Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 3493–3496

TETRAHEDRON LETTERS

An efficient and facile synthesis of substituted cinnoline and benzo[*h*]cinnoline derivatives

Mohsen Abdel-Motaal Gomaa*

Chemistry Department, *Faculty of Science*, *Minia University*, *61519 El-Minia*, *Egypt*

Received 4 February 2003; revised 27 February 2003; accepted 7 March 2003

Dedicated to Professor Dietrich Döpp on the occasion of his 65th birthday

Abstract—New substituted 3-amino-5,7,8-trihalo-6-hydroxycinnoline-4-carbonitriles **7** and **8** and the 3-amino-5-chloro-6-hydroxybenzo[*h*]cinnoline-4-carbonitrile **9** were synthesized in two-steps starting from tetrahalo-1,4-benzoquinones or dichloro-1,4-naphthoquinones, malononitrile and hydrazine.

Cinnolines and their derivatives are widely used in pharmaceuticals and agrochemicals. Recently cinnoline derivatives have been patented as agrochemical and pharmaceutical drugs. In agrochemistry they act as microbicides,[1] pollen suppressants,[2–4] fungicides[5] and herbicides.[6,7] In the pharmaceutical field they are mainly patented as bactericides.[8–11] Hence the chemistry of cinnolines has received much attention and many methods for their synthesis have been developed.

Cinnolines can be prepared by cyclization of monosubstituted or 1,2-disubstituted benzenes. The second type of synthesis is the more general and is exemplified by the preparation of 3,4-disubstituted cinnolines (R^1 = aryl or alkyl) from diazotized 2-vinylaniline derivatives (Scheme 1).[12]

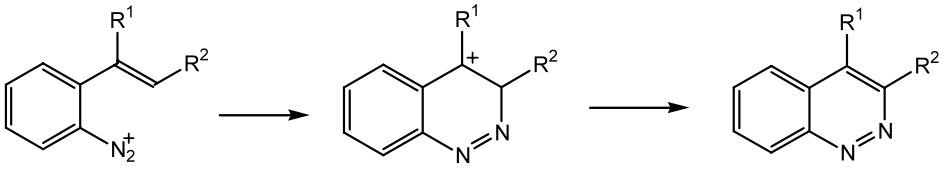
The other type of synthesis is exemplified by acid catalyzed cyclization of benzil monophenylhydrazone (Scheme 2).[12]

In 1997, Yoshida and co-workers reported a novel one-step synthesis of 3-aryl-4-cyanocinnolines from *p*-substituted acetophenone methylphenylhydrazones and tetracyanoethylene (TCNE). The reaction was performed in MeCN at 25°C for 5 days; the rationale of this novel reaction was not clarified.[13]

This work describes the synthesis of polysubstituted cinnolines and benzo[*h*]cinnoline in two steps starting from di- or tetrahalogenated *p*-quinones.

Quinones **1**–**3** were added to 2–3 mmol equiv. of malononitrile in boiling ethanol in the presence of traces of triethylamine to give the corresponding substitution products, the ylidenemalononitriles **4**–**6** in good yield 61–89% (Scheme 3) which were purified by recrystallization or by preparative thin-layer chromatography.

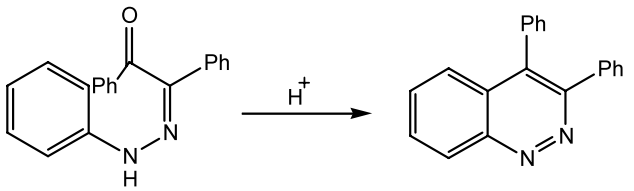
The structures of products **4**–**6** were assigned on the basis of their spectral data.[14] IR spectra showed sharp



Scheme 1.

Keywords: benzoquinone; naphthoquinone; cyclohexadiene; cinnoline; benzo[*h*]cinnoline.
* Fax: +20-86-342601; e-mail: mohsengomaa@link.net

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00686-5

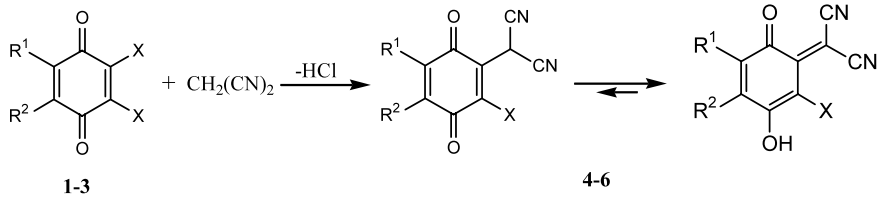


Scheme 2.

bands at $\nu = 3450$–3400 cm^{-1} assigned to the OH groups, absorptions at $\nu = 2222$–2205 cm^{-1} due to the CN groups and absorptions at $\nu = 1685$–1680 cm^{-1} for the C=O groups. ^{1}H NMR spectra showed exchangeable broad signals at $\delta = 10.21$–9.91 ppm which were attributed to the hydroxyl groups. The ^{13}C NMR showed signals at $\delta = 65.34$–62.79 ppm which were attributed to the sp^2 ylidenic carbon atom [$C(CN)_2$], at $\delta = 156.48$–151.52 ppm for the quaternary carbon atoms bearing hydroxyl groups (C-3 of **4**,**5** and C-4 of **6**), and $\delta = 172.23$–171.27 ppm for the carbonyl groups (C-6 of **4**,**5** and C-1 of **6**).

When equivalent amounts of ylidenes **4**–**6** and hydrazine hydrate were mixed in ethanol and warmed for just 5 min, the cinnoline derivatives **7**–**9** were formed (Scheme 4). The products were purified by recrystallization or by preparative thin-layer chromatography. It was thus possible to prepare multigram quantities of the crystalline products **7**–**9** in a short time and in good yields 60–88%.

The structures of cinnolines **7**–**9** were assigned on the basis of their spectral data.[15] IR spectra showed absorptions at $\nu = 3450$ cm^{-1} for the hydroxyl groups, absorptions at $\nu = 3134$–3380 cm^{-1} for the amino groups, and absorptions at $\nu = 2200$–2210 cm^{-1} for the cyano groups. The ^{13}C NMR spectra showed signals at $\delta = 75.18$–73.00 ppm for the carbon atoms bearing cyano groups (C-4), and signals at $\delta = 158.62$–153.40 ppm for the quaternary carbon atoms bearing hydroxyl groups (C-6) and signals at $\delta = 170.29$–165.33 ppm for C-3. The ^{13}C DEPT spectra showed only nine quaternary carbon atoms for compounds **7** and **8** and 13 quaternary carbon atoms for **9**. Thus, the number of signals attributable to quaternary carbon atoms excludes open structures and supports the cyclic structures **7**–**9** (Scheme 4).



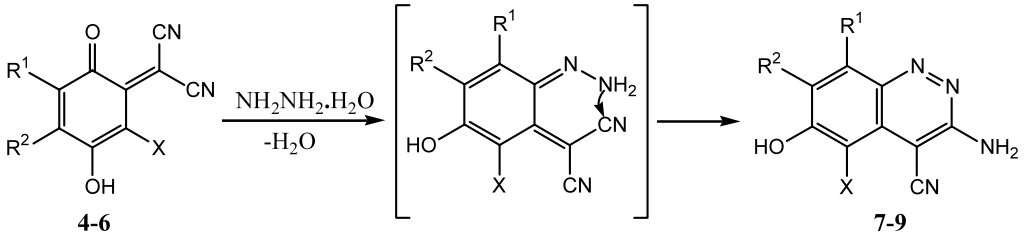
1-3 **4-6**

1,4: $R^1 = R^2 =$ X = Cl

2,5: $R^1 = R^2 =$ X = Br

3,6: $R^1 = R^2 =$; X = Cl

Scheme 3.



4-6 **7-9**

4,7: $R^1 = R^2 =$ X = Cl

5,8: $R^1 = R^2 =$ X = Br

6,9: $R^1 = R^2 =$  ; X = Cl

Scheme 4.

In conclusion, a versatile two-step synthesis of polysubstituted cinnolines and benzo[*h*]cinnoline from readily available starting materials is disclosed. Since the chemistry of cinnolines has hitherto remained almost unexplored because of the lack of versatile synthetic methods, this finding will contribute to the study of cinnolines, especially of biologically active ones which are of current interest as immunomodulators and anxiolytics.[13]

Acknowledgements

Thanks are due to Professor D. Döpp for some NMR measurements and mass spectra at Institut für Chemie, Universität Duisburg-Essen, Duisburg, Germany.

References

1. Ischikawa, H.; Umeda, T.; Hara, T.; Kajikawa, K. Jpn. Patent 04187677 A2 92076; *Chem. Abstr. 117*, 165929g.
2. Labovitz, J.; Guilford, W.; Liang, Y.; Fang, L.; Patterson, T. Eur. Patent 363236 A1 900411; *Chem. Abstr. 113*, 226421b.
3. Mizutani, M.; Shiroshita, M.; Okuda, H.; Mito, N.; Sakaki, M. Eur. Patent 320782 A2 890621; *Chem. Abstr. 112*, 114186b.
4. Patterson, T. G. VS Patent 5129940 A 920714; *Chem. Abstr. 117*, 186659j.
5. Coghlan, M. J.; Driekorn, B. A.; Suhr, R. G.; Jourdan, G. P. Eur. Patent 326328 A2 890802, *Chem. Abstr. 112*, 55907u.
6. Mizutani, M.; Shiroshita, M.; Sakaki, M.; Mito, N.; Okuda, H. Eur. Patent 320793 A2 890621; *Chem. Abstr. 111*, 232847v.
7. Munro, D.; Bit, R. A. UK Patent 2189238 A1 871021; *Chem. Abstr. 108*, 150499g.
8. Inoue, S.; Yasaki, A.; Mochizuki, H.; Tutsumi, H., Murata, M.; Sakane, K. Jpn. Patent 05213951 A2 930824; *Chem. Abstr. 120*, 134503w.
9. Tutsumi, H.; Terasawa, T.; Barret, D.; Murata, M.; Sakane, K.; Yazaki, A.; Inoue, S. Jpn. Patent 9215584 A1 920217 *Chem. Abstr. 118*, 254944w.
10. Yokomoto, M.; Yazaki, A.; Hayashi, N.; Hatono, S.; Ioue, S.; Kuramoto, Y. Eur. Patent 4700578 A1 920212; *Chem. Abstr. 117*, 7943c.
11. Miyamoto, K.; Matsumoto, J.; Nakamura, S. Jpn. Patent 02096570 A2 900409; *Chem. Abstr. 113*, 97619w.
12. Gilchrist, T. L. *Heterocyclic Chemistry*; Pitman Publishing, 1985; pp. 327–329 and references cited therein.
13. Matsubara, Y.; Horikawa, A.; Yoshida, Z.-I. *Tetrahedron Lett.* **1997**, *38*, 8199–8202.
14. To a solution of quinone **1**–**3** (1.0 mmol) in 10 ml of ethanol, a malononitrile solution (3.0 mmol, 0.198 g) in 5.0 ml of ethanol and three drops of triethylamine were added and heated under reflux for 3–6 h with stirring. After this period the solution was cooled, and the precipitates containing the ylidenemalononitriles **4**–**6**, removed by filtration and purified by recrystallization from ethyl acetate. The filtrates contained the rest of the ylidenes and unreacted quinones. Thus, the filtrate was subjected to plc using toluene/ethyl acetate (2:1). The faster zones contained unreacted quinones while the slower contained compounds **4**–**6** which were recrystallized from ethyl acetate.
(2,4,5-Trichloro-3-hydroxy-6-oxocyclohexa-2,4-dien-1-ylidene)malononitrile **4**, deep yellow crystals (0.24 g, 70%) mp 245°C (EtOAc). ^{1}H NMR (DMSO-d_6): $\delta=10.21$ (br, 1H, OH). ^{13}C NMR (DMSO-d_6): $\delta=64.35$ [$C(CN)_2$], 104.21 (C-2), 112.94 (C≡N), 133.10 (C-4), 138.70 (C-5), 151.52 (C-3), 169.02 (C-1), 171.62 (C-6). IR (KBr): $\nu=$ 3400 (OH), 2222 (C≡N), 1685 (C=O) cm^{-1}. MS: m/z (%) = 280 (M^{+4}, 22), 278 (M^{+2}, 94), 276 (M^+, 100), 251 (42), 249 (41), 186 (53), 158 (23). Anal. calcd for $C_9HCl_3N_2O_2$ (275.6): C, 39.22; H, 0.37; N, 10.17. Found: C, 39.15; H, 0.33; N, 10.15.
(2,4,5-Tribromo-3-hydroxy-6-oxocyclohexa-2,4-dien-1-ylidene)malononitrile **5**, orange crystals (0.27 g, 61%) mp 236°C (EtOAc). ^{1}H NMR (DMSO-d_6): $\delta=10.18$ (br, 1H, OH). ^{13}C NMR (DMSO-d_6): $\delta=65.34$ [$C(CN)_2$], 95.35 (C-2), 112.56 (C≡N), 130.07 (C-4), 134.33 (C-5), 156.48 (C-3), 168.68 (C-1), 171.27 (C-6). IR (KBr): $\nu=3420$ (OH), 2205 (C≡N), 1679 (C=O) cm^{-1}. MS: m/z (%) = 413 (M^{+6}, 15), 411 (M^{+4}, 35), 409 (M^{+2}, 34), 407 (M^+, 10), 349 (50), 347 (100), 345 (51), 82 (24). Anal. calcd for $C_9HBr_3N_2O_2$ (408.8): C, 26.44; H, 0.25; N, 6.85. Found: C, 26.32; H, 0.23; N, 6.83.
(3-Chloro-4-hydroxy-1-oxonaphthalen-2(1*H*)-ylidene)-malononitrile **6**, yellow crystals (0.23 g, 89%) mp 203–205°C (EtOAc). ^{1}H NMR (DMSO-d_6): $\delta=7.52$ (d, $^3J=$ 8.52 Hz, 1H, Ar-H), 7.57–7.65 (m, 2H, Ar-H), 7.91 (d, $^3J=8.77$ Hz, 1H, Ar-H), 9.91 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): $\delta=62.79$ [$C(CN)_2$], 106.13 (C-3), 113.64 (C≡N), 123.83, 127.10, 130.10, 131.51 (all aryl *C*H), 130.61 (C-8a), 134.30 (C-4a), 154.82 (C-4), 172.24 (C-2), 175.89 (C-1). IR (KBr): $\nu=3450$ (OH), 2210 (C≡N), 1680 (C=O) cm^{-1}. MS: m/z (%) = 259 (M^{+2}, 17), 257 (M^+, 39), 43 (76), 36 (100). Anal. calcd for $C_{13}H_5ClN_2O_2$ (256.7): C, 60.83; H, 1.96; N, 10.92. Found: C, 60.71; H, 1.85; N, 10.89.
15. **Reaction of ylidenes 4–6 with hydrazine hydrate**: An ethanol solution of the ylidenemalononitrile **4**–**6** (0.1 g) and hydrazine hydrate (0.05 g, 1 mmol) was warmed for 5 min. The color turned from yellow to brown and a brown precipitate was readily formed. The precipitate was cooled, filtered and recrystallized from aqueous DMF to give products **7**–**10**.
3-Amino-5,7,8-trichloro-6-hydroxycinnoline-4-carbonitrile **7**, brown solid (0.92 g, 88%) mp >360°C. ^{1}H NMR (DMSO-d_6): $\delta=7.68$ (s, 1H, OH), 7.82 (s, 2H, NH_2).^{13}C NMR (DMSO-d_6): $\delta=74.50$ (C-4), 108.85 (C-5), 115.20 (C≡N), 115.91 (C-4a), 128.08 (C-7), 133.78 (C-8), 135.55 (C-8a), 153.40 (C-6), 165.99 (C-3). IR(KBr): $\nu=3450$ (OH), 3281, 3143 (NH_2), 2210 (C≡N) cm^{-1}. MS: m/z (%) = 292 (M^{+4}, 6), 290 (M^{+2}, 19), 288 (M^+, 20), 254 (10), 36 (100). Anal. calcd for $C_9H_3Cl_3N_4O$ (289.7): C, 37.32; H, 1.04; N, 19.35. Found: C, 37.28; H, 1.01; N, 19.20.
3-Amino-5,7,8-tribromo-6-hydroxycinnoline-4-carbonitrile **8**, brown solid (0.62, 60%) mp >360°C. ^{1}H NMR (DMSO-d_6): $\delta=6.84$ (s, 3H, OH, and NH_2). ^{13}C NMR (DMSO-d_6): $\delta=75.18$ (C-4), 98.51 (C-5), 117.53 (C≡N), 128.55 (C-7), 129.36 (C-8), 130.49 (C-4a), 136.97 (C-8a), 158.62 (C-6), 165.33 (C-3). IR(KBr): $\nu=3430$ (OH), 3290,

3200 (NH_2), 2200 (C≡N) cm^{-1}. MS: m/z (%) = 426 (M^{+6}, 31), 424 (M^{+4}, 96), 422 (M^{+2}, 100), 420 (M^+, 32), 344 (53), 208 (14), 82 (94), 80 (100). Anal. calcd for $C_9H_3Br_3N_4O$ (422.9): C, 25.56; H, 0.72; N, 13.25. Found: C, 25.43; H, 0.69; N, 13.20.

3-Amino-5-chloro-6-hydroxybenzo[*h*]cinnoline-4-carbonitrile **9**, brown solid (0.7 g, 66%), mp >360°C. ^{1}H NMR (DMSO-d_6): δ = 6.77 (br, 2H, NH_2), 7.56–7.66 (m, 2H, Ar-H), 8.19 (d, ^3J = 9.33 Hz, 1H, Ar-H), 8.65 (d, ^3J = 9.03 Hz, 1H, Ar-H). ^{13}C NMR (DMSO-d_6): δ = 73.00 (C-4), 104.82 (C-5), 118.00 (C≡N), 122.66, 124.66, 128.49, 129.44 (all aryl *C*H), 129.66 (C-4a), 131.39 (C-6a), 131.81 (C-10a), 137.30 (C-10b), 156.91 (C-6), 170.29 (C-3). IR(KBr): v = 3460 (OH), 3380, (NH_2), 2200 (C≡N) cm^{-1}. MS: m/z (%) = 272 (M^{+2}, 36), 270 (M^+, 100), 242 (28), 179 (19), 151 (23), 44 (26). Anal. calcd for $C_{13}H_7ClN_4O$ (270.7): C, 57.67; H, 2.61; N, 20.69. Found: C, 57.45; H, 2.50; N, 20.55.