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New aromatic rearrangement accompanying ring closure of 2-arylpropylidenemalonodinitriles to 1-aminonaphthalene-2-carbonitriles

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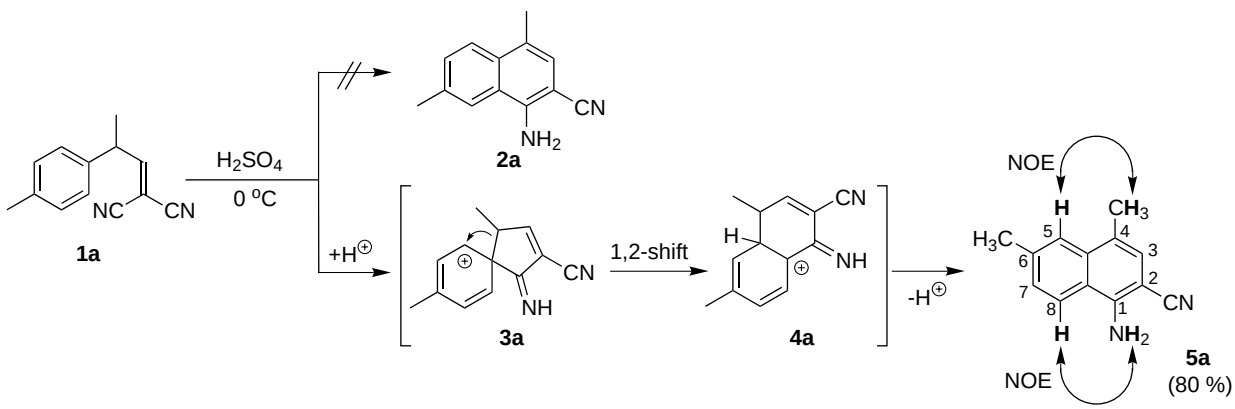
Abstract—Cyclization and a rearrangement in concentrated sulfuric acid of 2-(4-substituted-phenyl)propylidenemalonodinitriles (**1**) into 1-amino-4-methyl-6-substituted-naphthalene-2-carbonitriles (**5**) appears to involve a series of steps such as *ipso* electrophilic attack of the protonated nitrile function on the *para* position of the phenyl group, opening of a spirobenzenium cation or its transformation, and ring reclosure to the naphthalene framework with participation of the secondary alkyl carbocation as an active electrophile. © 2001 Elsevier Science Ltd. All rights reserved.

Our preliminary investigations revealed that derivatives of 1-aminonaphthalene-2-carbonitrile having short alkyl groups on either or both rings of the naphthalene system are potent fungicides against such phytopathogenic fungi as *Fusarium culmorum*, *Alternaria brassicicola*, *Botrytis cinerea*, and *Penicillium expansum*. The fungicidal activity of these compounds is comparable or higher than the activity of some commercial fungicides. The aminonitriles needed for these investigations are conveniently synthesized through cyclization, in strong acids, of a variety of alkylidenemalonodinitriles which have phenyl or substituted-phenyl groups at the appropriate distance along the alkyl chain, from the nitrile functions.[1,2] The starting alkylidenemalonodinitriles are mostly obtained from phenyl-substituted aldehydes or ketones.[3] This route to naphthalene aminonitriles has attracted our attention as it could allow the introduction of another alkyl group in the second ring of naphthalene, beside an alkyl group being present at the '4' position of the above mentioned aminonitrile. Thus, we hoped that by employing the approach outlined here, the number of naphthalene aminonitriles available for screening of their antifungal activity will be considerably increased.



Scheme 1. Cyclization and rearrangement of 2-(4-methylphenyl)propylidenemalonodinitrile (**1a**) to 1-amino-4,6-dimethylnaphthalene-2-carbonitrile (**5a**).

Keywords: arylalkylidenemalonodinitriles; cyclization; rearrangement; aminonitriles.

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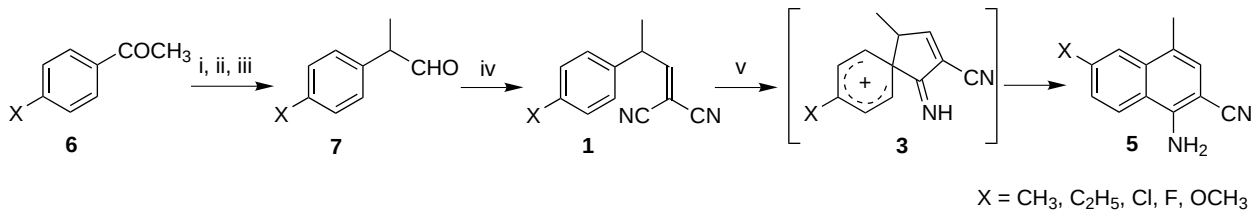
Dissolving **1a** in ice-cold concentrated sulfuric acid for 2 h followed by quenching the solution with ice afforded an aminonitrile with mp 146–147°C in 80% yield. Initially we presumed that the cyclization of **1a** occurred in a straightforward manner, with ring closure in the *meta* position with respect to the methyl group of the benzene ring, and gave **2a**. However, the ^{1}H NMR spectra and NOE experiments showed that the cyclization product had the structure **5a**, being a derivative of 1,7-dimethylnaphthalene (Scheme 1).

It became apparent that during cyclization either a migration of the methyl group in **1a** occurred or a rearrangement of the whole carbocyclic system had taken place. The structure of **5a** was further supported by its conversion to 4,6-dimethylnaphthalene-1-amine through the removal of the nitrile group from **5a**, and finally by the deamination of this amine to 1,7-dimethylnaphthalene. Aminonitrile **5a** (300 mg, 1.53 mmol) and sodium hydroxide (0.76 g, 19 mmol) were dissolved in ethanol (100 ml). The solution was heated in a 300 ml autoclave at 240°C (~3.5 MPa) for 4 h. The mixture was diluted with water (50 ml) and ethanol was removed. A dark oil which separated from the solution was extracted with toluene. Dry hydrogen chloride was passed through the toluene solution to afford 268 mg (85%) of 4,6-dimethylnaphthalene-1-amine hydrochloride. The hydrochloride was converted into the semisolid free amine which, after sublimation under reduced pressure and recrystallization from *n*-hexane, gave 219 mg (81%) of colorless needles with mp 71.5°C.

4,6-Dimethylnaphthalene-1-ammonium chloride was diazotized at 0°C and treated with 30% hypophosphorous acid. The usual work-up of the reaction mixture afforded 1,7-dimethylnaphthalene in 51% yield. Its spectroscopic properties were identical with those of an authentic sample of the hydrocarbon.

After unequivocal establishment of the structure of **5a**, it became apparent that during cyclization of **1a** a rearrangement of the whole carbocyclic system had taken place. We rejected the possibility of a migration of the methyl group which was initially present in the benzene system of **1a**. Such a migration of the methyl group to the neighboring position, accompanying the straightforward cyclization to **2a**, appears less feasible due to the low nucleophilicity of **2a** or potential intermediate products related to **2a**. We present in Scheme 1 a hypothetical mechanism describing the cyclization of **1a** to **5a** and a rearrangement of the carbon framework of **1a**. We assume that the methyl function of the *p*-tolyl group of **1a** activates its *para* position and allows *ipso* electrophilic attack on that position which leads to the spirobenzenium cation **3a**. In the next step **3a** might undergo a 1,2-alkyl shift which gives **4a**. There is also a possibility of ring opening of **3a** with an involvement of the secondary carbocation as an active electrophile. The presence of such a carbocation could have an influence on a rearrangement of **1a** into **5a** in relatively high yield.

In contrast to the results presented in Scheme 1, an attempt to cyclize 2-methyl-3-(2-methylphenyl)prop-1-en-1,1-dicarbonitrile, an isomer of **1a**, to 1-amino-3,5-dimethylnaphthalene-2-carbonitrile, failed to give any isolable product. Although a magenta coloration of the solution of this dinitrile in sulfuric acid might indicate the presence of a spirobenzenium cation similar to **3a**, the ring opening of the cation appears to give a very reactive and unstable primary carbocation which presumably undergoes side reactions competing with the cyclization. Successful rearrangement of other dinitriles **1** into **5** in moderate to high yields might thus depend on the presence of more stable electrophiles in the intermediate stages of the cyclization. In order to investigate the scope of the rearrangement and to evaluate the influence of substituents on the benzene ring of **1** on the outcome of the reaction, several dinitriles **1** were



Scheme 2. Synthesis of 1-amino-4-methyl-6-substituted-naphthalene-2-carbonitriles **5** from acetophenones **6**. *Reagents and conditions*: (i) $ClCH_2COOC_2H_5$, NaH/CH_3CN; (ii) $NaOH/C_2H_5OH$; (iii) HCl/H_2O; (iv) $CH_2(CN)_2$, CH_3COOH, CH_3COONH_4/C_6H_6; (v) H_2SO_4, 0°C.

Table 1. Preparation of aldehydes **7**, dinitriles **1** and aminonitriles **5**

1, **5**, **7**	X	Yield of **7** (%)	Yield of **1** (%)	Yield of **5** (%)	Mp of **5** (°C)
a	CH_3	63	80	80	146–147
b	C_2H_5	45	71	61	105–106
c	Cl	58	77	92	180–180.5
d	F	65	69	25	152–153
e	OCH_3	40	68	66	166–167.5

prepared. The dinitriles were synthesized from acetophenones **6** essentially following the reported procedures for the preparation of aldehydes **7** and the condensation of **7** with malonodinitrile (Scheme 2, Table 1).[3,4]

The dinitriles were cyclized in the following manner: **1** (3.0 mmol) was slowly added dropwise while stirring into ice-cold concentrated sulfuric acid (5 ml). The solution turned yellow, orange and finally dark red. After 2 h at 0°C, the solution was poured onto ice to give a pale yellow precipitate. After the usual work-up, the product was chromatographed on silica gel and sublimed under reduced pressure.[5]

The presence of the first order substituents in **1** at the *para* position with the respect to the site of the electrophilic attack, resulted in a relatively high yield of the rearranged aminonitriles **5**. However, fluorine-substituted **1d** gave **5d** in a disappointingly low yield while chlorine-substituted **1c** afforded **5c** in nearly quantitative yield. Since the methoxy group does not migrate during aromatic rearrangements, cyclization of **1d** to **5d** furnished additional support to the mechanism presented in Scheme 1. As in the case of **5a**, the structure of the other aminonitriles **5** was established through NOE experiments.

The results presented here involve a study on the cyclization of dinitriles **1** having symmetrical, *para*-substituted phenyl groups. However, an investigation of the rearrangement of arylalkylidenemalonodinitriles which have unsymmetrical or unsymmetrically substituted aryl groups seems to promise interesting results. By employing the synthetic approach presented here, new routes to some polycyclic aromatic systems might be designed.

Acknowledgements

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5. All new compounds **1a**–**e** and **5a**–**e** gave satisfactory analytical and spectroscopic data. Selected spectra and physical data: Compound **1a** (yellowish oil, bp 126–128°C/3 hPa): ^{1}H NMR ($CDCl_3$): δ 7.29 (d, J=10.9 Hz, 1H), 7.19 (d, J=7.8 Hz, 2H), 7.13 (d, J=7.9 Hz, 2H), 4.06–4.13 (m, 1H), 1.53 (d, J=6.9 Hz, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 171.7, 138.1, 136.2, 130.1 (2C), 126.8 (2C), 112.0, 110.6, 42.5, 87.5, 21.0, 19.5. Anal. calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.44; H, 6.21; N, 14.14%. Compound **5a** (pale yellow needles from methanol, mp 146–147°C): ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H), 2.54 (s, 3H), 4.91 (br. s, 2H), 7.09 (s, 1H), 7.36 (dd, 1H, J=8.5, 1.5 Hz), 7.67 (d, 1H, J=1.5 Hz), 7.71 (d, 1H, J=8.5 Hz); ^{13}C NMR ($CDCl_3$): δ 18.7, 21.9, 88.5, 118.9, 120.4, 121.6, 124.0, 124.5, 125.8, 127.9, 135.3, 138.9, 147.0. Anal. calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.40; H, 6.11; N, 14.22%. 4,6-Dimethylnaphthalene-1-amine (colorless needles from *n*-hexane, mp 71.5°C): ^{1}H NMR ($CDCl_3$): δ 7.71 (dd, J=8.6, 1.6 Hz, 1H), 7.70 (d, J=1.6 Hz, 1H), 7.28 (d, J=8.6 Hz, 1H), 7.06 (d, J=7.3 Hz, 1H), 6.59 (d, J=7.3 Hz, 1H), 3.93 (br. s, 2H), 2.55 (s, 3H), 2.52 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 140.4, 135.1, 133.4, 126.8, 126.6, 124.2, 124.0, 122.3, 121.1, 108.8, 21.9, 18.9. Anal. calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 83.99; H, 7.64; N, 8.22%.