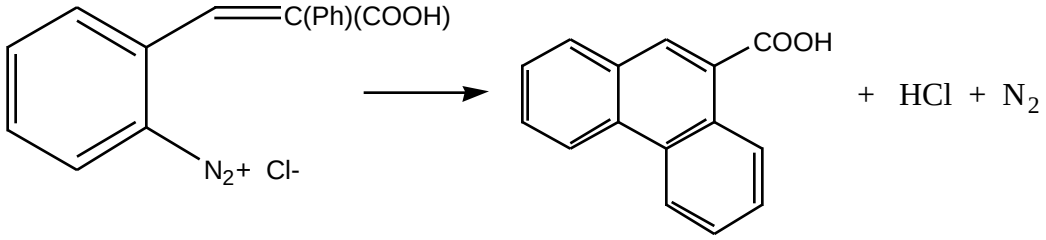
151 136 269 18

(2) 

269 34 239 64

(3) 

239 47 36.45 286.45 36

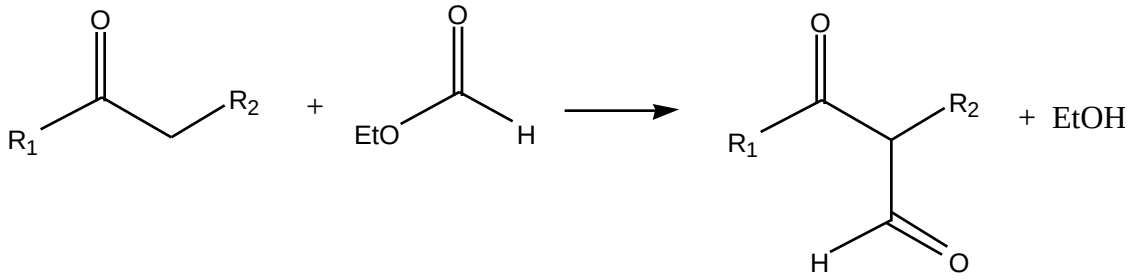
(4) 

286.45 222 36.45 28

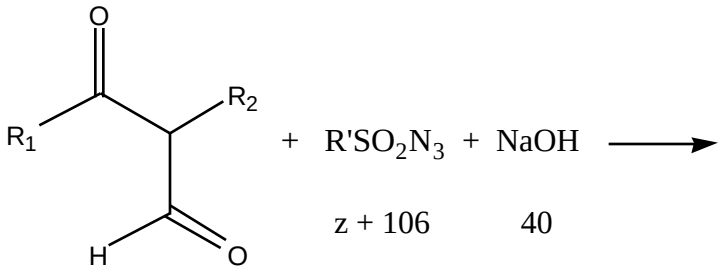
Step	**E**	**AE**
1	0.067	0.94
2	0.27	0.79
3	0.13	0.89
4	0.29	0.78
Overall	**0.66**	**0.60**

Regitz diazo group transfer reaction

Regitz, M., *Angew. Chem. Int. Engl. Ed.*, **1967**, 6, 733

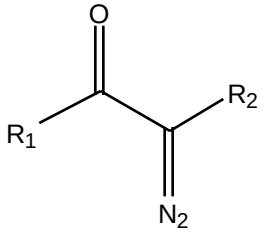
(1) 

x + y + 42 74 x + y + 70 46

(2) 

+ $R'SO_2N_3$ + NaOH

x + y + 70 z + 106 40



$R'SO_2NH_2$ + HCOONa

x + y + 68 z + 80 68

R1 = x; R2 = y; R' = z

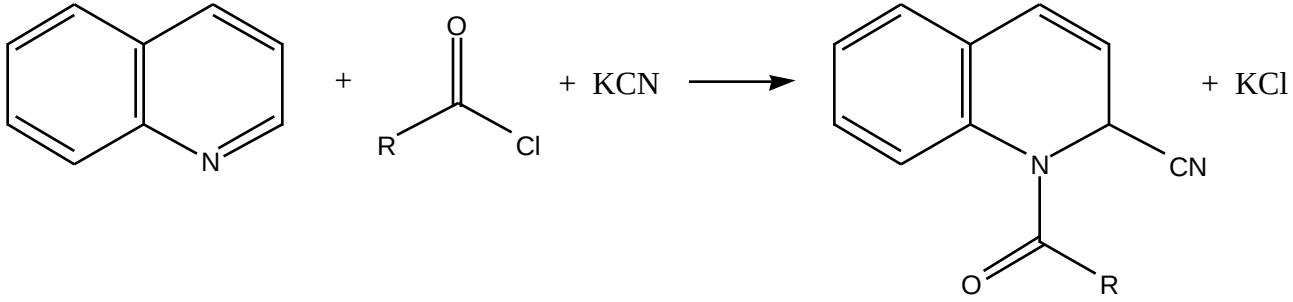
Step	**E**	**AE**	**E(max)**	**AE(min)**
1	46/[x + y + 70]	[x + y + 70]/[x + y + 116]	0.64	0.61
2	[z + 148]/[x + y + 68]	[x + y + 68]/[x + y + z + 216]	[z + 148]/70	70/[z + 218]
Overall	[194 + z]/[x + y + 68]	[x + y + 68]/[x + y + z + 262]	**[z + 194]/70**	**70/[z + 264]**

Z	E(max)	AE(min)
Me	2.99	0.25
$CH_3C_6H_4$	4.07	0.20

Reissert reaction

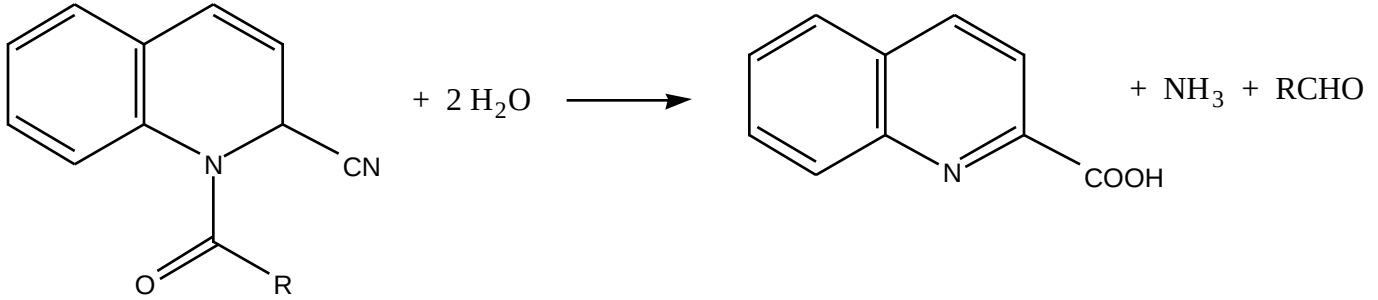
Reissert, A. *Chem. Ber.* **1905**, 38, 1603; 3415

(1)



129 x + 63.45 65 x + 183 74.45

(2)



x + 183 36 173 17 x + 29

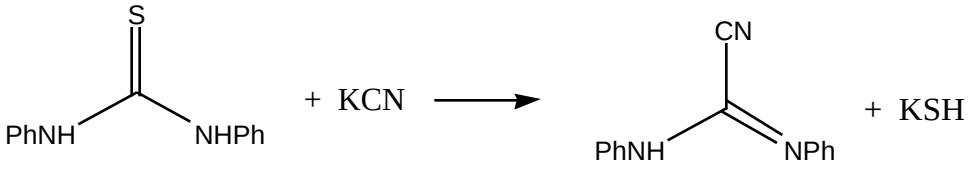
R = x

Step	E	AE	E(max)	AE(min)	
1	74.45/[x + 183]	[x + 183]/[x + 257.45]	0.40	0.71	
2	[x + 46]/173	173/[x + 219]	0.35	0.74	(R = Me)
Overall	[x + 120.45]/173	173/[x + 293.45]	**0.78**	**0.56**	(R = Me)

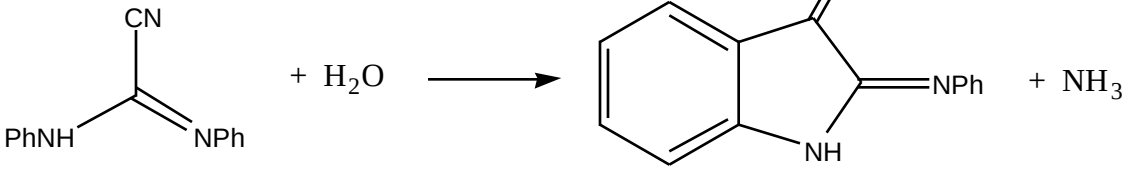
Sandmeyer synthesis of isatins

Sandmeyer, T. *Z. Farb. Textile Chem.* **1903**, 2, 129

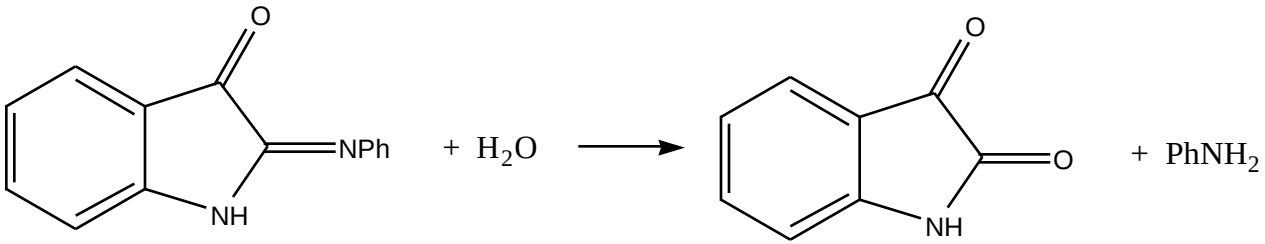
Sandmeyer, T. *Helv. Chim. Acta* **1919**, 2, 234

(1) 

228 65 221 72

(2) 

221 18 222 17

(3) 

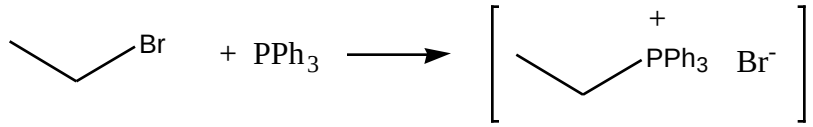
222 18 147 93

Step	E	AE
1	0.33	0.75
2	0.077	0.93
3	0.63	0.61

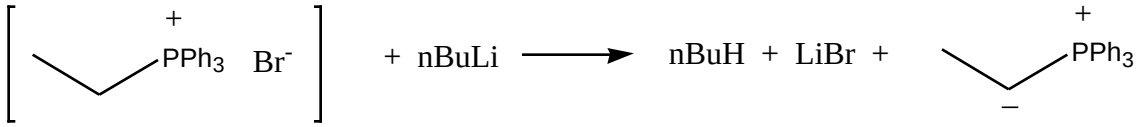
Overall 1.24 0.45

Schlosser modification of Wittig reaction

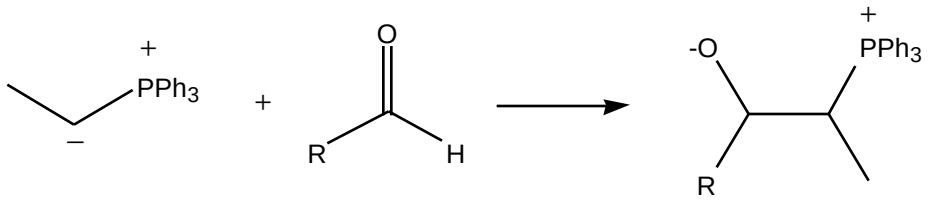
Schlosser, M.; Christmann, F.K.; Piskala, A.; Coffinet, D., *Synthesis* **1971**, 29
Schlosser, M.; Coffinet, D., *Synthesis* **1971**, 380
Schlosser, M.; Coffinet, D., *Synthesis* **1972**, 575
Schlosser, M.; Christmann, F.K., *Synthesis* **1969**, 38

(1) 

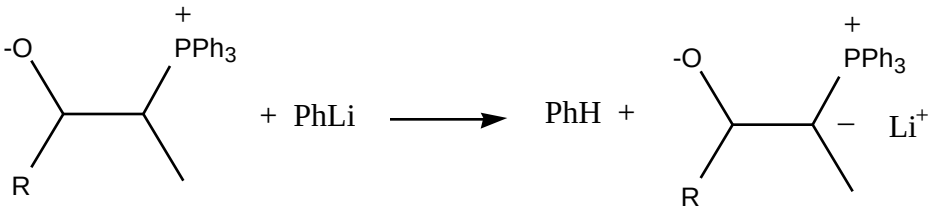
108.9 262 370.9

(2) 

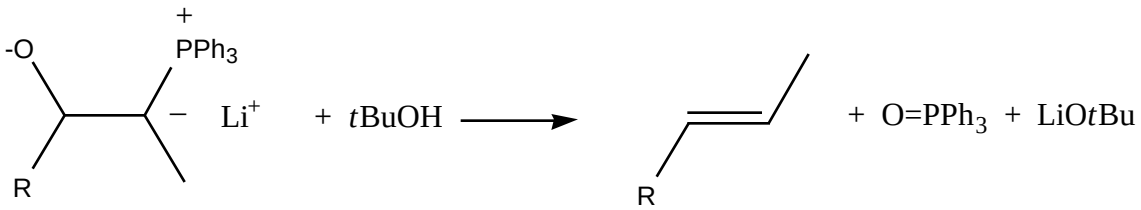
370.9 64 58 86.9 290

(3) 

290 x + 29 x + 319

(4) 

x + 319 84 78 x + 325

(5) 

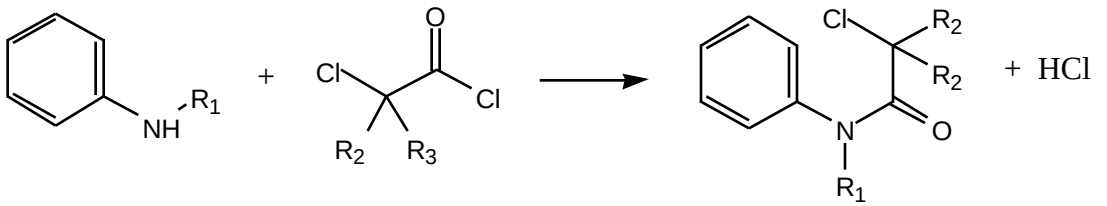
x + 325 74 x + 41 278 80

R = x

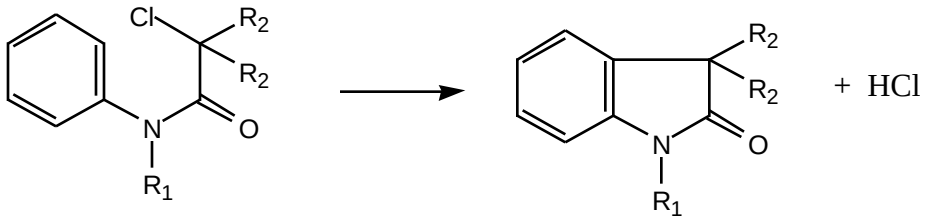
Step	**E**	**AE**	**E(max)**	**AE(min)**
1	0	1	0	1
2	0.50	0.67	0.50	0.67
3	0	1	0	1
4	78/[x + 325]	[x + 325]/[x + 403]	0.24	0.81
5	358/[x + 41]	[x + 41]/[x + 399]	8.52	0.105
Overall	580.9/[x + 41]	[x + 41]/[x + 621.9]	**13.83**	**0.067**

Stolle synthesis of indoles
Stolle, R. *Chem. Ber.* **1913**, 46, 3915

Stolle, R. *Chem. Ber.* **1914**, 47, 2120

(1) 

x + 92 y + z + 110.9 x + y + z + 166.45 36.45

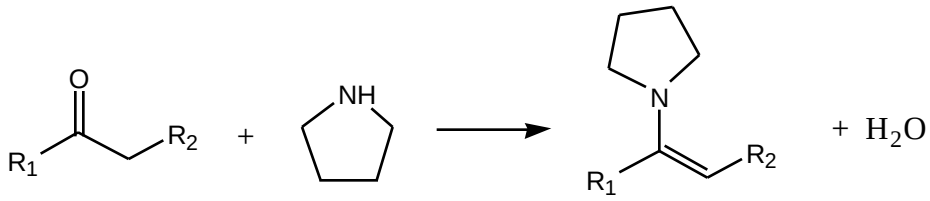
(2) 

x + y + z + 166.45 x + y + z + 130 36.45

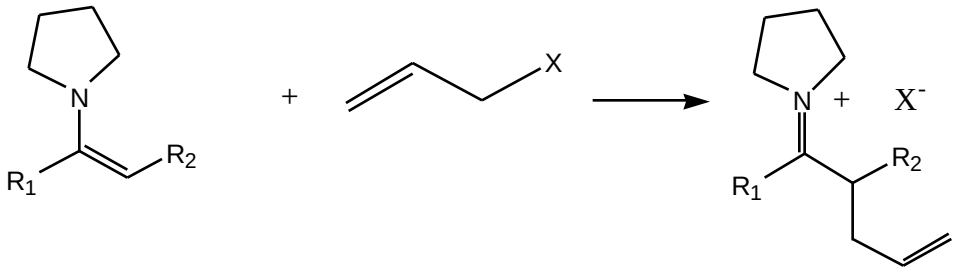
R1 = x; R2 = y; R3 = z

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	36.45/[x + y + z + 166.45]	[x + y + z + 166.45]/[x + y + z + 202.9]	0.22	0.82
2	36.45/[x + y + z + 130]	[x + y + z + 130]/[x + y + z + 166.45]	0.27	0.78
Overall	72.9/[x + y + z + 130]	[x + y + z + 130]/[x + y + z + 202.9]	**0.55**	**0.65**

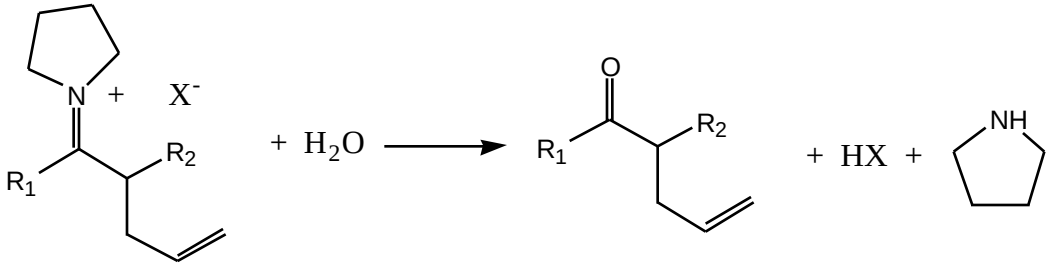
Stork enamine synthesis
Stork, G.; Terrell, R.; Szmuszkovicz, J., *J. Am. Chem. Soc*. **1954**, 76, 2029

(1) 

y + z + 42 71 y + z + 95 18

(2) 

y + z + 95 x + 41 x + y + z + 136

(3) 

x + y + z + 136 18 y + z + 100 x + 1 71

R1 = y; R2 = z; X = x (halide)

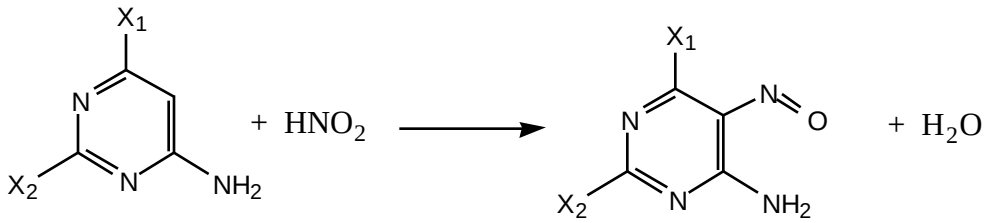
Step	**E**	**AE**	**E(max)**	**AE(min)**
1	18/[y + z + 95]	[y + z + 95]/[y + z + 113]	0.19	0.84
2	0	1	0	1

3	[x + 72]/[y + z + 100]	[y + z + 100]/[x + y + z + 172]	[x + 72]/102	102/[x + 174]
Overall	[x + 1]/[y + z + 100]	[y + z + 100]/[x + y + z + 101]	**[x + 1]/102**	**102/[x + 103]**

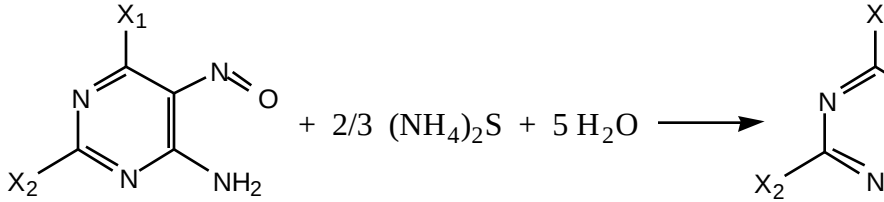
X	**E(max)**	**AE(min)**
Cl	0.36	0.74
Br	0.79	0.56
I	1.25	0.44

Traube synthesis of purines

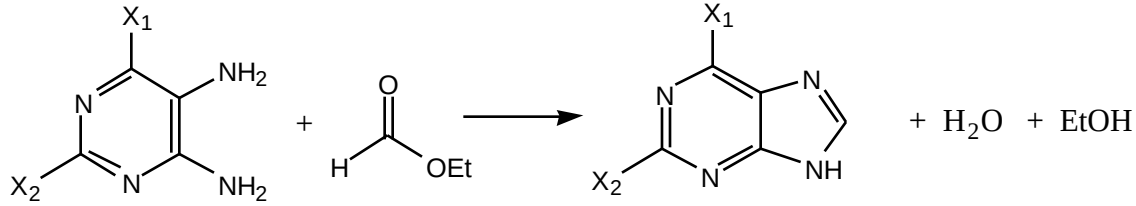
Traube, W. *Chem. Ber.* **1900**, 33, 1371; 3035

(1)  + HNO_2 + H_2O

x + y + 93 47 x + y + 122 18

(2)  + 2/3 $(NH_4)_2S$ + 5 H_2O + 4/3 NH_4OH + 2/3 SO_2

x + y + 122 45.33 90 x + y + 108 46.67 42.67

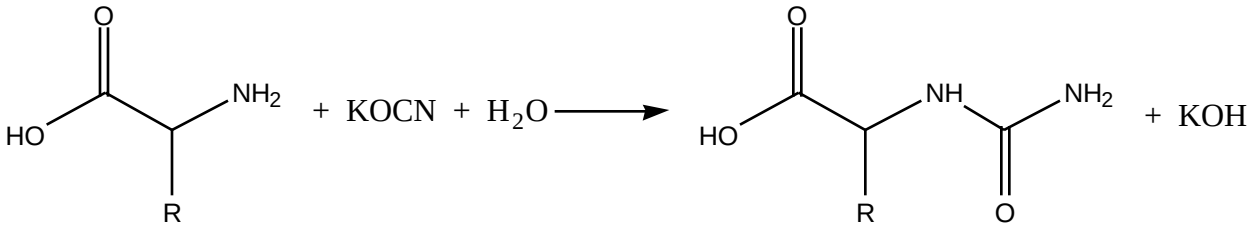
(3)  + H_2O + EtOH

x + y + 108 74 x + y + 118 18 46

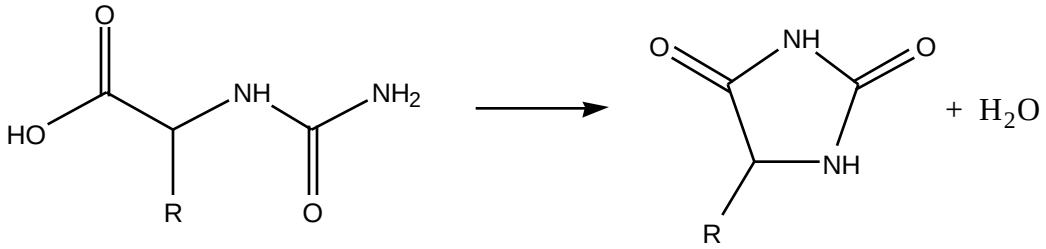
X1 = x; X2 = y

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	18/[x + y + 122]	[x + y + 122]/[x + y + 140]	0.15	0.87
2	89.34/[x + y + 108]	[x + y + 108]/[x + y + 197.34]	0.81	0.55
3	64/[x + y + 118]	[x + y + 118]/[x + y + 182]	0.53	0.65
Overall	153.34/[x + y + 118]	[x + y + 118]/[x + y + 271.34]	**1.28**	**0.44**

Urech synthesis of hydantoins
Urech, F. *Ann. Chem.* **1873**, 165, 99

(1) 

x + 74 81 18 x + 117 56

(2) 

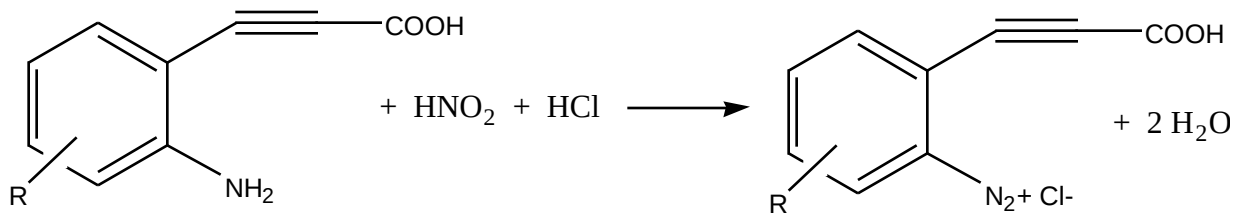
x + 117 x + 99 18

R = x

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	56/[x + 117]	[x + 117]/[x + 173]	0.47	0.68
2	18/[x + 99]	[x + 99]/[x + 117]	0.18	0.85
Overall	56/[x + 99]	[x + 99]/[x + 155]	**0.56**	**0.64**

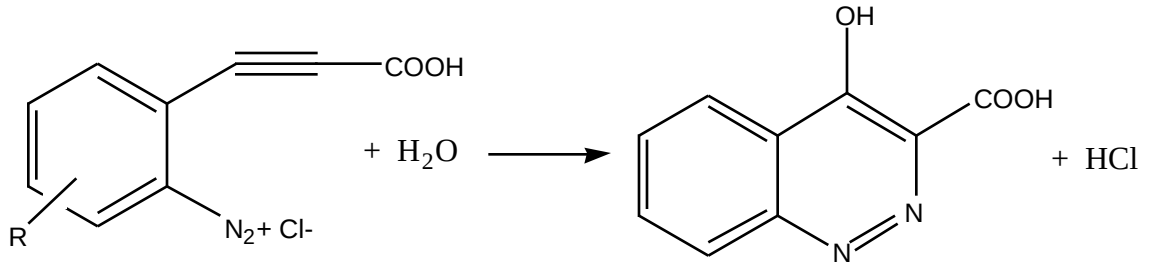
von Richter cinnoline synthesis
von Richter, V. *Chem. Ber.* **1883**, 16, 677

(1)



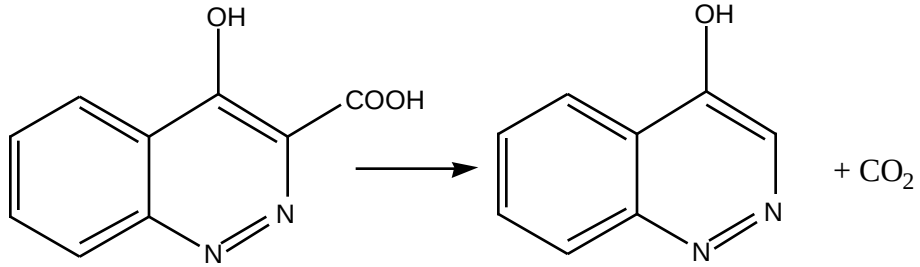
x + 157 47 36.45 x + 204.45 36

(2)



x + 204.45 18 x + 186 36.45

(3)



x + 186 x + 142 44

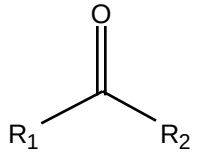
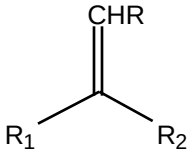
R = x (sum of substituents)

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	36/[x + 204.45]	[x + 204.45]/[x + 240.45]	0.17	0.85
2	36.45/[x + 186]	[x + 186]/[x + 222.45]	0.19	0.84
3	44/[x + 142]	[x + 142]/[x + 186]	0.30	0.77
Overall	62/[x + 142]	[x + 142]/[x + 208]	**0.42**	**0.70**

Wittig reaction
Wittig, G.; Schöllkopf, U., *Chem. Ber*. **1954**, 87, 1318

(1) $PPh_3 + RCH_2Br \longrightarrow [Ph_3P^+-CH_2R\ Br^-]$

263 z + 93.9 z + 356.9

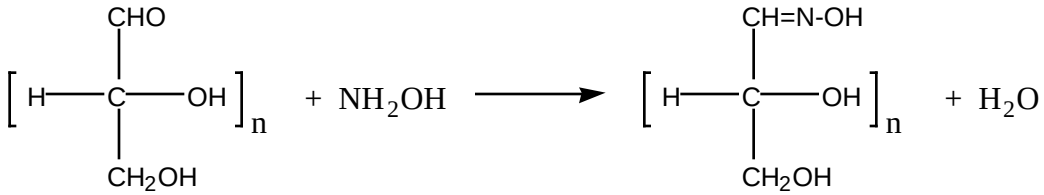
(2) $[Ph_3P^+-CH_2R\ Br^-] +$  $\longrightarrow$  $+ O{=}PPh_3 + HBr$

z + 356.9 x + y + 28 x + y + z + 25 281 80.9

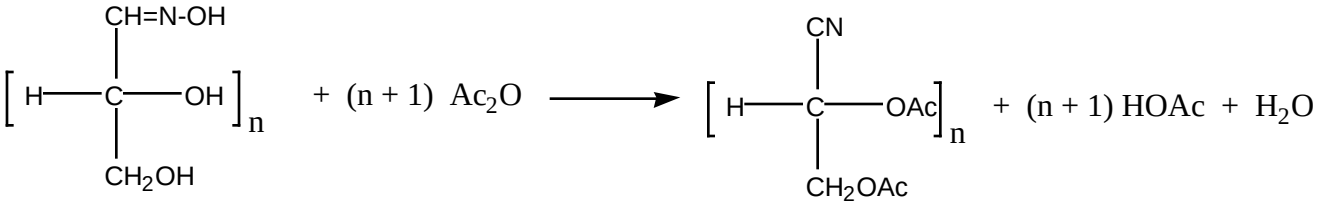
R1 = x; R2 = y; R = z

Step	**E**	**AE**	**E(max)**	**AE(min)**
1	0	1	0	1
2	361.9/[x + y + z + 25]	[x + y + z + 25]/[x + y + z + 386.9]	**12.93**	**0.072**
Overall	361.9/[x + y + z + 25]	[x + y + z + 25]/[x + y + z + 386.9]	**12.93**	**0.072**

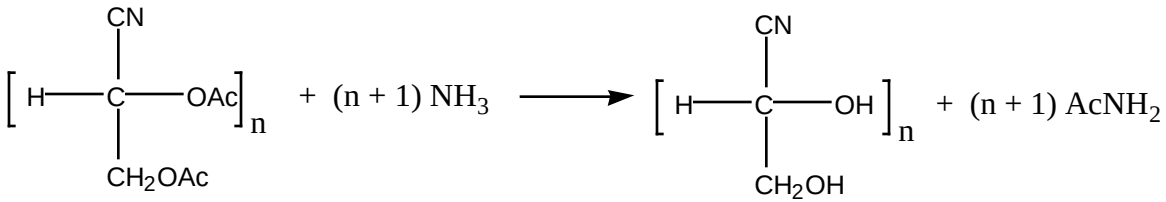
Wohl degradation
Wohl, A., *Chem. Ber*. **1893**, 26, 730
Wohl, A., *Chem. Ber*. **1899**, 32, 3666

(1) 

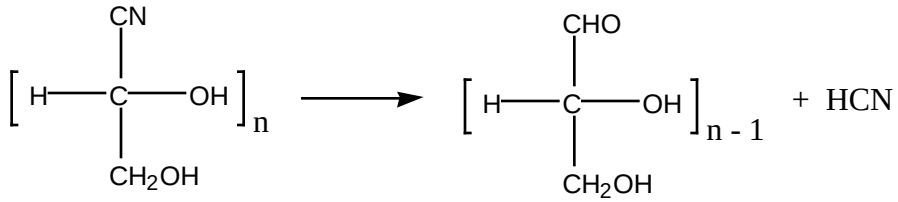
30n + 60 33 30n + 75 18

(2) 

30n + 75 102 (n + 1) 72n + 99 60 (n + 1) 18

(3) 

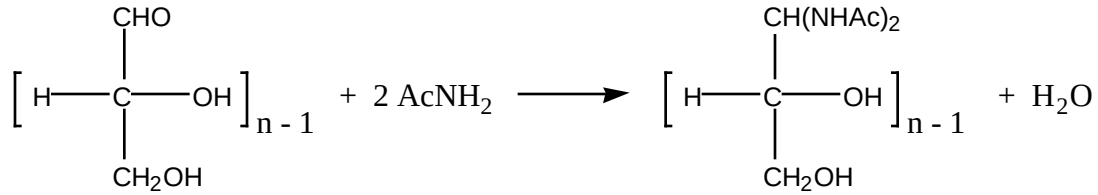
72n + 99 17 (n + 1) 30n + 57 59 (n + 1)

(4) 

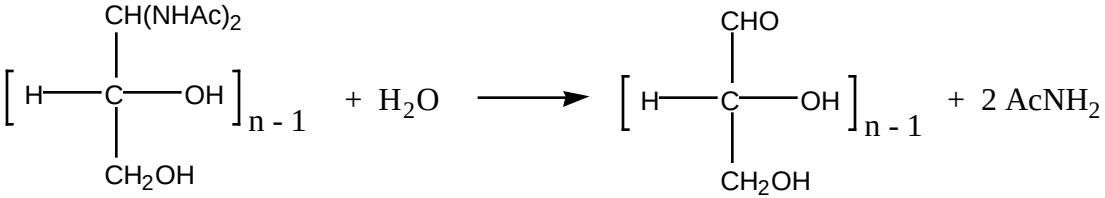
30n + 57 30(n - 1) + 60 27

(5) $HCN + AgNO_3 \longrightarrow AgCN + HNO_3$

27 170 134 63

(6) 

30(n - 1) + 60 118 30(n - 1) + 160 18

(7) 

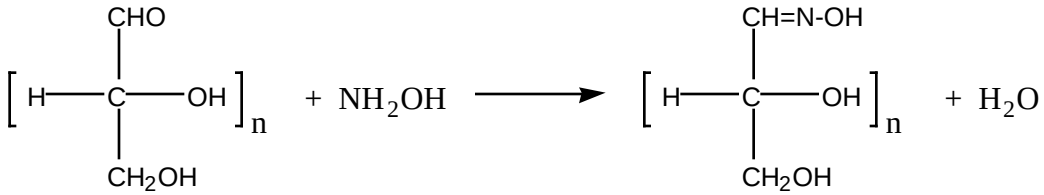
30(n - 1) + 160 18 30(n - 1) + 60 118

Step	**E**	**AE**
1	18/[30n + 75]	[30n + 75]/[30n + 93]
2	[60n + 78]/[72n + 99]	[72n + 99]/[132n + 177]
3	[59n + 59]/[30n + 57]	[30n + 57]/[89n + 116]
4	27/[30n + 30]	[30n + 30]/[30n + 57]
5	0	1
6	18/[30n + 130]	[30n + 130]/[30n + 148]
7	118/[30n + 30]	[30n + 30]/[30n + 148]
Overall	[119n + 352]/[30n + 30]	[30n + 30]/[149n + 382]

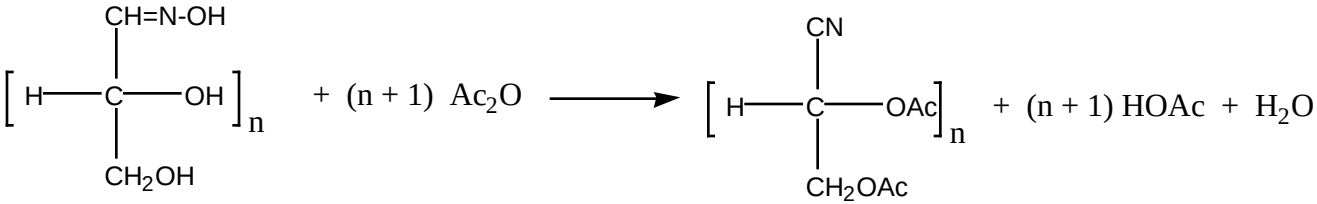
n	**E**	**AE**
3 (5 carbon sugars)	5.91	0.14
4 (6 carbon sugars)	5.52	0.15

Zemplen degradation

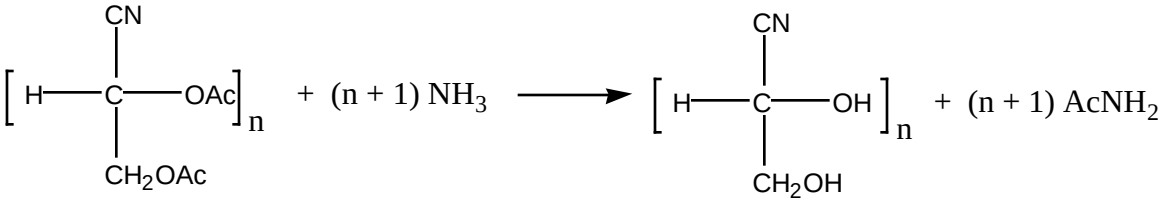
Zemplen, G. *Chem. Ber.* **1926**, 59B, 1254; 2402
Zemplen, G. *Chem. Ber.* **1927**, 60B, 1555

(1) 

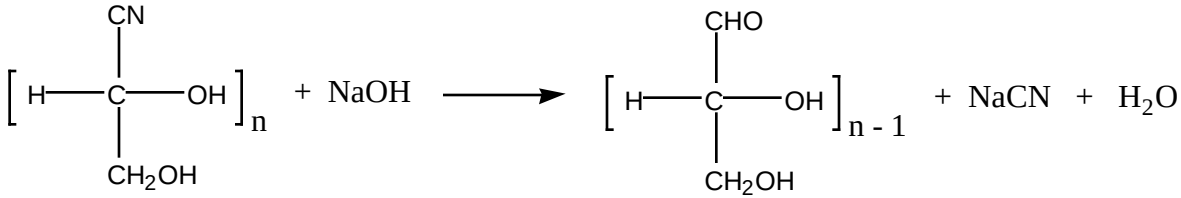
30n + 60 33 30n + 75 18

(2) 

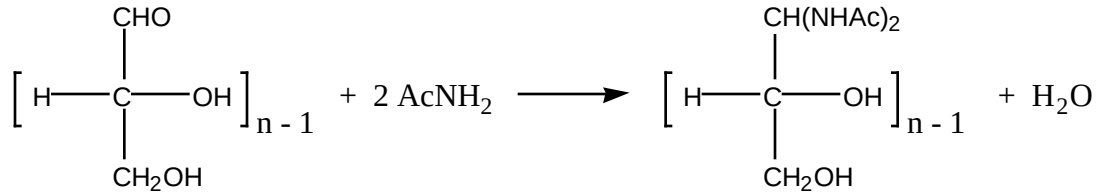
30n + 75 102 (n + 1) 72n + 99 60 (n + 1) 18

(3) 

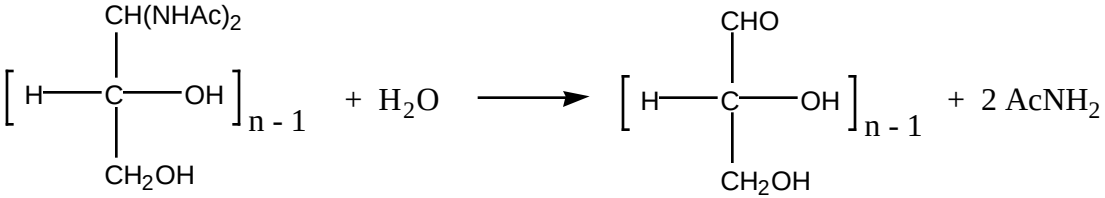
72n + 99 17 (n + 1) 30n + 57 59 (n + 1)

(4) 

30n + 57 40 30(n - 1) + 60 49 18

(5) 

30(n - 1) + 60 118 30(n - 1) + 160 18

(6) 

30(n - 1) + 160 18 30(n - 1) + 60 118

Step	**E**	**AE**
1	18/[30n + 75]	[30n + 75]/[30n + 93]
2	[60n + 78]/[72n + 99]	[72n + 99]/[132n + 177]
3	[59n + 59]/[30n + 57]	[30n + 57]/[89n + 116]
4	67/[30n + 30]	[30n + 30]/[30n + 97]
5	18/[30n + 130]	[30n + 130]/[30n + 148]
6	118/[30n + 30]	[30n + 30]/[30n + 148]
Overall	[119n + 222]/[30n + 30]	[30n + 30]/[149n + 252]

n	**E**	**AE**
3 (5 carbon sugars)	4.83	0.17
4 (6 carbon sugars)	4.65	0.18