for

Diverting Reactive Intermediates Toward Unusual Chemistry – Unexpected Anthranil Products from Davis-Beirut Reaction

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SI Scheme 1. Alternative reaction network examined at the SMD(DMF)-M06-2X/6-31+G(d,p) level of theory. Comments: (i) The TSS for attack on the nitro group (top row; based on a structure with a constrained reasonable forming bond distance of 2.1 Å) is predicted to be at least 10 kcal/mol above the TS for cyclization. We were not able to find the TSS for N-N cleavage (top row), but the conformer needed for the cleavage reaction is higher in energy than the TSS for HO- loss. The TSS is for N-N cleavage (anionic version of top row) is predicted to be nearly 30 kcal/mol higher in energy than the TSS for competing HO- loss. (ii) The mechanism involving the spiro intermediate (2^{nd} row) is energetically viable, but hydroxide loss is strongly preferred. (iii) The TSS for benzimidazole anion attack on the nitroso to make 5-5-6-5 systems (anionic version of 3^{rd} row) is predicted to be approximately 3 kcal/mol higher in energy than that leading directly to the benzisoxazole precursor. The [2.2.2] bicycle is predicted to be >70 kcal/mol above the final ketone 6-6-5-6 product. (iv) The nitrene (4^{th} row) is predicted to be >50 kcal/mol higher in energy than the anthranil product.



Scheme 2. More detailed picture of main reaction network.

Computational details All calculations were carried out with Gaussian09 (Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision D.02, Wallingford, CT, 2009). Geometries were optimized at the SMD(DMF)-M06-2X/6-31+G(d,p) level of theory (Zhao, Y. and Truhlar, D. G. Theor. Chem. Acc. 2008, 120, 215-241 ; Zhao, Y. and Truhlar, D. G. Acc. Chem. Res. 2008, 41, 157-167; Marenich, A. V., Cramer, C. J., and Truhlar, D. G. (2009) The Journal of Physical Chemistry B 113, 6378-6396.). Various conformations were considered. All structures were characterized as minima or transition state structures by vibrational analysis. Energies reported in the text are relative free energies at 298K. Coordinates for computed structures are available as a separate file.

Optimizing reaction conditions

NO₂

	N NH 4a	conditions ^a →	6a	
entry	base	solvent	temp	yield ^b
1 ^c	КОН	MeOH	r.t.	n.d. ^d
2 ^{<i>c</i>}	КОН	MeOH	35 °C	n.d. ^d
3 ^c	КОН	MeOH	45 °C	20.4%
4 ^{<i>c</i>}	КОН	MeOH	70 °C	33.6%
5	КОН	THF	70 °C	18.9%
6	КОН	<i>i</i> -PrOH	70 °C	28.7%
7	NaOH	<i>i</i> -PrOH	70 °C	41.7%
8	NaO <i>t</i> Bu	<i>i</i> -PrOH	70 °C	41.9%
9 ^e	NaO <i>t</i> Bu	<i>i</i> -PrOH	70 °C	35.3%
10 ^f	NaO <i>t</i> Bu	<i>i</i> -PrOH	70 °C	20.2%
11	K ₂ CO ₃	<i>i</i> -PrOH	70 °C	n.d. ^d
12	Na ₃ PO ₄ 12 H ₂ O	<i>i</i> -PrOH	70 °C	trace
13	DBU	<i>i</i> -PrOH	70 °C	n.d. ^d
14	Ру	<i>i</i> -PrOH	70 °C	n.d. ^d
15	TEA	<i>i</i> -PrOH	70 °C	n.d. ^d
16	NaO <i>t</i> Bu	<i>i</i> -PrOH	70 °C	n.d. ^d
17	NaO <i>t</i> Bu	DMSO	150 °C	0%
18	NaO <i>t</i> Bu	PhMe	120 °C	21.5%
19	NaO <i>t</i> Bu	CCI ₄	75 °C	trace
20	NaO <i>t</i> Bu	<i>p-</i> xylene	160°C	21.9%
21	NaO <i>t</i> Bu	DMA	160 °C	28.7%
22	NaO <i>t</i> Bu	1,4-dioxane	100 °C	trace
23	NaO <i>t</i> Bu	MeCN	80 °C	trace
24	NaO <i>t</i> Bu	DMF	125 °C	32.3%
25 ⁹	NaO <i>t</i> Bu	DMF	125 °C	27.0%
26″	NaO <i>t</i> Bu	DMF	125 °C	54.3%
27″	NaO <i>t</i> Bu	<i>i</i> -PrOH	70 °C	43.2%
28 [°]	NaOtBu	DMF	125 °C	21.7%
29'	NaOtBu	DMF	125 °C	10.2%
30	NaOtBu	DMF	r.t.	trace
31"	NaOtBu	DMF	45 °C	20.6%
32'' 33 ^h	NaO <i>t</i> Bu NaO <i>t</i> Bu	DMF DMF	160 °C	20.4% 48.3%

^asubstrate **4a** (0.2 mmol), base (1 mmol), solvent (4 mL), 6 h. ^bIsolated yield. ^c With 10% H₂O. ^dIncomplete conversion. ^eBase was dropwise added to heated reaction mixture. ^fStarting material was dropwise added to heated reaction mixture. ^gWith 0.2 g MgSO₄. ^hWith 0.2g 4 Å molecular sieves.

















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X-ray crystallography

The crystallographic data were collected by using Bruker SMART APEX II or APEX II duo diffractometer equipped with monochromatic Mo K α (λ = 0.71073 Å) and Cu K α (λ = 1.54178 Å) radiation. The diffraction data were reduced by SAINT software¹ and absorption correction were applied with SADABS software.² The crystal structures were solved with direct methods by using SHELXTL package³ and refined with SHELXL 2013 program. The hydrogen atoms were refined with a riding model, except imidazole hydrogens which were located with electron density map. CCDC numbers for each compounds are **4h** (1551036), **6a** (1551037) and **7** (1551038).





Thermal ellipsoid plot for **4h** showing the displacement ellipsoids drawn at the 50% probability.





Thermal ellipsoid plot for **6a** showing the displacement ellipsoids drawn at the 50% probability.

Figure S3. X-ray crystal structure of compound (7)



Thermal ellipsoid plot for **7** showing the displacement ellipsoids drawn at the 50% probability.

	4h	ба	7
Empirical formula	C ₁₆ H ₁₅ N ₃ O ₄	C ₁₄ H ₉ N ₃ O	C ₅₈ H ₄₀ Cl ₄ N ₁₂ O ₆
Formula weight	313.31	235.24	1142.82
T (K)	93(2)	88(2)	90(2)
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	Fdd2	C2/c	$P2_1/n$
Color/Shape	Brown/Block	Yellow/Prism	Yellow/Block
a (Å)	36.553(5)	28.443(9)	19.7261(6)
<i>b</i> (Å)	10.5914(15)	5.5707(14)	14.1348(4)
<i>c</i> (Å)	15.847(2)	15.837(8)	20.9034(7)
a (deg)	90	90	90
b (deg)	90	121.19(2)	112.3410(12)
<i>g</i> (deg)	90	90	90
V (Å ³)	6135.2(15)	2146.6(14)	5390.9(3)
Z	16	8	4
$\rho_{\text{calcd}} (\text{g cm}^{-3})$	1.357	1.456	1.408
$\mu (\mathrm{mm}^{-1})$	0.100	0.096	2.530
Crystal size (mm)	0.34 x 0.33 x 0.16	0.22 x 0.11 x 0.08	0.40 x 0.23 x 0.19
θ range (deg)	2.23 to 27.48	1.67 to 27.51	7.55 to 68.40
Data / restraints / parameters	3523 / 1 / 214	2384/0/167	9401 / 0 / 747
GOF on F ²	1.068	1.036	1.039
R1/wR2 [I>2sigma(I)]	0.0395/0.1059	0.0407/0.1010	0.0667/0.1876
R1/wR2 (all data)	0.0404/0.1064	0.0597/0.1119	0.0712/0.1934
Extinction coefficient Largest diff. peak/hole (e·Å ⁻³)	0.281 / -0.319	0.214 / -0.252	1.227 / -1.185

Table S1. Crystallographic parameters of 4h, 6a and 7

References:

- 1. Bruker (2007). SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.
- 2. Bruker (2001). SADABS. Bruker AXS Inc., Madison, Wisconsin, USA.
- 3. G. M. Sheldrick, Acta Cryst. 2008, A64, 112-122.