Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 3435–3438

Novel synthesis of α-arylnaphthalenes from diphenylacetaldehydes and 1,1-diphenylacetones

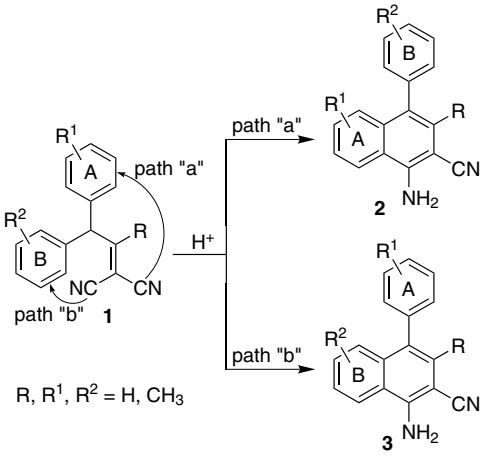
Bartłomiej Kozik, Jarosław Wilamowski, Maciej Góra and Janusz J. Sepioł*

Department of Organic Chemistry, Jagiellonian University, Ingardena 3, PL-30-060 Kraków, Poland

Received 12 February 2006; revised 3 March 2006; accepted 9 March 2006
Available online 30 March 2006

Abstract—A two-step synthesis of 1-amino-4-arylnaphthalene-2-carbonitriles from diphenylacetaldehydes and 1,1-diphenylacetones involves condensation of the carbonyl compounds with malonodinitrile and cyclization of the aryl-ylidenemalonodinitriles obtained in concentrated sulfuric acid. The benzannulation reaction is accompanied with a quasi-aromatic rearrangement. Some of synthesized aminonitriles reveal considerable biological activity against phytopathogenic fungi.
© 2006 Elsevier Ltd. All rights reserved.

1-Arylnaphthalenes have attracted considerable attention due to their physical and chemical properties. As an important class of biaryls, arylnaphthalenes constitute building blocks in a variety of natural products and biologically active compounds.[1] They are also useful for the synthesis of advanced materials such us conducting polymers,[2] chiral ligands[3] and liquid crystals.[4] Arylnaphthalenes also have the ability to form atropoisomers, especially in such cases where two naphthyl moieties of a chiral compound are connected at their α positions.[5] By far the most efficient methods for the preparation of arylnaphthalenes are based on various cross-coupling reactions such as Ullmann, Stille, Suzuki or Grignard reagents.[1,6] Other approaches for the synthesis of arylnaphthalenes include benzannulation reactions.[7] In the present letter we report an efficient synthesis of 1-amino-4-phenyl(aryl)naphthalene-2-carbonitriles of the general formula **2** or **3** either from 2,2-diphenylethanals or from 1,1-diphenylpropan-2-ones (Scheme 1).



Scheme 1.

There is a variety of aldehydes and ketones, which on condensation with malonodinitrile, afford ylidenemalonodinitriles having a structure suitable for cyclization to isomeric, aromatic aminonitriles. These varieties include 1-arylalkan-2-ones, 1,3-diarylpropan-2-ones, 2-arylalkanals, 2-arylcycloalkanones, 2-(1-cycloalken-1-yl)cycloalkanones, 2-cycloalkylidenecycloalkanones and other unsaturated ketones.[8] Under strongly acidic conditions, via a series of protonation–deprotonation processes, the dinitriles obtained from these carbonyl compounds are transformed into six-carbon unsaturated cyclic imines.[8c,f] In the final stage, the imines unobtrusively tautomerize to the aromatic, vicinal aminonitriles. The newly formed benzene ring possesses a two-carbon unit derived from the malonodinitrile moiety of the starting ylidenemalonodinitrile, and is usually annulated to another aromatic unit such as a benzene or naphthalene. Unhindered tautomerization of the intermediate iminonitrile appears to be essential for the successful outcome

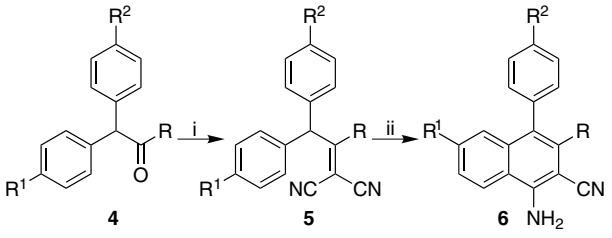
Keywords: 1-Arylnaphthalenes; Aromatic aminonitriles; Rearrangement; Cyclization; Fungistatic activity.
* Corresponding author. Tel.: +48 6083 80373; fax: +48 1263 40515; e-mail: sepiol@chemia.uj.edu.pl

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.03.054

of the reaction. The transformation of the dinitriles **1** into aminonitriles **2** or **3** involves hybridization changes of some carbon atoms of the assembled benzene ring. Thus, the reported method could be of use in syntheses of axially chiral α-arylnaphthalenes from appropriate dinitriles having the general formula **1**. Chirality exchange from sp^3 central chirality to axial chirality has been of great interest in studies of asymmetric reactions.[9]

The above mentioned criteria are met by 2,2-diphenylethanal (**4a**), its derivatives **4b** and **4c**, 1,1-diphenylpropan-2-one (**4d**) and also by the ketones **4e** and **4f**, which are all precursors of **5a–f** (Scheme 2 and Table 1). Surprisingly, a survey of chemical literature revealed that with the exception of **5a**, no report had been published on the preparation of aryl-alkylidenemalonodinitriles from **4b–f**.[10] Similarly, cyclization reactions of alkylidenemalonodinitriles **1** to aromatic aminonitriles of the type **2** or **3** appear to be unexplored to date. The present studies might thus be useful for the exploitation of compounds related to **1** in the syntheses of a limited variety of carbocyclic, aromatic aminonitriles.

The reported condensation of aldehyde **4a** with malonodinitrile had been catalyzed by potassium fluoride and gave **5a** in moderate yield, along with its isomer.[10] In a search for a better procedure for synthesizing **5a** we condensed **4a** with malonodinitrile in boiling benzene in the presence of $NH_4OAc/AcOH$ as a catalyst and with continuous removal of water. Difficulties in isolation of the dinitrile **5a** from the reaction mixture prompted us to design a more effective method. Thus, condensation of **4a** with malonodinitrile in anhydrous ethanol with piperidine as a catalyst furnished **5a** in 78% yield.[11,12a] However, using the same method, dinitrile **5c** was obtained in lower yield.[12b]



Scheme 2. Reagents and conditions: (i) $CH_2(CN)_2$, piperidine, EtOH, 5 min (**4a**,**c**) or $CH_2(CN)_2$, piperidine–AcOH/NH_4OAc, C_6H_6, 5–17 h (**4b**,**d–f**); (ii) concd H_2SO_4, −15 °C→−5 °C, 1 h.

Therefore, aldehyde **4b** was condensed with malonodinitrile using the standard method (Table 1).[13] Methyl-substituted aldehyde **4b** was prepared by oxidation of 4-methylstilbene with perbenzoic acid, followed by rearrangement of the resulting oxirane using bismuth(III) perchlorate oxide hydrate ($BiOClO_4{\cdot}xH_2O$) as a catalyst.[14] Similarly, pinacol rearrangement of 1,2-bis(4-methylphenyl)ethane-1,2-diol in glacial acetic acid, catalyzed by sulfuric acid, gave dimethyl derivative **4c** in good yield.[15]

To investigate the scope of the synthesis of 1-amino-4-arylnaphthalene-2-carbonitriles **6** we required different 1,1-diarylalkan-2-ones. Ketone **4e** was obtained from phenylacetone according to the published procedure.[16] Preparation of diarylpropanone **4f** was based on pinacol rearrangement[15] of 1,1-diarylpropane-1,2-diol.[17] Condensation of ketones **4d–f** with malonodinitrile gave the dinitriles **5d–f** in moderate yields (Table 1).[13]

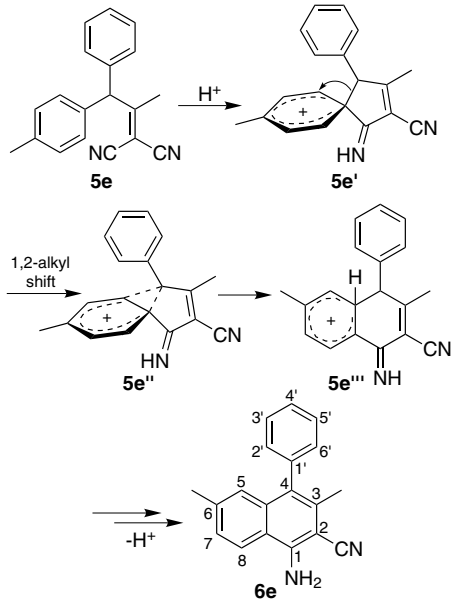
Cyclization of **5a** and **5d** in concentrated sulfuric acid occurred in a straightforward manner to give aminonitriles **6a** and **6d**, respectively, in high yields.[18] The pathways of ring closure of ylidenemalonodinitriles **5b–c** and **5e–f** in concentrated sulfuric acid were more complex in comparison with the straightforward cyclization of dinitriles **5a** and **5d**. Our studies were also aimed at establishing the preference of the attack of the protonated nitrile group on the substituted or unsubstituted benzene ring—as outlined in Scheme 1. Cyclization of **5b** and **5e** might occur along path 'a' or path 'b' to give vicinal aminonitriles of the general structure **2** or **3**, with the new aromatic ring being annulated to the benzene system 'A' or 'B' (Scheme 1).

In our earlier communications we reported that some aryl-alkylidenemalonodinitriles undergo cyclization in strong acids via an unusual pathway.[8l,m] The pathway appears to involve the *ipso* electrophilic attack of the activated nitrile group and the formation of a spirobenzenium- or spiroarenium cation connected to a five-carbon carbocyclic, unsaturated ring, arising from the ylidenemalonodinitrile moiety. The crucial rearrangement of the spiroarenium cation leads to stable, vicinal aminonitriles. In the present investigations the dinitriles **5b**, **5c**, **5e** and **5f** had the structure suitable for the electrophilic *ipso* attack of the nitrile group at the *para* position with respect to the methyl group on the phenyl substituent. All the above mentioned dinitriles underwent cyclization and a rearrangement. The electrophilic

Table 1. Synthesis of dinitriles **5**, and cyclization of **5** to aminonitriles **6**

Compound	R	R^1	R^2	**4**→**5** (yield, %)	**5**[a], mp (°C)	**5**→**6** (yield, %)	**6**[a], mp (°C)
4a–6a	H	H	H	78	110–111[10]	90	116–117[b]
4b–6b	H	CH_3	H	41	95–97[b]	79	172–174[b]
4c–6c	H	CH_3	CH_3	36	110–112[b]	60	182.5–183.5[b]
4d–6d	CH_3	H	H	27	100–101[b]	90	169–171[c]
4e–6e	CH_3	CH_3	H	45	oil[b]	71	117–119[b]
4f–6f	CH_3	CH_3	CH_3	45	oil[b]	77	169.5–170[b]

[a] The structures of all compounds were in agreement with their IR and NMR spectra.
[b] The results of elemental analysis for new compounds were in agreement with the calculated values.
[c] The IR and ^1H NMR data were in agreement with the values in Ref. 22. However, the mp of **6d** is not given in this reference.



Scheme 3.

attack and cyclization at the methyl substituted benzene ring in **5b** and **5e** predominated (Scheme 3). NMR studies allowed for unambiguous assignment of the structures of the aminonitriles.[19] The position of the methyl group at C-6 of naphthalene **6e** was established through 2D NMR experiments. The mechanism of the quasi-aromatic rearrangement is presented in Scheme 3.

The electrophilic *ipso* attack of the active nitrile function of **5e** leads to the spirobenzenium cation **5e′**. The alkyl shift (**5e″**) gives **5e‴**, which after losing the proton tautomerizes to **6e**. Recently published results of a similar quasi-aromatic rearrangement seem to involve *allylic*-type carbocations in the alkyl-shift stage.[8l,m] The rearrangements discussed here appear to be the first example of cyclization involving the *benzylic*-type carbocation. The stability of this carbocation may have contributed to the relatively high yield of **6e**.

The synthetic approach presented in this letter involves the synthesis of α-arylnaphthalenes through a one-stage construction of the naphthalene system. This approach might potentially be employed in the synthesis of some chiral α-arylnaphthalenes equipped with versatile amino and nitrile functions.

Furthermore, according to our earlier studies, 1-aminonaphthalene-2-carbonitriles possessing short alkyl groups at the '4' position are highly active against some phytopathogenic fungi such as *Fusarium culmorum*, *Alternaria brassicicola*, *Botrytis cinerea* and others.[20] In connection with these studies, we presumed that the aminonitriles having phenyl or aryl groups at the '4' position might also exhibit fungicidal activity. Preliminary tests of aminonitriles **6a**–**f** revealed their diverse biological activity against some phytopathogenic fungi. Aminonitrile **6a** showed considerable fungistatic activity.[21]

Acknowledgement

The support of this research by the Jagiellonian University within project No. DS 74 is gratefully acknowledged.

References and notes

1. Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.
2. (a) Yamamoto, T.; Maruyama, T.; Zhou, Z.; Ito, T.; Fukada, T.; Yoneda, Y.; Begum, F.; Ikeda, T.; Sasaki, S.; Takezoe, H.; Fukada, A.; Kubota, K. *J. Am. Chem. Soc.* **1994**, *116*, 4832–4845; (b) Papillon, J.; Schulz, E.; Gelinas, S.; Lessard, J.; Lemaire, M. *Synth. Met.* **1998**, *96*, 155–160.
3. (a) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187–208; (b) Narasaka, K. *Synthesis* **1991**, 1–11.
4. (a) Piao, G.; Akagi, K.; Shirakawa, H.; Kyotani, M. *Curr. Appl. Phys.* **2001**, *1*, 121–123; (b) Akagi, K.; Piao, G.; Kaneko, S.; Higuchi, I.; Shirakawa, H.; Kyotani, M. *Synth. Met.* **1999**, *102*, 1406–1409.
5. (a) Cammidge, A. N.; Crepy, K. V. L. *Tetrahedron* **2004**, *60*, 4377–4386; (b) Hattori, T.; Takeda, A.; Yamabe, O.; Miyano, S. *Tetrahedron* **2002**, *58*, 233–238, and references cited therein.
6. Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303.
7. (a) Lee, K. Y.; Kim, S. C.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 977–980; (b) Nishii, Y.; Yoshida, T.; Asano, H.; Wakasugi, K.; Morita, J.-i.; Aso, Y.; Yoshida, E.; Motoyoshiya, J.; Aoyama, H.; Tanabe, Y. *J. Org. Chem.* **2005**, *70*, 2667–2678, and references cited therein.
8. For leading review articles and publications on this subject, see e.g.: (a) Taylor, E. C.; McKillop, A. In *The Advances in Organic Chemistry*; Taylor, E. C., Ed.; The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles; Interscience: New York, 1970; Vol. 5, pp 79–308; (b) Bamfield, P.; Gordon, P. F. *Chem. Soc. Rev.* **1984**, *13*, 441–488; (c) Campaigne, E.; Schneller, S. W. *Synthesis* **1976**, 705–716; (d) Fatiadi, A. J. *Synthesis* **1978**, 165–204, and 241–282; (e) Freeman, F. *Chem. Rev.* **1980**, *80*, 329–350; (f) Campaigne, E.; Maulding, D. R.; Roelofs, W. L. *J. Org. Chem.* **1964**, *29*, 1543–1549; (g) Sepiol, J.; Kawalek, B.; Mirek, J. *Synthesis* **1977**, 701–704; (h) Sepiol, J.; Mirek, J.; Soulen, R. L. *Pol. J. Chem.* **1978**, *52*, 1389–1394; (i) Sepioł, J. *Synthesis* **1983**, 559–563; (j) Gorecki, T.; Sepiol, J. J. *Synlett* **1994**, 533–534; (k) Wilamowski, J.; Osman, D.; Machaj, A.; Kawałek, B.; Sepioł, J. J. *J. Prakt. Chem.* **1995**, *337*, 234–236; (l) Sepiol, J. J.; Wilamowski, J. *Tetrahedron Lett.* **2001**, *42*, 5287–5289; (m) Sepiol, J. J.; Gora, M.; Luczynski, M. K. *Synlett* **2001**, 1383–1386; (n) Krasodomski, W.; Łuczyński, M. K.; Wilamowski, J.; Sepioł, J. J. *Tetrahedron* **2003**, *59*, 5677–5683.
9. Nishii, Y.; Wakasugi, K.; Koga, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2004**, *126*, 5358–5359.
10. Zimerman, H. C.; Armesto, D.; Amezua, M.; Gannet, T. *J. Am. Chem. Soc.* **1979**, *101*, 6367–6383.
11. Aldehyde **4a** and ketone **4d** are commercially available from *Fluka Chemie AG* and *Aldrich-Chemical Co Ltd*, respectively.
12. (a) Preparation of 3,3-diphenyl-1-propene-1,1-dicarbonitrile (**5a**): a solution of diphenylacetaldehyde (**4a**) (1.14 g, 5.8 mmol), malonodinitrile (0.38 g, 5.8 mmol), piperidine (40 μL) and anhydrous ethanol (5 mL) were heated to reflux for 5 min and then slowly cooled in an ice-bath. The resulting colourless precipitated solid was washed with a small amount of chilled ethanol. Dinitrile **4a** was obtained as small white crystals; 1.11 g (78%); mp

110–111 °C (Ref. 10; mp 107.5–113 °C); (b) dinitrile **5c** was synthesized in the same manner as **5a**, and was isolated by column chromatography (SiO_2/CCl_4) followed by recrystallization from petroleum ether (bp 60–90 °C).

13. General procedure for the preparation of diarylalkylidenemalonodinitriles **5b,d-f**: a solution of the carbonyl compound **4b**,**d**–**f** (14 mmol), malonodinitrile (1.0 g, 15 mmol), glacial acetic acid (0.7 g, 12 mmol), ammonium acetate (0.5 g, 6.5 mmol), piperidine (0.4 g, 5 mmol) and benzene (30 mL) were heated for 10–17 h (**4b**: 5 h) with continuous water separation. The reaction mixture was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude products were purified by vacuum distillation (**5e**: 141–144 °C/1 mmHg) or by column chromatography (**5b**: SiO_2/CCl_4; **5d**: SiO_2/toluene; **5f**: flash chromatography SiO_2/toluene and then SiO_2/petroleum ether (bp 60–90 °C)–ethyl acetate, 25:1).
14. Anderson, A. M.; Blazek, J. M.; Garg, P.; Payne, B. J.; Mohan, R. S. *Tetrahedron Lett.* **2000**, *41*, 1527–1530.
15. Amedio, J. C., Jr.; Bernard, P. J.; Fountain, M.; Van Wagenen, G., Jr. *Synth. Commun.* **1998**, *28*, 3895–3906.
16. Cragoe, E. J., Jr.; Pietruszkiewicz, A. M.; Robb, C. M. *J. Org. Chem.* **1958**, *23*, 971–980.
17. (a) Stoermer, R. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 2288–2306; (b) Hatch, M. J.; Cram, D. J. *J. Am. Chem. Soc.* **1953**, *75*, 38–44.
18. General procedure for the preparation of aminonitriles **6a**–**f**: the ylidenemalonodinitriles **5a**–**f** (150 mg) were dissolved in chilled concentrated sulfuric acid (5 mL). After stirring at −5 to −15 °C (ice + NaCl bath) for 1 h, the resulting brown solution was poured onto crushed ice. The obtained suspension was neutralized with aq NaOH, extracted with chloroform, dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Crude aminonitriles were purified by column chromatography (**6c**,**e**,**f**: SiO_2/toluene) or by vacuum sublimation (**6a**,**b**,**d**). An analytical sample of 1-amino-3,6-dimethyl-4-phenylnaphthalene-2-carbonitrile (**6e**) was obtained as small beige crystals through recrystallization from cyclohexane.
19. Spectroscopic data of **6e**:^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.27 (s, 3H, C3–CH_3), 2.35 (s, 3H, C6–CH_3), 5.08 (br s, 2H, NH_2), 7.07 (s, 1H, C5–H), 7.17–7.20 (m, 2H, C2′–H, C6′–H), 7.28 (dd, $J = 8.5$ Hz and $J = 1.6$ Hz, 1H, C7–H), 7.41–7.45 (m, 1H, C4′–H), 7.47–7.51 (m, 2H, C3′–H, C5′–H), 7.70 (d, $J = 8.5$ Hz, 1H, C8–H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.49 (C3–CH_3), 21.89 (C6–CH_3), 91.29 (C-2), 118.40 (CN), 118.44, 120.85 (C-8), 126.48 (C-5), 127.19 (2C; C-7, C-4′), 128.56 (2C; C-3′, C-5′), 128.93, 130.73 (2C; C-2′, C-6′), 132.53 (C-3), 135.49, 138.90, 139.10, 147.87 (C-1); IR (KBr) 3457, 3372, 3254 (NH_2), 3054, 3023, 2920, 2851, 2199 (CN), 1652 (NH_2), 1623, 1574, 1506, 1440, 1369, 1257, 1159, 1071, 815, 776, 722, 695 cm^{-1}. Anal. Calcd for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29%. Found: C, 83.85; H, 5.97; N, 10.18. The HMBC spectrum of **6e** revealed correlation through three bonds between C-1 (δ 147.87 ppm) and the proton bonded to the C-8 carbon atom (Scheme 3). The resonance of this proton appeared at δ 7.70 as a doublet with a coupling constant of 8.5 Hz. This doublet arose through coupling ($J = 8.5$ Hz) with the neighbouring proton connected to C-7 (δ 7.28 ppm). This proton was also coupled over four bonds to the proton at C-5 ($J = 1.6$ Hz). The signal of the proton at C-5 appeared as a broad singlet at δ 7.07 and had an unclear multiplet structure. All acquired data indicate the location of the methyl group at the '6' position of **6e**.
20. Wilamowski, J.; Kulig, E.; Sepiol, J. J.; Burgiel, Z. J. *Pest Manage. Sci.* **2001**, *57*, 625–632.
21. A comparison of the fungistatic activity of 1-amino-4-phenylnaphthalene-2-carbonitrile (**6a**) and a commercial fungicide—captan (data in brackets) against four phytopathogenic fungi: *Fusarium culmorum*: 93 (743); *Alternaria brassicicola* 30 (11); *Botrytis cinerea* 11 (18); *Penicillium expansum* 20 (45). The data were recorded for the EC_{50} level of activity and are expressed as mg/dm^3 concentrations.
22. (a) Kobayashi, K.; Uneda, T.; Takada, K.; Tanaka, H.; Kitamura, T.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1996**, 25–26; (b) Kobayashi, K.; Uneda, T.; Takada, K.; Tanaka, H.; Kitamura, T.; Morikawa, O.; Konishi, H. *J. Org. Chem.* **1997**, *62*, 664–668.