Supplement
A Green Chemistry Comparative Analysis of the Syntheses of (E)-4-Cyclobutyl-2-[2-(3-Nitrophenyl)ethenyl] thiazole, Ro 24-5904

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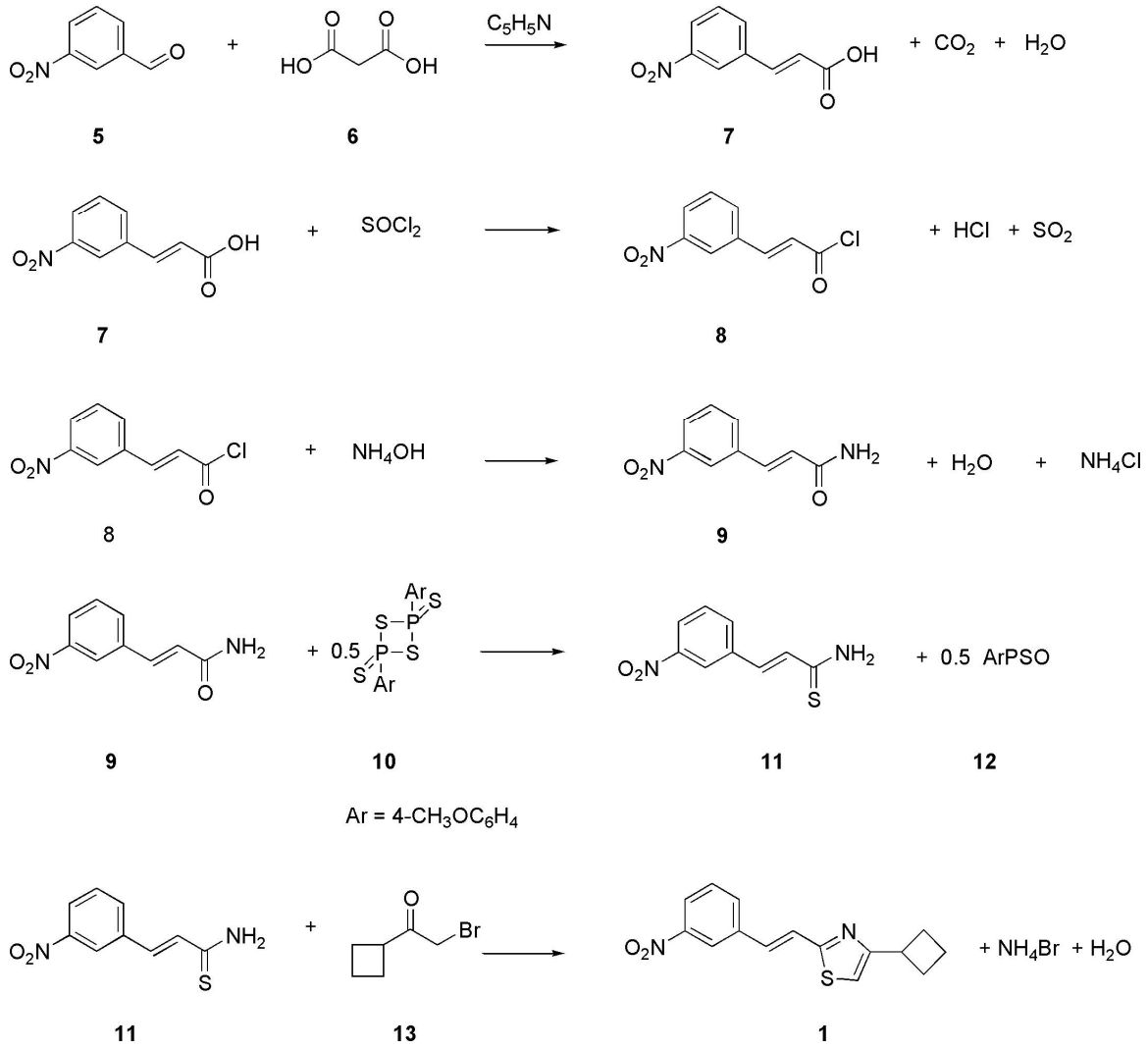
Andraos' Metrics and Calculations for the Malonic Acid, Wittig-Horner and Claisen Syntheses if Ro 24-5904 (**1**)



Scheme S1. Malonic Acid Synthesis of Ro 24-5904 (**1**)

Table S1. Molecular Weight Data from the Balanced Chemical Equations for the Malonic Acid Synthesis of Ro 24-5904 (1)

Reaction	Byproducts	MW Byproducts	MW (product) (p_j)
1	CO_2 H_2O	44.01 18.01 62.02	193.16
2	SO_2 HC1	64.06 36.46 100.52	211.6
3	NH_4Cl 2 H_2O	53.49 36.02 89.51	192.17
4	1/2 ArPSO	93.09	208.24
5	NH_4Br 2 H_2O	97.94 36.02 133.96	286.35

$$E_{mw} = \frac{\Sigma \text{Molecular weights of the byproducts}}{\text{Molecular weight of the product}} \qquad \text{Atom Economy (AE)} = \frac{1}{1 + E_{mw}}$$

$$\text{Stoichiometric Factor (SF)} = 1 + \frac{\Sigma \text{Mass of excess reagents}}{\text{MW of product} + \Sigma \text{MW of reagents}}$$

$$\text{Reaction Mass Efficiency (RME)} = \frac{\varepsilon\,(\text{AE})}{\text{SF}} \quad \text{where } \varepsilon = \text{Yield}$$

$$E_m = \frac{1}{\text{RME}} - 1$$

$\bar{\omega}_j$ = Cumulative waste for each step$_j$ for x moles of final target product

$$= p_j(Em)_j\left(\frac{x}{\prod \varepsilon_k}\right)$$ where x = 1 for 1 mole of final target product and

$\prod \varepsilon_k$ = multiplicative chain of reaction yields connecting the product from step j to the final target product

$$(E_{mw})_{overall} = \frac{\Sigma \text{MW of byproducts}}{\text{MW of final target product}} \qquad AE_{overall} = \frac{1}{1 + (E_{mw})_{overall}}$$

$$(E_m)_{overall} = \quad (E_m)_{overall} = \frac{\Sigma \bar{\omega}_j}{p_j x}$$

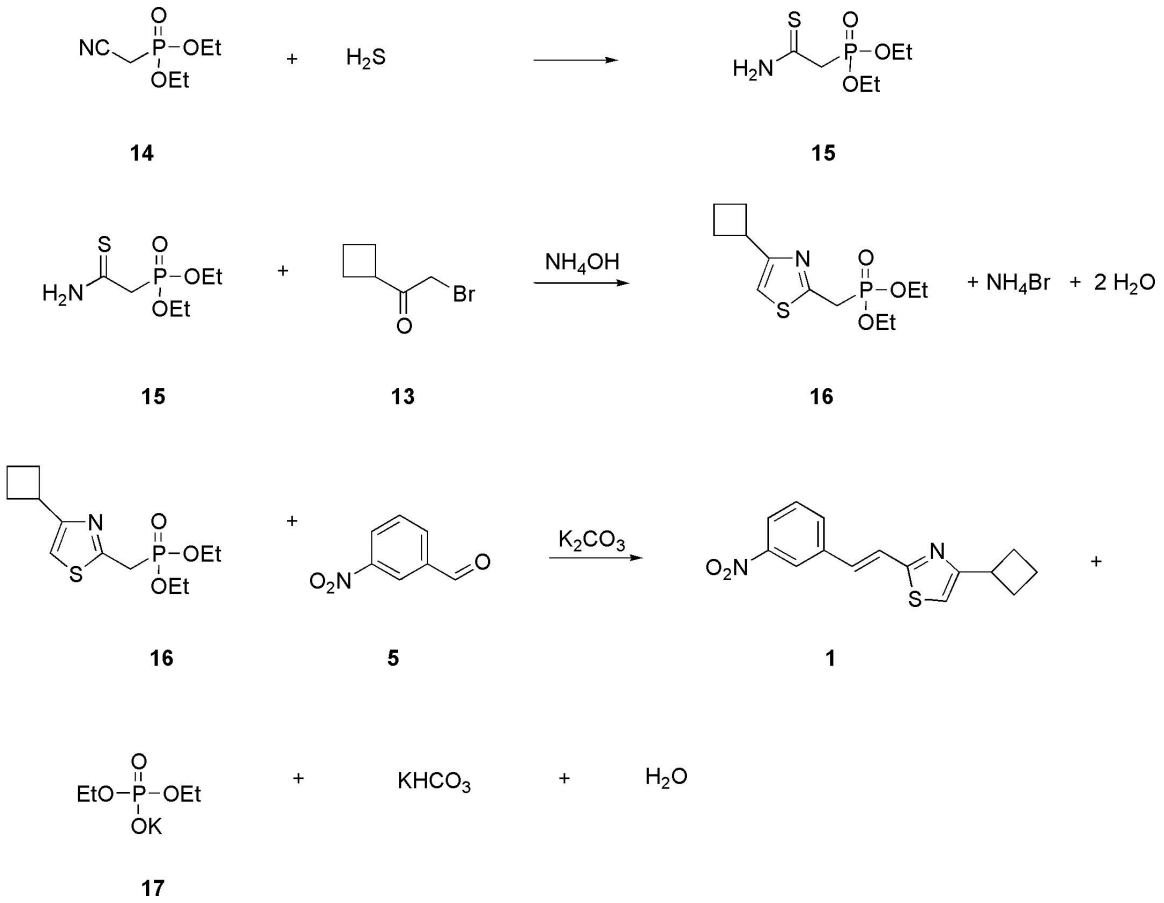
Table S2. Stoichiometric Factor Raw Data and Yields for the Malonic Acid Synthesis of Ro 24-5904 (1)

Step	Compound	Equivalent Mass	Excess Mass	Yield
1	Malonic Acid	104.06	10.41	90%
2	Thionyl Chloride	118.87	59.49	90%
3	Ammonium Hydroxide	70.10	140.20	90%
4	Lawesson's Reagent **10**	101.24	0.00	90%
5	**13**	177.04	17.70	100%
Overall				65.6%

Table S3. Andraos' Metrics for the Malonic Acid Synthesis

Rxn	MW(p_j)	ε	SF	E_{mw}	AE	RME	E_m	Mass waste $\overline{\omega}_j$ [1]
1	193.16	0.9	1.048	0.321	0.757	0.650	0.615	142.54
2	211.6	0.9	1.191	0.475	0.678	0.512	1.458	248.52
3	192.17	0.9	1.498	0.466	0.682	0.410	3.886	307.31
4	208.24	0.9	1.000	0.447	0.691	0.622	0.608	126.57
5	286.35	1.0	1.046	0.468	0.681	0.651	0.615	153.27
Overall				1.673	0.374	0.226	3.416	978.20

[1]Actual waste in grams produced for each mole (286.35 g) of Ro 24-5904 (**1**)



Scheme S2. Wittig-Horner Synthesis of Ro 24-5904 (**1**)

Table S4. Molecular Weight Data from the Balanced Chemical Equations for the Wittig-Horner Synthesis of Ro 24-5904 (1)

Reaction	Byproducts	MW Byproducts	MW (product) (p_i)
1	None	00.00	211.22
2	NH_4Br 2 H_2O	133.96 36.02 100.52	289.33
3	$C_4H_4O_4K$ $KHCO_3$ H_2O	192.19 100.12 18.01 292.31	286.35

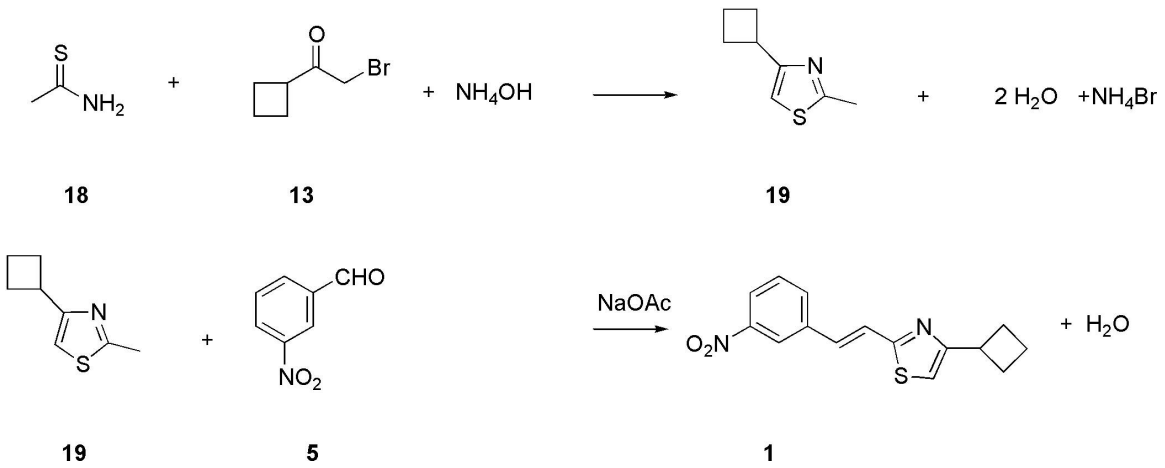
Table S5. Stoichiometric Factor Raw Data and Yields for the Wittig-Horner Synthesis of Ro 24-5904 (1)

Step	Compound	Equivalent Mass	Excess Mass	Yield
1	Hydrogen sulfide	34.08	13.05	85%
2	**13**	177.04	17.70	100%
3	**5**	151.12	4.96	94%
3	Potassium carbonate	138.21	275.80	
Overall				65.6%

Table S6. Andraos' Metrics for the Wittig-Horner Synthesis

Rxn	MW(p_j)	ε	SF	E_{mw}	AE	RME	E_m	Mass waste $\overline{\omega}_j$ [1]
1	211.22	0.85	1.062	0.000	1.000	0.801	0.249	55.99
2	289.33	1.00	1.099	0.587	0.630	0.573	0.745	229.45
3	286.35	0.94	1.486	1.021	0.495	0.313	2.193	627.93
Overall				1.614	0.382	0.239	3.190	913.40

[1]Actual waste in grams produced for each mole (286.35 g) of Ro 24-5904 (**1**)



Scheme S3. Claisen Condensation of Ro 24-5904 (**1**)

Table S7. Molecular Weight Data from the Balanced Chemical Equations for the Claisen Synthesis of Ro 24-5904 (1)

Reaction	Byproducts	MW Byproducts	MW (product) (p_j)
1	NH_4Br 2 H_2O	133.96 36.02 169.98	153.24
2	H_2O	18.01	286.35

Table S8. Stoichiometric Factor and Overall Yield for the Claisen Condensation of Ro 24-5904 (1)

Step	Compound	Equivalent Mass	Excess Mass	Yield
1	**13**	177.04	17.70	100%
2	**5**	151.12	306.26	74%
Overall				74%

Table S9. Andraos' Metrics for the Claisem Synthesis

Rxn	MW(p_j)	ε	SF	E_{mw}	AE	RME	E_m	Mass waste $\overline{\omega}_j$ [1]
1	153.24	1.00	1.070	1.109	0.474	0.443	1.257	260.36
2	286.35	0.74	2.060	0.063	0.941	0.347	1.882	538.81
Overall		0.74		0.657	0.604	0.264	2.791	799.17

[1]Actual waste in grams produced for each mole (286.35 g) of Ro 24-5904 (**1**)