Heteroatom Chemistry
Volume 13, Number 3, 2002

Facile Synthesis of 3-Spiroindolines

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Received 16 April 2001; revised 9 July 2001

ABSTRACT: *Cyanoacetyldiazoindol-2-one (**3**), the condensation product of cyanoacetohydrazide with isatin (**1**), could be cyclized in acidic medium via its C=N group and its enolic OH to give cyanomethyloxadiazole-spiroindoline (**4**). The presence of the methylcyano side chain could be invested—through oximation, diazotization, or condensation with aldehydes—to form polyfunctional spiroindolines* **5, 8–10**. *Also, a second route for preparing the title compound could be achieved through a nucleophilic attack on position 3 in the isatin derivatives, followed by subsequent ring closure to give* **6** *and* **7**. © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:207–210, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10020

INTRODUCTION

The reactivity and ease of preparation of cyanoacetohydrazide (**2**) can be utilized in heterocyclic synthesis. Previously, we have reported its utility in preparing pyridines [1] and pyrazoles [2]. In continuation, the present work is concerned with the preparation of 3-spiroindolines starting with **2**, because of the biological importance of this class of compounds [3–5] (Scheme 1).

RESULTS AND DISCUSSION

Cyanoacetohydrazide condensed readily with isatin (**1**) in acetic acid, affording the corresponding 3-cyanoacetyldiazoindol-2-one (**3**). It showed the ^{1}H NMR methylene signal and the IR CN absorption already detected in **2**, while its mass spectral data was compatible with $C_{11}H_8N_4O_2$ ($m/z = 228$).

When the indoline (**3**) was refluxed in acetic acid, a new compound having the same molecular formula as the parent was obtained. It had similar spectral characteristics of **3**, but showed only one IR CO absorption, and the ^{1}H NMR methylene singlet appeared at lower field $\delta = 4.4$ compared to the singlet observed in **3** at $\delta = 4.2$; the product also had a lower melting point and was detected at a different R_F value. According to this information and that contained in a previous report [6], the oxadiazolo-2-spiroindoline structure (**4**) was assigned to this product. It was probably formed through an intracyclization involving the enolic OH and the C=N group.

Starting with **4**, a number of spiro compounds could be obtained via simple procedures. Thus, when it was treated with nitrous acid, the oximino derivative (**5a**) was obtained, which showed a molecular ion peak at $m/z = 257$ and an additional (D_2O exchangeable) singlet at $\delta = 13.85$ with the absence of the methylene one.

On the other hand, when the same reaction was repeated with **3** instead of **4**, the reported 3-hydrazo-2-oxoindole was formed [7] through decyanoacetylation, a result which gave further confirmation of stucture **4**.

Furthermore, diazotization of **4**, using phenyldiazonium chloride, afforded the corresponding phenylhydrazone (**5b**). This structure was deduced from element analyses, spectral data and its mass spectrum, which showed the molecular ion peak at $m/z = 332$. Compound **4** condensed also with salicylaldehyde with the formation of the corresponding coumarin derivative (**8**) in which the coumarin

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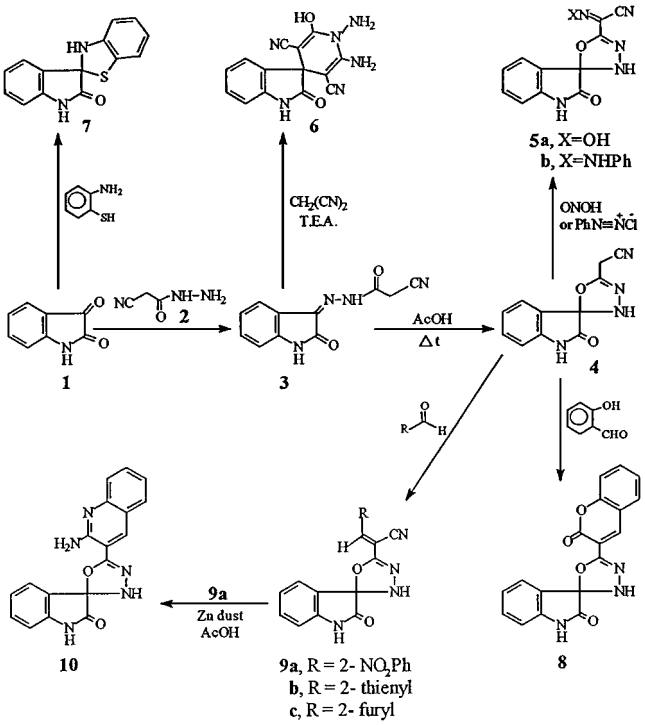

SCHEME 1

4-H appeared at $\delta = 9.10$ in its ^{1}H NMR spectrum and the coumarinyl CO at 1720 cm^{-1} in its IR spectrum.

The reactions of **4** with each of 2-nitrobenzaldehyde, thiophen-2-aldehyde, and 2-furaldehyde were carried out to give the corresponding benzylidenes (**9a-c**) in which the ylidene H was detected at $\delta \sim 8.9$ [8]. Compound **9a** was reduced with Zn dust in acetic acid, and the product lacked both the IR CN absorption and the ylidene signal. Instead, a new (D_2O exchangeable) one was found at $\delta = 6.80$–7.00 (2H) together with a singlet (1H) at $\delta = 8.45$; its mass spectral data gave a molecular ion peak at $m/z = 331$. From these data and previous results [2], the aminoquinolino structure (**10**) was assigned to this product. When compound **3** was refluxed with malononitrile in ethanol/triethylamine, a new product with a molecular formula compatible with $C_{14}H_{10}N_6O_2$ ($m/z = 294$) was obtained. It showed a twin CN absorption besides the indoline CO one and four (D_2O exchangeable) singlets at $\delta = 3.75$ (1H), 4.60 (2H), 5.95 (2H), and 9.90 (1H). Based on these data as well as previous reports [9], the indolin-3-spiropyridine structure (**6**) was indicated. It is assumed that an intraylidene exchange occurred under the experimental conditions used [10], followed by spontaneous attack by malononitrile in a Michael-type addition to give **6**, as the spectral data excluded a product formation via the direct Michael addition to the C=N group in **3**.

Furthermore, 2-aminothiophenol reacted with **1** to afford a single compound having one IR CO absorption, and two (D_2O exchangeable 1H each) ^{1}H NMR signals in addition to those of the aromatic protons. From these data, the benzothiazolospiroindoline structure (**7**) was assigned to this product. Although compound **7** had previously been obtained via the deoxygenation of 3-(2-nitrophenylthio)indole with triethyl phosphite, together with other products [11], the present method offers a simple route for its preparation as a sole product in a very good yield.

EXPERIMENTAL

Melting points are uncorrected and were taken on an Electrothermal 9100 apparatus. IR spectra were recorded with a Carl Zeiss spectrophotometer model UR10 in KBr pellets. ^{1}H NMR spectra were determined with a Jeol 270 MHz (internal TMS). Mass spectra were recorded with a Finigan SSQ 7000 mass spectrometer. Microanalyses were performed by the Central Service Laboratory at Cairo University and the Microanalytical Unit at the National Research Center.

*3-Cyanoacetyldiazo-indol-2-(1H)-one (**3**) and Benzothiazol-(3H)-2-spiro-3-indol-2-(1H)-one (**7**)*

A mixture of **1** (10 mmol) with **2** (10 mmol) or **1** (10 mmol) with 2-aminothiophenol (10 mmol) was refluxed in ethanol (30 ml) for 1 h. A precipitate was formed in the hot solution, filtered off, and crystallized.

*3-Cyanoacetyldiazo-indol-2-(1H)-one (**3**)*

M.p. 230–232°C; yield 90% (ethanol). ^{1}H NMR (D_2O, DMSO-d_6, TMS) δ 4.20 (s, 2H, CH_2), 6.90–7.10 (m, 2H, indole 5-H, 6-H), 7.45–8.10 (m, 2H, indole 4-H, 7-H), 10.85 (s, 1H, indole NH), 11.60 (s, 1H, NH). IR (KBr) ν 3250, 3200 (NH), 2250 (CN), 1730, 1700 (2CO). MS: m/z (M^+ 228). Anal. Calcd. for $C_{11}H_8N_4O_2$ (228.204): C, 57.89; H, 3.53; N, 24.55. Found: C, 57.70; H, 3.40; N, 24.30.

*Benzothiazol-(3H)-2-spiro-3-indol-2-(1H)-one (**7**)*

M.p. 228°C; yield 85% (acetic acid). ^{1}H NMR (D_2O, DMSO-d_6, TMS) δ 6.50–6.65 (m, 2H, indole 5-H, 6-H), 6.85–7.35 (m, 6H, indole 4-H, 7-H and benzothiazole H), 7.55 (s, 1H, benzothiazole NH), 10.40 (s, 1H,

indole NH). IR (KBr) ν 3200 (NH), 1700 (CO). Anal. Calcd. for $C_{14}H_{10}N_2O$ S (254.304): C, 66.12; H, 3.96; N, 11.02; S, 12.61. Found: C, 66.00; H, 3.70; N, 10.80; S, 12.30.

*5-Cyanomethyl-1,3,4-oxadiazol-(3H)-2-spiro-3-indol-2-(1H)-one (**4**)*

Compound **3** (10 mmol) was refluxed in acetic acid (25 ml) for 2 h. The solution was partially concentrated, cooled, the precipitate that had formed was filtered off and crystallized from acetic acid: M.p. 207–209°C, yield 80%. ^{1}H NMR (D_2O, DMSO-d_6, TMS) δ 4.40 (s, 2H, CH_2), 6.90–7.05 (m, 2H , indole 5-H, 6-H), 7.35–7.45 (m, 2H , indole 4-H, 7-H), 11.25 (s, 1H, indole NH), 12.60 (s, 1H, oxadiazole NH). IR (KBr) ν 3200 (NH), 2260 (CN), 1720 (CO). MS: *m/z* (M^+ 228). Anal. Calcd. for $C_{11}H_8N_4O_2$ (228.204): C, 57.89; H, 3.53; N, 24.55. Found: C, 57.60; H, 3.40; N, 24.30.

*5-(1-Hydroxyimino)cyanomethyl-1,3,4-oxadiazol-(3H)-2-spiro-3-indol-2-(1H)-one (**5a**)*

To a solution of **4** (10 mmol) in acetic acid (25 ml), a solution of sodium nitrite (20 mmol in 2 ml H_2O) was added dropwise with stirring and the solution was allowed to stand for 3 h. Water was then added to the reaction mixture until precipitation commenced; the solid, thus formed, was filtered off and crystallized from acetic acid: M.p. > 300°C; yield 45%. ^{1}H NMR (D_2O, DMSO-d_6, TMS) δ 6.95–7.10 (m, 2H, indole 5-H, 6-H), 7.40–7.60 (m, 3H, indole 4-H, 7-H and oxadiazole NH), 11.35 (s, 1H, indole NH), 13.85 (s, 1H, OH). IR (KBr) ν 3280–3200 (OH, NH), 2220 (CN), 1700 (CO). MS: *m/z* (M^+ 257). Anal. Calcd. for $C_{11}H_7N_5O_3$ (257.206): C, 51.36; H, 2.74; N, 27.23. Found: C, 51.20; H, 2.60; N, 27.00.

*5-(1-Phenyldiazo)cyanomethyl-1,3,4-oxadiazol-(3H)-2-spiro-3-indol-2-(1H)-one (**5b**)*

Phenyldiazonium chloride was added to an ice-cooled solution of **4** (10 mmol) in DMF (25 ml) in the presence of Na acetate trihydrate (5 g) with stirring for 10 min, then the ice bath was removed and stirring was continued at room temperature. After 3 h, water was added to the solution and the precipitate obtained was filtered off and crystallized from acetic acid: M.p. 291–293°C; yield 80%. ^{1}H NMR (D_2O, DMSO-d_6, TMS) δ 6.95–7.70 (m, 9H, indole H and Ph), 11.40 (s, 1H, indole NH), 12.45 (s, 2H, oxadiazole NH and diazo NH). IR (KBr) ν 3250–3200 (NH), 2220 (CN), 1700 (CO). MS: m/z (M^+ 332). Anal. Calcd. for $C_{17}H_{12}N_6O_2$ (332.32): C, 61.44; H, 3.64; N, 25.29. Found: C, 61.20; H, 3.40; N, 25.00.

*Reactions of **4** with Aldehydes or **3** with Malononitrile*

General Procedure. A mixture of **4** (10 mmol) with an equimolecular amount of the proper aldehyde, or **3** (10 mmol) with malononitrile (10 mmol) was refluxed in ethanol (30 ml) in the presence of triethylamine (3–4 drops) for 1–2 h. A precipitate formed in the hot solution; it was collected by filtration and finally crystallized from acetic acid.

*1,2-Diamino-3,5-dicyano-6-hydroxypyridin-4-spiro-3-indol-2-(1H)-one (**6**)*

M.p. 222–224°C; yield 40%. ^{1}H NMR (D_2O, DMSO-d_6, TMS) δ 3.75 (br s, 1H, OH), 4.60 (s, 2H, NH_2), 5.95 (s, 2H, NH_2), 6.60–7.15 (m, 4H, indole H), 9.90 (br s, 1H, indole NH). IR (KBr) ν 3290–3100 (OH, NH_2, NH), 2220, 2200 (2CN), 1710 (CO). MS: *m/z* (M^+ 294). Anal. Calcd. for $C_{14}H_{10}N_6O_2$ (294.27): C, 57.14; H, 3.43; N, 28.56. Found: C, 57.00; H, 3.20; N, 28.30.

*5-(3-Coumarinyl)-1,3,4-oxadiazol-2-spiro-3-indol-2-(1H)-one (**8**)*

M.p. > 300°C; yield 70%. ^{1}H NMR (D_2O, DMSO-d_6, TMS) δ 6.85–7.65 (m, 8H, indole H and coumarin 5-H to 8-H), 8.60 (s, 1H, oxadiazole NH), 9.10 (s, 1H, coumarin 4-H), 11.00 (s, 1H, indole NH). IR (KBr) ν 3200 (NH) , 1720, 1700 (CO). Anal. Calcd. for $C_{18}H_{11}N_3O_4$ (333.29): C, 64.86; H, 3.33; N, 12.61. Found: C, 64.70; H, 3.10; N, 12.30.

*5-(2-Nitro-cinnamonitril-2-yl)-1,3,4-oxadiazol-2-spiro-3-indol-2-(1H)-one (**9a**)*

M.p. 245–247°C; yield 85%. ^{1}H NMR (D_2O, DMSO-d_6, TMS) δ 6.95–7.10 (m, 2H, indole 5-H, 6-H), 7.40–7.60 (m, 2H, indol 4-H, 7-H), 7.85–8.25 (m, 4H, 2-NO_2 Ph), 8.90 (s, 1H, ylidene H), 11.45 (s, 1H, indole NH), 13.95 (br s, 1H, oxadiazole NH). IR (KBr) ν 3250 (NH), 2200 (CN), 1710 (CO). Anal. Calcd. for $C_{18}H_{11}N_5O_4$ (361.31): C, 59.83; H, 3.07; N, 19.39. Found: C, 59.70; H, 2.90; N, 19.10.

*5-[1-(2-Thienyl)acrylonitril-2-yl]-1,3,4-oxadiazol-2-spiro-3-indol-2-(1H)-one (**9b**)*

M.p. 297–299°C; yield 80%. ^{1}H NMR (D_2O, DMSO-d_6, TMS) δ 6.95–7.15 (m, 2H, indole 5-H, 6-H), 7.35–7.45 (m, 2H, indole 4-H, 7-H), 7.60 (dd, $J = 8$ Hz, 1H, thiophene 3-H), 8.10 (dd, $J = 8$ Hz , 1H, thiophene 4-H), 8.25 (dd, $J = 8$Hz, 1H, thiophene 5-H), 8.75 (s, 1H, ylidene CH), 11.20 (s, 1H, indole NH), 13.40 (s, 1H,

NH). IR (KBr) ν 3200, (NH), 2220 (CN), 1705 (CO). Anal. Calcd. for $C_{16}H_{10}N_4O_2S$ (322.334): C, 59.62; H, 3.13; N, 17.38; S, 9.95. Found: C, 59.30; H, 3.00; N, 17.10; S, 9.60.

*5-[1-(2-Furyl)acrylonitril-2-yl]-1,3,4-oxadiazol-2-spiro-3-indol-2-(1H)-one (**9c**)*

M.p. 292–294°C; yield 85%. ^{1}H NMR (D_2O, DMSO-d_6, TMS) δ 6.85–6.95 (m, 2H, furan 3-H, 4-H), 7.05–7.15 (m, 1H, indole 5-H), 7.35–7.65 (m, 3H, indole 6-H, 4-H, 7-H), 8.25 (s, 2H, furan 5-H and ylidene CH), 11.35 (s, 1H, indole NH), 13.90 (br s, 1H, NH). IR (KBr) ν 3200 (NH), 2220 (CN), 1710 (CO). Anal. Calcd. for $C_{16}H_{10}N_4O_3$ (306.27): C, 62.74; H, 3.29; N, 18.29. Found: C, 62.60; H, 3.10; N, 18.00.

*5-(2-Aminoquinolin-3-yl)-1,3,4-oxadiazol-2-spiro-3-indol-2-(1H)-one (**10**)*

To a solution of **9a** (10 mmol) in acetic acid (20 ml) maintained at 60°C, Zn dust (0.5 g) was added portionwise with stirring and this was continued for 2 h. Afterwards, the mixture was filtered, the filtrate concentrated, and the precipitate that had been collected was crystallized from acetic acid: M.p. < 300°C; yield 35%. ^{1}H NMR (D_2O, DMSO-d_6, TMS) δ 6.80–7.00 (m, 4H, indole 5-H, 6-H and NH_2), 7.15–7.70 (m, 6H, indole 4-H, 7-H and quinoline 5-H to 8-H), 8.45 (s, 1H, quinoline 4-H), 9.50 (br s, 1H, oxadiazole NH), 10.85 (s, 1H, indole NH). IR (KBr) ν 3250–3200 (NH_2, NH), 1710 (CO). MS: m/z (M^+ 331). Anal. Calcd. for $C_{18}H_{13}N_5O_2$ (331.32): C, 65.25; H, 3.95; N, 21.14. Found: C, 65.10; H, 3.80; N, 21.00.

REFERENCES

[1] Haggag, B. M.; Chabaka, L. M.; Allam, Y. A.; Nawwar, G. A. M. Polish J Chem 1997, 71, 52.
[2] Nawwar, G. A. M.; Allam, Y. A. J Chem Res Synop 1993, 1, 456.
[3] Robertson, D. W. Eur Pat 178876, 1986; Chem Abstr 1986, 105, 66459z.
[4] Dandia, A.; Upreti, M.; Rani, B.; Pant, U. C. J Chem Res Synop 1998, 752; J Chem Res Miniprint 1998, 3348.
[5] Schwartz, R. C.; Hirsch, C. F.; Sigmuna, J. M; Pettibone, D. J. US Patent 4 803 217, 1989; Chem Abstr 1989, 111, 132572h.
[6] Dopp, D.; Gomaa, M. A. M.; Henkel, G.; Nour El-Din, A. M. J Chem Soc, Perkin Trans 2 1996, 573.
[7] Diesbach, H.; Heppner, E. Helv Chim Acta 1949, 32, 687.
[8] Nawwar, G. A. M.; Shafik, N. A. Collect Czech Chem Commun 1995, 60, 2200.
[9] Nawwar, G. A. M. Quatar Univ Sci J 1994, 14(2), 252.
[10] Hammad, M. A.; Nawwar, G. A. M.; Gemeie, G. E.; EL-nagdi, M. H. Heterocycles 1985, 23, 2177.
[11] Jackson, A. H.; Johnson, D. N.; Shannon, P. V. R. J Chem Res Synop 1988, 9, 272.