SYNTHESIS OF 4-AMINO-3-CYANO-2-MORPHOLINOQUINOLINE

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Abstract

The 4-amino-3-cyano-2-morpholinoquinoline was obtained *via* intramolecular Thorpe-Ziegler cyclization of 4-cyano-N^4-(2-cyanophenyl)morpholine-4-carboximido-thioate **3** to afford the intermediate 3,1-benzothiazepine **4**. Compound **4** undergoes ring contraction to give the quinoline **5** by base catalyzed sulfur atom elimination. IR, ^{1}H, ^{13}C NMR and X-ray structural analysis confirmed the structure of the isolated new products **3** and **5**.

Introduction

Several benzothiazepines posses wide spectrum of biological activities as cardiovascular, vasodilator, antiarhytmic, haemodynamic effects, antinuclear activity, calcium antagonistic, spasmolytic activities (1), *etc.* We decided to synthesize 3,1-benzothiazepine for the biological activity evaluation.

Discussion

The new heterocyclic ring system 3,1-benzothiazepine could be easily prepared from 2-isothiocynatobenzonitrile **1** by the following reaction sequence. The reaction of morpholine with 2-isothiocynato-benzonitrile **1** afforded the thiourea derivatives **2** (2) (Scheme 1). This thiourea **2** reacts with chloroacetonitrile *via* regioselective alkylation reaction at the sulfur atom to afford the isothiourea derivatives **3**. Compounds **3** were expected to undergo an intramolecular addition reaction by the C-nucleophilic attack at the available nitrile group to give the desired 3,1-benzothiazepine **4**. Our attempts to synthesize **4** were not successful and instead the 4-amino-3-cyano-2-morpholinoquinolines **5** were formed.

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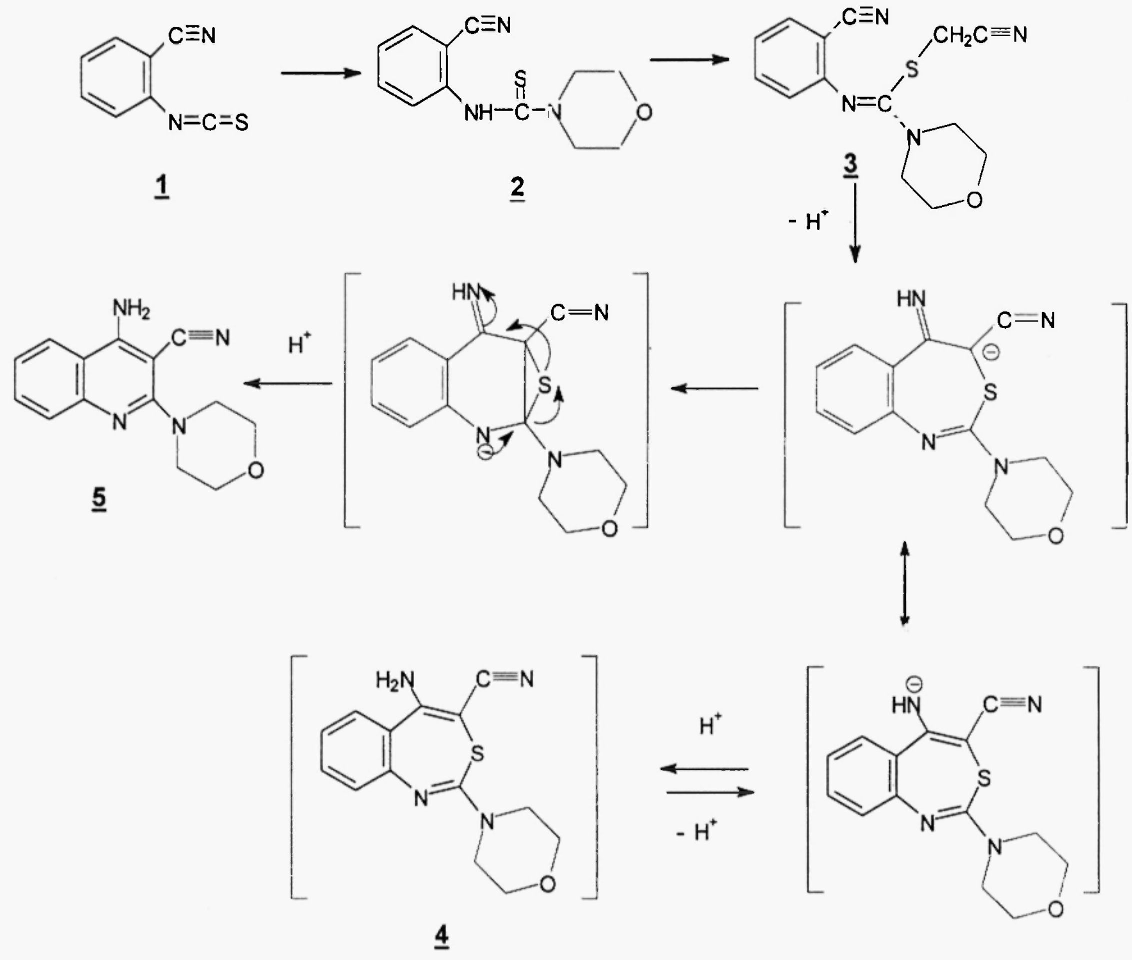
The synthesis of 3,1-benzothiazepine 4 from the isothiourea derivatives 3 was realized on the base of the catalysed intramolecular Thorpe-Ziegler cyclization of isothiourea 3.



Scheme 1.

The cyclization of the isothiourea 3 in the presence of sodium hydride in dimethyl sulfoxide solution gave the quinoline derivative 5 . Formation of this product could be explained if we claim the formation of the intermediary 3,1-benzothiazepine **4** that rapidly converts to the quinoline derivative 5.

This conversion could be explained as follows: The first step is the deprotonation of the benzothiazepine derivative 4, which will produce a 8π system, a bond between C2 and C4 is then formed to produce a thiiran derivative, which will spontaneously eliminate the sulfur atom and finally give the quinoline derivative by ring contraction of the seven member ring to the thermodynamically stable six member ring. The previous explanation follows the base catalyzed sulfur atom extraction from 2,5,6-trisubstituted 1,3,4-thiadiazines as reported by Pfeiffer (3). This also agrees with results obtained by Fodor (4), which underwent ring transformation of 2-methoxycarbonyl-3-aryl-4,5-dihydro-1,4-benzothiazepines to 3-aryl-4-methoxy-carbonylisoquinolines in the presence of activated manganese oxide.

Structures **3** and **5** were confirmed by IR, ^{1}H, ^{13}C NMR and X-ray structural analysis (5,6) (Figure 1).

Conclusion

The intramolecular Thorpe-Ziegler cyclization of 4-cyano-N^4-(2-cyanophenyl)-morpholine-4-carboximidothioate **3** afforded the 4-amino-3-cyano-2-morpholino-quinoline **5** *via* base catalyzed sulfur elimination of the intermediate 3,1-benzothiazepine derivative **4**.

Experimental

General details. Purity of compounds **3** and **5** were proved by the elemental analysis on an (Erba) instrument 1102 and results were in accord with calculated.. NMR spectra were measured on a Bruker Avance DRX-500 spectrometer. Both X-ray intensity data were collected at 120(2) K on a KUMA KM4 kapa four-circle diffractometer with MoK α radiation (λ 0.71073 Å). The structures were solved by direct methods (program: SHELXS-97) and refined by weighted full-matrix least-squares on F^2 (SHELXL-97). All non-hydrogens were refined anisotropically, hydrogens were localized from difference Fourier map and refined isotropically.

4-Cyano-N^4-(2-cyanophenyl) morpholine-4-carboximidothioate **3**. To a solution of **2** (1.235 g, 5 mmol) (2) in $CHCl_3$ (40 mL) was added triethylamine (1.4 mL, 10 mmol) and chloroacetonitrile (0.5 mL, 7 mmol). The reaction mixture was refluxed for 5h. The solvent was then evaporated. The oily residue was cooled till solidification and crystallized from ethyl alcohol.

Yield 1.12 g (78 %) m.p 66-67 °C; Anal. Calcd for $C_{14}H_{14}N_4OS$ (286.35): C, 58.72; H, 4.93; N, 19.57; S, 11.20 Found: C, 58.56; H, 4.84; N, 19.65; S, 11.11.; ^{1}H NMR ($CDCl_3$) δ / ppm 3.45 (s, 2H, SCH_2), 3.67 (t, 4H, $2NCH_2$, J = 5.12 Hz), 3.77 (t, 4H, $2OCH_2$, J = 5.12 Hz), 7.02-7.56 (m, 4H, Ar); ^{13}C NMR (DMSO-d_6) δ / ppm 18.15 (SCH_2), 49.32 (NCH_2), 55.53 (OCH_2), 104.92 (CN), 115.73 (CN), 117.96 (C_q), 122.35 (CH), 122.77 (CH), 132.93 (CH), 133.51 (CH), 152.37 (C_q), 153.59 (C_q). Crystallographic data for **3** (5).

4-Amino-3-cyano-2-morpholinoquinoline **5**. The isothiourea **3** (1.43 g, 5 mmol) was dissolved in DMSO (5 mL). To stirred solution was added NaH (0.24 g, 10 mmol) and the stirring was continued over night. The reaction mixture was poured over 100 mL of water. The precipitated solid was collected and crystallized from acetonitrile.

Yield 0.78 g (62 %): mp 224-225 °C (decomp.); Anal. Calcd for $C_{14}H_{14}N_4O$ (254.29): C, 66.13; H, 5.55; N, 22.03. Found: C, 65.94; H, 5.41; N, 21.97.; ^{1}H NMR ($CDCl_3$) δ / ppm: 3.64 (t, 4H, $2NCH_2$, J = 5.12 Hz), 3.88 (t, 4H, $2OCH_2$, J = 5.12 Hz), 5.62 (s, 2H, NH_2), 7.26-7.75 (m, 4H, Ar);

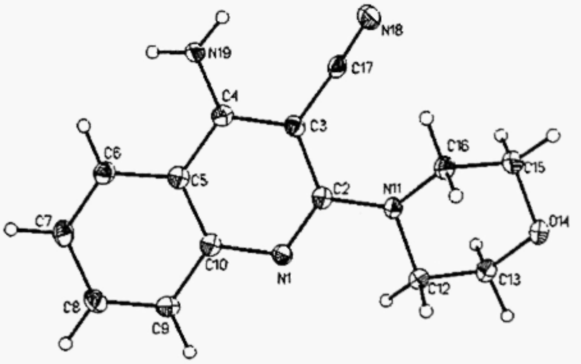


Figure. 1. X-ray structure of 4-amino-3-cyano-2-morpholinoquinoline 5.

^{13}C NMR (DMSO-d_6) δ / ppm 49.86 (NCH_2), 66.51 (OCH_2), 76.81 (C_q), 114.90 (CN), 117.91 (C_q), 123.15 (CH), 123.55 (CH), 127.98(CH), 132.51 (CH), 147.96 (C_q), 158.30 (C_q), 160.24 (C_q). Mass spectrum, m/z (I_r/%): 254 (42), 223 (39), 211 (18), 209 (36), 198 (16), 197 (93), 196 (28), 170 (18), 169 (100), 142 (38), 141 (37), 114 (18), 86(19). Crystallographic data for 5 (6).

Acknowledgments

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References

(1) A. Levai, J. Heterocyclic Chem., 37, 199, (2000), and references there in.
(2) P. Pazdera, D. Ondráček, *CS Patent*, 264 942 B1, C 07 C 157 / 09 (1990).
(3) W-D. Pfeiffer, E. Dilk, E. Bulka, *Wissenschaft. Z. der EMAU Greifswald*, 27, 135, (1978).
(4) L. Fodor, J. Szabo, G. Bernath, P. Sohar, *17th International Congress of Heterocyclic Chemistrv. Austria, Vienna* **1999**, PO-7.
(5) Crystallographic data for 3: $C_{14}H_{14}N_4OS$, M = 286.35, monoclinic crystal system, S.G. P-1, a = 11.6702(10) Å, b = 10.0820(6) Å, c = 13.0581(12) Å, α = 90(5) °, β= 111.096(10) °, γ = 90°, V = 1433.4(2) Å^3, Z = 4, D_{calc} = 1.327 Mg.m^{-3}. Number of collected / independent reflections was 7769 / 2515; R_{int} = 0.0227. The final R indices [I>2σ(I)] : R1 = 0.0305, wR2 = 0.0800, the largest diff. peak and hole were 0.226and –0.243 e. Å^{-3}. Coordination have been deposited at the CCDC, deposition number CCDC 149677.
(6) Crystallographic data for 5: $C_{14}H_{14}N_4O$, M = 254.29, triclinic crystal system, S.G. P-2(1)/n, a = 5.1501(7) Å, b = 9.7940(13) Å, c = 12.647(2) Å, α= 99.786(11) °, β= 92.226(11) °, γ = 103.220(12)°, V = 610.0(2) Å^3, Z = 2, D_{calc} = 1.385 Mg.m^{-3} . Number of collected / independent reflections was 3329 / 2090; R_{int} = 0.0265. The final R indices [I>2σ(I)] : R1 = 0.0339, wR2 = 0.0833, the largest diff. peak and hole were 0.169 and -0.254 e. Å^{-3}. Coordination have been deposited at the CCDC, deposition number CCDC 149678.

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