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SYNTHESIS OF 2-AMINO-4H-3,1-BENZOXAZINES FROM DIPHENYL CYANOCARBONIMIDATE. FACILE REPLACEMENT OF THE N-CYANOIMINE FUNCTION BY NITROGEN NUCLEOPHILES

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The reaction of 2-aminobenzylalcohol (2) with diphenyl cyanocarbonimidate (1) gave 2-N-cyanoimino-4H-3,1-benzoxazine (3). The cyanoimino group can be readily replaced by amines to give a variety of 2-amino-4H-3,1-benzoxazines.

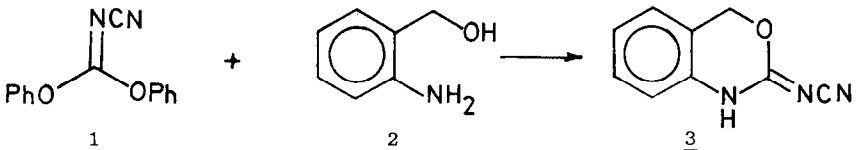
INTRODUCTION

Diphenyl cyanocarbonimidate (1) has found considerable use in the preparation of heterocyclic systems.[1] In common with a number of other one-carbon compounds that contain a divalently bound heteroatom and two singly bound electron-withdrawing groups,[2] it undergoes nucleophilic addition with subsequent loss of an electron-withdrawing group to restore the double bond and this process can occur twice. The reactions can be carried out sequentially with two different nucleophiles or a bidentate nucleophile can be used, in both cases mainly 5-membered ring heterocycles having been prepared.[1] In many of these reactions the cyanogroup has been involved in the cyclization step,[1] but we have recently shown that appropriately chosen nucleophiles can be added sequentially and cyclised through functional groups on the nucleophile rather than through the cyano group.[3] As part of the on-going investigation of 1 as a one carbon synthon, we have examined the reaction of 1 with 2-aminobenzyl alcohol (2), initially hoping that reaction would occur only at the amino group. We have found, however, that 2 acts as a bidentate nucleophile to give the 6-membered ring and that the N-cyanoimino group of the benzoxazine so formed is susceptible to further nucleophilic attack, leading to a general synthesis of 2-aminobenzoxazines. Previous synthetic methods for preparing 2-amino-4H-3,1-benzoxazines have involved reaction of 2 with isocyanates or isothiocyanates and subsequent cyclisation,[4] or reaction of 2-chloromethylisocyanates with amines.[5]

RESULTS AND DISCUSSION

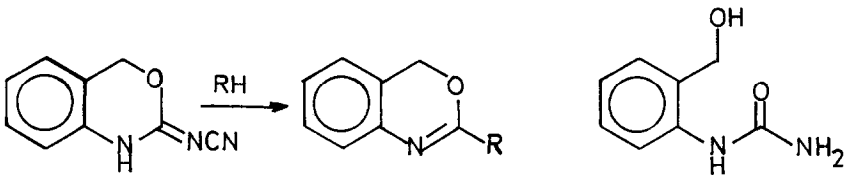
Treatment of 1 and 2-aminobenzyl alcohol in boiling 2-propanol gave 2-N-cyanoimino-4H-3,1-benzoxazine (3) in 61% yield. The mass spectral and analytical data were in accord with the assigned structure. The ^{1}H NMR spectrum showed signals at δ 11.51 (bs, 1H, NH), 7.32 (t, J = 8.0 Hz, 1H, H-7), 7.24 (d, J = 7.0 Hz, 1H, H-5), 7.13 (t, J = 7.5 Hz, 1H, H-6), 7.00 (d, J = 8.0 Hz, 1H, H-8), 5.53 (s, 2H, H-4), and the ^{13}C NMR spectrum showed signals at δ 159.3 (C-2), 133.3 (C-1a), 129.2 (C-7), 124.7 (C-5), 124.1 (C-6), 118.1 (C-4a), 114.8 (C-9), 114.7

(C-8), and 69.1 (C-4). The correlations were made by a 2D heteronuclear COSY experiment. We prefer the tautomer shown for the structure of 3 rather than that with the double bond endocyclic from the chemistry which follows.



1 2 3

Treatment of 3 with benzylamine in boiling propan-2-ol gave 2-benzylamino-1,3-benzoxazine (4a) in 79% yield. The melting point (130.5 - 132 °C) was similar to that in the literature (125 - 126 °C) and the spectroscopic data were in accord with the assigned structure (see Table). Nucleophilic addition appears to have occurred at the C=N carbon with subsequent ejection of H_2NCN. Presumably, even if one of the other groups is preferentially displaced, being attached by the other ligand it can then reundergo nucleophilic addition, whereas the H_2NCN group is lost. The NH group is now exocyclic and appears at much higher field in the ^1H NMR spectrum than the endocyclic NH proton in 3. The reaction of 3 with butylamine gave the corresponding 2-aminobenzoxazine 4b and similarly pyrrolidine gave 4c. Both of these reaction were also carried out in boiling 2-propanol but the reaction with ammonia had to be carried out in a sealed tube at 90 °C. Besides 2-amino-3,1-benzoxazine (4d), obtained in 41% yield, a small amount of 2-ureidobenzyl alcohol (5) was obtained, presumably arising from hydrolysis of 4d.

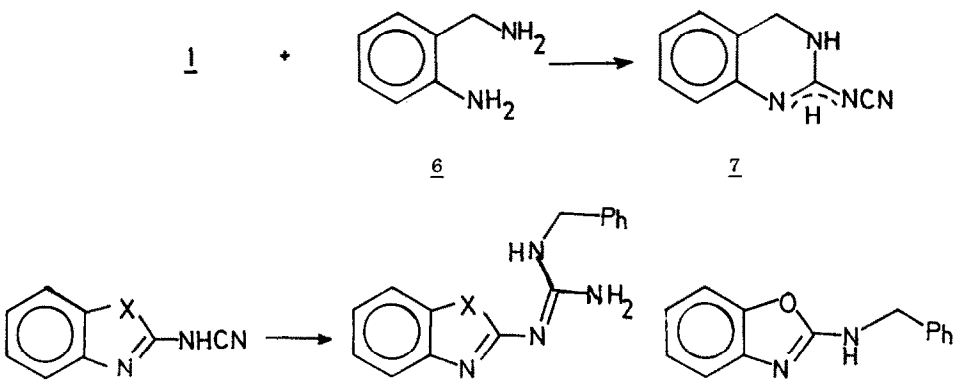


3 5

4a R = $NHCH_2Ph$
4b R = $NH(CH_2)_3CH_3$
4c R = $N(CH_2)_4$
4d R = NH_2

2-Aminobenzylamine (6) also acts as a bidentate ligand on reaction with 1, treatment in boiling 2-propanol giving 2-cyanoimino-3,4-dihydroquinazoline (7) in 76% yield. The mass spectral and analytical data were in accord with the assigned structure. The ^1H NMR spectrum showed absorptions at δ 10.2 (bs, 1H, NH), 8.12 (bs, 1H, NH), 7.18 (dt, J = 7.5, 1.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 6.98 (dt, J = 7.5, 1.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H) and 4.43 (s, 2H) and the ^{13}C NMR spectrum showed absorptions at δ 156.7, 135.1, 128.2, 126.1, 123.0, 117.8, 117.4, 114.8 and 42.1.

A number of attempts were made to react the N-cyanoimino group of 7 with amines in a way analogous to that with 3, but in all cases 7 was recovered unchanged. This difference in behaviour of two such closely related systems caused us to examine the N-cyano group in other systems.[6] 2-N-Cyanoaminobenzoxazole (8a) was prepared from 1 by the method of Webb and co-workers.[1] Treatment of 8a with benzylamine in boiling 2-propanol gave mainly (73%) the guanidine derivative 9a[3,4] together with 3% of 2-benzylaminobenzoxazole (10).[7] The mass spectrum of 9a was in accord with the assigned structure. The ^{1}H NMR spectrum (DMSO-d_6) showed a multiplet at δ 7.40-7.25 (8H), triplets at 7.13 (J = 7.0 Hz, 1H) and 7.04 (J = 7.4 Hz, 1H), and a doublet at 4.50 (J = 6.0 Hz, 2H) and the ^{13}C NMR spectrum had absorptions at δ 166.1, 158.1, 146.6, 142.4, 128.4, 127.2, 127.1, 127.0, 121.1, 115.5, 108.7 and 43.8.



Clearly in these systems the cyano group is more susceptible to nucleophilic addition and we presume this is at least partly due to the aromatic nature of the oxazole or imidazole ring which reduces the propensity to addition at C-2. It could also be argued that we have changed the group, since double bond migration has occurred, giving the N-cyanoamino rather than the N-cyanoimino derivative. That this is not likely to be the sole reason for this change of behaviour, however, finds support from the lack of reactivity of 7. There thus appear to be a number of factors determining the reactivity of the N-cyanoimino group and we are continuing to examine its behaviour in other environs in an attempt to elucidate them. It would seem probable that in those cases where the N-cyanoimino group is in a similar environment to 3 it will be susceptible to replacement and this extends the value of 1 as a one-carbon synthon.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on Varian VXR-400 or XL-200 spectrometers and are reported in δ units with Me_4Si as internal standard. Mass spectra were obtained on a VG-7070F spectrometer. IR spectra were obtained on Perkin-Elmer PE983 or PE781 spectrophotometers as KBr discs. Melting points were recorded on a Kofler hot-stage melting point apparatus and are uncorrected. Silica gel for chromatography was Woelm 32-63, 60A.

Table

Compound	^{1}H NMR and ^{13}C NMR Spectra, DMSO-d_6, δ
4a R = $PhCH_2NH$	^{1}H NMR, 7.47 (bs, 1H), 7.32 (m, 4H), 7.23 (m, 1H), 7.12 (dt, J = 7.5, 1.0 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 6.87 (dt, J = 7.5, 1.0 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 5.10 (s, 2H), 4.41 (bs, 2H); ^{13}C NMR, 155.1, 143.1, 139.9, 128.4, 128.2, 127.2, 126.7, 123.8, 121.6, 121.4, 120.9, 66.5, 44.0.
4b R = $NH(CH_2)_3CH_3$	^{1}H NMR, 7.11 (dt, J = 7.5, 1.0 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 6.88 (bs, 1H), 6.84 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 5.05 (s, 2H), 3.15 (m, 2H), 1.46 (m, 2H), 1.30 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR, 154.8, 143.4, 128.4, 123.7, 121.5, 121.1, 120.8, 66.3, 40.3, 31.2, 19.6, 13.8.
4c R = $N(CH_2)_4$	^{1}H NMR 7.12 (dt, J = 7.5, 1.5 Hz, 1H), 6.98 (dd, J = 7.5, 1.0 Hz, 1H), 6.84 (dt, J = 7.5, 1.0 Hz, 1H), 6.79 (dd, J = 8.0, 1.0 Hz, 1H), 5.14 (s, 2H), 3.39 (t, 4H), 1.84 (m, 4H); ^{13}C NMR, 153.3, 143.6, 128.5, 123.7, 121.0, 120.9, 120.7, 66.8, 46.2, 24.8.
4d R = NH_2	^{1}H NMR 7.12 (dt, J = 7.5, 1.0 Hz, 1H), 6.98 (d, J = 6.5 Hz, 1H), 6.86 (dt, J = 7.5, 1.0 Hz, 1H), 6.74 (d, J = 7.5 Hz, 1H), 6.52 (bs, 2H), 5.08 (s, 2H); ^{13}C NMR, 156.0, 143.6, 128.4, 123.7, 121.2, 121.1, 120.3, 66.2.

Preparation of 2-N-cyanoimino-1H,4H-3,1-benzoxazine (3) Diphenyl cyanocarbonimidate (1) (19.35 g, 81 mmol) and 2-aminobenzyl alcohol (2) (10.00 g, 81.3 mmol) were added to 2-propanol (80 mL) and the mixture stirred for 22 h. The resulting precipitate was removed by filtration, dried under reduced pressure and recrystallized from ethanol:water (1:1) as 3, 8.612 g, 49.8 mmol (61%), white crystals, mp 213 - 220 °C. MS *m/e* 173 (M^+, 95), 132 (100); ^{1}H NMR, see discussion; ^{13}C NMR, see discussion; IR 3424, 2922, 2195, 1648, 1639, 1595 cm^{-1}. Anal. Calcd for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.26. Found: C, 62.35; H, 4.05; N, 24.35.

Reaction of 3 with Benzylamine The benzoxazine 3 (0.200 g, 1.16 mmol) and benzylamine (0.136 g, 1.27 mmol) were added to 2-propanol (2 mL) and the mixture heated under reflux for 6 h. Crystals separated on cooling and the mixture was allowed to stand at room temperature for 14 h. The crystals were collected by filtration, washed with a little 2-propanol and dried under reduced pressure to give 4a, 0.219 g, 0.92 mmol (79%), mp 130.5 - 132 °C, lit[5] 125 - 126 °C. MS *m/e* 238 (M^+, 33), 106 (100); ^{1}H NMR, see Table; ^{13}C NMR, see Table; IR 3158, 3024, 2926, 1657, 1598, 1581, 1483, 1415 cm^{-1}.

Reaction of 3 with butylamine The reaction was carried out essentially as for benzylamine to give 4b (63%), mp 92.5 - 94.5 °C, lit[5] 91 - 92 °C. MS *m/e* 204 (M^+, 36), 132 (100); ^{1}H NMR, see Table; ^{13}C NMR, see Table; IR 3330, 2956, 2923, 1653, 1599, 1484 cm^{-1}.

Reaction of 3 with pyrrolidine The reaction was carried out essentially as for benzylamine. The resulting oil was purified by column chromatography, eluting with CH_2Cl_2:ether (15:1) to give 4c (58%), mp 70 - 70.5 °C, lit[5] 69 - 70 °C. MS *m/e* 202 (M^+, 78), 70 (100); ^{1}H NMR, see Table; ^{13}C NMR, see Table; IR 2959, 2872, 1620, 1578, 1481, 1455, 1333 cm^{-1}.

Reaction of 3 with ammonia Aqueous ammonia (10 mL, 0.880 g) and 3 (0.600 g, 3.47 mmol) were put into a glass tube which was then sealed. The tube was heated in an oil bath at 90 °C for 2 h when the contents had become straw coloured. The contents were frozen and the tube opened and allowed to come to room temperature. The solid was removed by filtration and dried under reduced pressure to give 4d (0.142 g, 28%). The solvent was removed from the filtrate under reduced pressure and the residue purified by column chromatography, eluting with CH_2Cl_2:MeOH (20:1) to give 4d (0.067 g, 13%), 5 (0.020 g, 3%) and unchanged 3 (0.036 g, 6%). A sample of 4d was recrystallized from benzene, mp 169 - 171 °C, lit[4] 160 °C. MS *m/e* 148 (M^+, 86), 78 (100); ^{1}H NMR, see Table; ^{13}C NMR, see Table; IR 3437, 3317, 3141, 2922, 2854, 1664, 1604, 1584, 1569 cm^{-1}. Compound 5, mp 159 - 161 °C, lit[4] *ca* 180 °C; MS *m/e* 166 (M^+, 51), 43 (100); ^{1}H NMR (DMSO-d_6) δ 7.79 (dd, J = 8.0, 1.0 Hz, 1H), 7.26 (dd, J = 7.5, 1.5 Hz, 1H), 7.16 (dt, J = 7.5, 1.0 Hz, 1H), 6.94 (dt, J = 7.5, 1.0 Hz, 1H), 6.15 (bs, 2H, NH), 4.45 (s, 2H); IR 3412, 3320, 3159, 2999, 1658, 1578, 1545, 1391 cm^{-1}.

Preparation of 2-Cyanoimino-1,2,3,4-tetrahydroquinazoline (7) 2-Aminobenzylamine (6) (0.200 g, 1.64 mmol) and 1 (0.389 g, 1.63 mmol) were dissolved in 2-propanol and the solution heated to reflux for 15 h. The solvent was removed under reduced pressure and the residual solid triturated with ether. The undissolved solid was removed by filtration and was then extracted with CH_2Cl_2 in a soxhlet extractor. The residual solid in the extractor was collected as 7. On cooling the CH_2Cl_2 a solid precipitated which was recovered by filtration as 7 and combined with that from the extractor, 0.213 g, 1.24 mmol (76%), mp 255 - 258 °C. MS *m/e* 172 (M^+, 100); ^{1}H NMR, see discussion; ^{13}C NMR, see discussion; IR 3432, 3211, 2177, 1654, 1618, 1559, 1495 cm^{-1}. Anal. Calcd for $C_9H_8N_4$: C,

62.78; H, 4.68; N, 32.54. Found: C, 62.80; H, 4.83; N, 32.20.

Reaction of 7 with benzylamine Benzylamine (0.068 g, 0.64 mmol) and 7 (0.100 g, 0.58 mmol) were dissolved in DMF and heated to reflux for 6 h. The recovered solid (0.073 g) was identified as unchanged 7 (73%).

Reaction of 2-N-Cyanoaminobenzoxazole (8a) with benzylamine Benzylamine (0.189 g, 1.77 mmol) and 8a[1] (0.250 g, 1.57 mmol) were added to 2-propanol (5 mL) and the mixture heated to reflux for 15 h. The volume was reduced to *ca* 2 mL by evaporation and the precipitated white solid removed by filtration, washed with 2-propanol and dried under reduced pressure as 9a (0.278 g). The solvent was removed from the filtrate to give a yellow oil that was purified by chromatography eluting with CH_2Cl_2:MeOH (65:1) to give 9a (0.026 g) and 10, 0.019 g, 0.08 mmol (5%). The combined yield of 9a was 0.304 g, 1.14 mmol (73%), mp 168 - 169 °C, MS *m/e* 266.1169 ($C_{15}H_{14}N_4O$ required 266.1168), 266 (M^+, 40), 91 (100); ^1H NMR, see discussion; ^{13}C NMR, see discussion; IR 3471, 3158, 2198, 1629, 1614, 1594, 1542, 1494 cm^{-1}.

2-Benzylaminobenzoxazole (10), mp 113 - 114 °C, lit[7] 115 - 116 °C, MS *m/e* 224.0966 ($C_{14}H_{12}N_2O$ requires 224.0949), 224 (M^+, 42), 91 (100); ^1H NMR (DMSO-d_6) δ 8.48 (t, 1H), 7.40-7.32 (m, 5H), 7.26 (m, 2H), 7.11 (dt, J = 7.5, 1.0 Hz, 1H), 6.98 (dt, J = 7.5, 1.5 Hz, 1H), 4.52 (d, J = 6.0 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 160.4, 146.0, 141.0, 137.0, 126.3, 125.1, 125.0, 121.5, 118.1, 113.5, 106.5, 43.6; IR 3434, 2918, 2865, 1668, 1587, 1462, 1373 cm^{-1}.

Reaction of 2-Cyanoaminobenzimidazole (8b) with benzylamine Benzylamine (0.226 g, 2.12 mmol) and 8b[1] (0.223 g, 1.41 mmol) were added to DMF (5 mL) and the mixture heated to reflux for 15 h. The solvent was removed under reduced pressure and the resulting brown oil purified by chromatography, eluting with CH_2Cl_2:cyclohexane (1:1) to give 9b, 0.103 g, 0.39 mmol (28%), recrystallized from benzene, mp 145 - 146 °C. MS *m/e* 265 (M^+, 81), 49 (100), ^1H NMR (DMSO-d_6) δ 11.11 (bs, 1H), 7.35 (m, 6H), 7.25 (m, 1H), 7.16 (bs, 2H), 6.92 (m, 2H), 4.49 (d, J = 6 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 158.8, 157.5, 140.1, 128.3, 127.2, 126.8, 119.5, 119.3, 43.7; IR 3448, 3326, 3194, 1658, 1619, 1584, 1539, 1513 cm^{-1}. Anal. Calcd for $C_{15}H_{15}N_5$: 67.91; H, 5.70; N, 26.40. Found: C, 67.62; H, 5.93; N, 26.43.

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