Preparation of (*E,E*)-4-Amino-1-aryl-3-cyano-4-methoxy-2-azabutadienes

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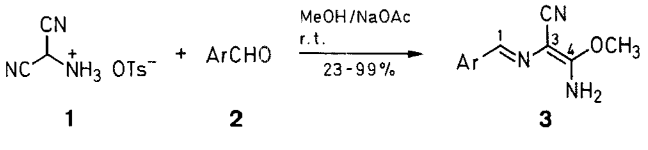
Aromatic aldehydes react with ammoniopropanedinitrile *p*-toluenesulfonate (ammoniomalononitrile tosylate, AMNT) to give (*E,E*)-4-amino-1-aryl-3-cyano-4-methoxy-2-azabutadienes.

Although the Diels-Alder reaction of heterodienophiles has been extensively used in the synthesis of six-membered heterocycles, the use of 2-azadienes has received much less attention, probably owing to the lack of general methods for the synthesis of 2-azadiene derivatives.[1-6] Of particular interest are highly functionalized donor-substituted 2-aza-1,3-dienes, which would considerably widen the scope of the reaction. During the course of our studies on the extensive chemistry of propanedinitrile (malononitrile) and its derivatives,[7-10] we observed that commercially available ammoniopropanedinitrile *p*-toluenesulfonate (ammoniomalononitrile tosylate, AMNT, **1**)[11] reacted with aromatic aldehydes **2** to give (*E,E*)-4-amino-1-aryl-3-cyano-4-methoxy-2-azabutadienes **3** (Tables 1, 2).

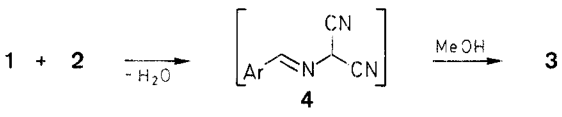


2, 3	Ar	2, 3	Ar
a	Ph	e	4-$NO_2C_6H_4$
b	2-BrC_6H_4	f	2-naphthyl
c	2-ClC_6H_4	g	4-HOC_6H_4
d	2-$NO_2C_6H_4$		

The reaction of benzaldehyde, 2-naphthylenecarbaldehyde, and 4-hydroxybenzaldehyde with AMNT (**1**) gave soluble 2-aza-1,3-butadienes **3a**, **3f**, and **3g**, respectively (Method A).

In addition to 2-aza-1,3-butadiene **3a**, the reaction of benzaldehyde with AMNT (**1**) afforded an unidentified compound (mp 100–103 °C). *trans*-2,2,5,5-Tetracyano-3,6-di(2-naphthyl)piperazine (6%) was isolated along with (*E,E*)-2-aza-butadiene **3f** from AMNT (**1**) and 2-naphthylenecarbaldehyde. The reaction of 2-bromo-, 2-chloro-, 2-nitro-, and 4-nitrobenzaldehyde with AMNT (**1**) gave the respective insoluble (*E,E*)-2-azabutadienes **3b**, **3c**, **3d**, **3e** in excellent yields (Method B).

A reasonable mechanism for diastereoselective formation of the (*E,E*)-2-azabutadienes **3** involves addition of AMNT (**1**) to the carbonyl carbon atom of the aldehyde to give an intermediate carbinolamine, which eliminates water to form an imine **4**.[12,13] Reaction of imine **4** with methanol affords an imidate, which tautomerizes to the highly functionalized (*E,E*)-2-azabutadienes **3**.[14] The (*E,E*)-2-azabutadiene structure **3** was assigned based on the X-ray crystal structure analysis of (*E,E*)-4-amino-3-cyano-1-(4-hydroxyphenyl)-4-methoxy-2-azabutadiene (**3g**).[15]



The highly functionalized (*E,E*)-2-azabutadienes **3** should find widespread use in the synthesis of heterocycles and in mechanistic studies of cycloadditions.[1-6,16,17]

Melting points were determined in open capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Robertson Laboratory, Inc., Florham Park, NJ.

High resolution mass spectra (HRMS) were obtained with a VG 7070E-HF mass spectrometer (70 eV). Chemical ionization mass spectra (CIMS, 2-methylpropane) and electron impact mass spectra (EIMS) were obtained with a Finnigan 9610 GC-EI-CI mass spectrometer with a Nova 3 data system operating at an ionization potential of 70 or 100 eV. ^{1}H-NMR spectra were recorded on a General Electric Model QE 300 (300 MHz), or on a General Electric Model QE 500 (500 MHz) spectrometer using TMS as internal standard. ^{13}C-NMR spectra were recorded on a General Electric Model QE 300 (75 MHz), spectrometer and chemical shifts are reported relative to the central solvent (DMSO-d_6) resonance at $\delta = 43.5$. IR spectra were obtained with a Perkin-Elmer 283 spectrophotometer, calibrated with the 1601 cm^{-1} absorption of polystyrene.

Analytical TLC was performed on Analtech Uniplate 10 × 20 cm (250 μ thick) silica gel GF prescored glass plates, which were developed in a solvent mixture of EtOAc/hexanes (1 : 2). After the solvent had risen to the top, the plates were checked under UV light and/or immersed in phosphomolybdic acid and charred to visualize compounds. Flash column chromatography[18,19] was performed on 100–200 mesh silica gel.

The aromatic aldehydes were distilled or recrystallized from aqueous EtOH immediately before use. Their boiling points, melting points, and their IR, ^{1}H-NMR, and ^{13}C-NMR spectra agreed with literature values.

(*E,E*)-4-Amino-1-aryl-3-cyano-4-methoxy-2-azabutadienes 3; General Procedures:

Method A, *for Soluble Dienes* **3a**, **3f**, **3g**: To an aluminum foil covered 50 mL round bottomed flask containing a mixture of AMNT (**1**; 1.17 g, 4.6 mmol), abs. MeOH (20 mL), and anhydrous NaOAc (0.38 g, 4.6 mmol) is added dropwise aldehyde **2** (4.6 mmol) with stirring at 22–24 °C. The mixture is stirred at 22–24 °C until no AMNT (**1**) is visible on a TLC plate developed in EtOAc/hexanes (1 : 2). The reaction mixture is filtered, the filtrate diluted with a 1 : 1 solution of Et_2O and EtOAc (100 mL), and the organic layer is washed with water (2 × 100 mL). The organic layer is dried ($MgSO_4$), and the solvent is removed *in vacuo*. The residue is chromatographed on silica gel (EtOAc/hexanes, 1 : 2) to afford pure (*E,E*)-2-azabutadienes **3a**, **3f**, **3g** (Tables 1 and 2).

Method B, *for Insoluble Dienes* **3b–e**: To an aluminum foiled covered 50 mL round-bottomed flask containing a mixture of AMNT (**1**; 1.17 g, 4.6 mmol), dry MeOH (15 mL), and anhydrous NaOAc (0.38 g, 4.6 mmol) is added, with stirring at 22–24 °C, a solution of aldehyde **2** (4.6 mmol) in dry MeOH (5 mL) during a 5 min period. TLC (EtOAc/hexanes, 1 : 2) is used to monitor the reaction. After the consumption of **1**, the mixture is filtered, the solid product is washed with dry MeOH (2 mL), dried, and recrystallized from either MeOH or EtOAc/hexanes (Tables 1 and 2).

Table 1. (*E*,*E*)-4-Amino-1-aryl-3-cyano-4-methoxy-2-aza-butadienes **3a**–**g** Prepared

Product	Method	Reaction Time (h)	Yield[a] (%)	mp (°C)	Molecular Formula[b]	HRMS[c]		IR (Nujol) ν (cm^{-1})		
						calc.	observed	NH	C≡N	C=N
3a	A	24	50	134–135	$C_{11}H_{11}N_3O$ (201.2)	201.0902	201.0908	3300, 3400	2170	1610
3b	B	3	92	205–206	$C_{11}H_{10}BrN_3O$ (280.1)	279.0007	278.9983	3260, 3440	2180	1635
3c	B	6	99	214–215	$C_{11}H_{10}ClN_3O$ (235.7)	235.0512	235.0449	3280, 3440	2180	1635
3d	B	72	80[d]	210–212	$C_{11}H_{10}N_4O_3$ (246.2)	246.0753	246.0751	3290, 3420	2180	1630
3e	B	13	99	178–183	$C_{11}H_{10}N_4O_3$ (246.2)	246.0753	246.0753	3200, 3600	2180	1630
3f	A	24	69	202–203	$C_{15}H_{13}N_3O$ (251.3)	251.1058	251.1058	3300, 3440	2175	1640
3g	A	24	23	165–167	$C_{11}H_{11}N_3O_2$ (217.2)	217.0851	217.1095	3300, 3395	2140	1630

[a] Yield of recrystallized product.

[b] Satisfactory microanalyses obtained: C ±0.06, H ±0.05, N ±0.09.

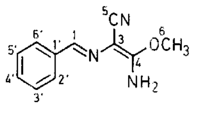
[c] Electron impact high resolution mass spectroscopy.

[d] Although TLC suggested that the reaction may be complete after 24 h, the reaction mixture was stirred an additional 48 h in order to optimize the yield.

Table 2. NMR Data of Compounds **3a**–**g**

Compound	^{1}H-NMR (DMSO-d_6/TMS)	^{13}C-NMR (DMSO-d_6) δ[a]										
		C-1	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
3a	4.04 (s, 3H, OCH_3); 7.96 (s, 1H, HC=N); 7.78 (s, 2H, NH_2); 7.38–7.94 (m, 5H_{arom})	146.41	84.09	171.11	120.32	60.51	141.37	132.39	130.84	132.48	130.84	132.39
3b	4.05 (s, 3H, OCH_3); 8.20 (s, 1H, HC=N); 7.99 (s, 2H, NH_2); 7.30–8.42 (m, 4H_{arom})	143.56	84.78	171.46	120.05	60.59	139.18	126.52	132.08	136.80	131.52	133.80
3c	4.05 (s, 3H, OCH_3); 8.25 (s, 1H, HC=N); 7.99 (s, 2H, NH_2); 7.37–8.34 (m, 4H_{arom})	141.02	84.88	171.46	120.08	60.59	137.90	135.91	131.65	133.49	131.02	133.55
3d	4.07 (s, 3H, OCH_3); 8.25 (s, 1H, HC=N); 8.11 (s, 2H, NH_2); 7.57–8.61 (m, 4H_{arom})	139.38	85.23	171.72	119.56	60.66	134.83	151.22	128.07	132.31	132.31	136.58
3e	4.07 (s, 3H, OCH_3); 7.93 (s, 1H, HC=N); 8.18 (s, 2H, NH_2); 8.14–8.26 (m, 4H_{arom})	142.67	85.26	171.79	119.54	60.69	147.63	131.08	127.59	150.20	127.59	131.08
3f	3.97 (s, 3H, OCH_3); 7.86 (s, 1H, HC=N); 7.76 (s, 2H, NH_2); 7.50–8.24 (m, 7H_{arom})	–	84.50	171.20	120.33	60.60	127 ~ 140[b]					
3g	4.01 (s, 3H, OCH_3); 7.88 (s, 1H, HC=N); 7.55 (s, 2H, NH_2); 6.86–7.77 (m, 4H_{arom})	147.30	84.01	170.62	120.69	60.50	132.90	132.60	119.40	162.35	119.40	132.60

[a] Numbering of carbon atoms:



[b] Aromatic carbon atoms.

Acknowledgement is made to the National Science Foundation (CHE 86-19651) for partial support of this research and for financial assistance toward the purchase of the mass spectrometers and NMR spectrometers. We would also like to thank the Niels Clauson-Kaas Laboratory for a generous sample of AMNT.

Received: 29 November 1988; revised: 15 March 1989

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