REACTION OF o-ISOCYANATOBENZOYL CHLORIDE WITH CYANOTRIMETHYLSILANE. FORMATION OF 4-OXO-4H-BENZOXAZINE-2-CARBONITRILE AND ITS RING TRANSFORMATION TO 3,4-DIHYDRO-1H-1,3,4-BENZOTRIAZEPINE-2,5-DIONES

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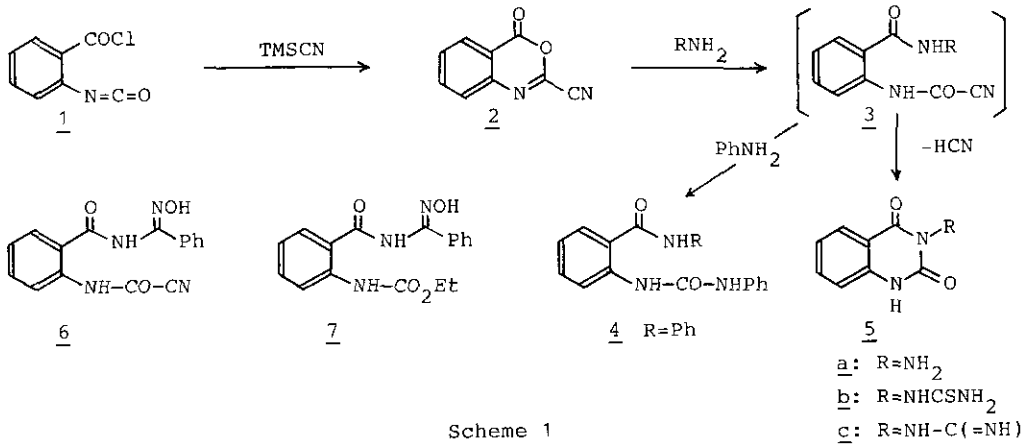
Abstract——— Reaction of o-isocyanatobenzoyl chloride (1) with cyanotrimethylsilane gave 4-oxo-4H-3,1-benzoxazine-2-carbonitrile (2), which was transformed to 3,4-dialkyl-3,4-dihydro-1H-1,3,4-benzotriazepine-2,5-diones (9) on treatment with 1,2-dialkylhydrazines. Halogenation of 9 gave 7-halotriazepines 10.

Cyanotrimethylsilane (TMSCN)[1] reacts with acyl chlorides to give acyl cyanide.[2] On the other hand, it reacts with isocyanates to afford 5-iminodiazolidinediones through cyanoformamide intermediate.[3] In the course of studies on the synthesis of heterocycles using organosilicon reagents,[4] o-isocyanatobenzoyl chloride (1) attracted our attension since it has two reactive groups mentioned above in the ortho position in a benzene ring. The reaction of 1 with TMSCN appears to give a new functionalized benzene derivative, which would serve as a building block for heterocycles. However, the reaction proceeded in an unexpected way to give 4-oxo-4H-3,1-benzoxazine-2-carbonitrile (2). Then, we have studied the reactivities of this relatively unknown heterocycle[5] and found its ring transformation to 3,4-dihydro-1H-1,3,4-benzotriazepine-2,5-diones (9). Treatment of 1 with excess TMSCN in chloroform under reflux gave 2[6] in 54% yield (Scheme 1). This cyclization process is similar to that found by Misra et al.,[7] who reported the formation of 2-phenyl-4H-3,1-benzoxazin-4-one from 1 and phenylmagnesium bromide. 2-Alkyl- or aryl-4H-3,1-benzoxazin-4-ones (acylanthranils) are known to undergo ring opening to yield o-amidobenzamide or 2,3-disubstituted quinazolin-4-ones on treatment with amines.[8] However, the reaction of 2 with amines would proceed in a different way because of the presence of the cyano group as a good leaving group. Indeed, when a mixture of 2 and aniline in chloroform



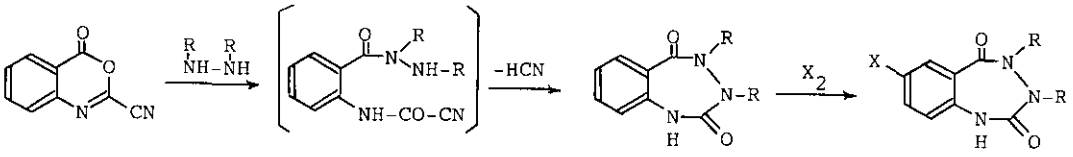
Scheme 1

was stirred at room temperature, urea 4[9] was obtained in 45% yield, whereas 3-substituted quinazoline-2,4-diones 5a[10] (54%), 5b (57%), and 5c (61%) were formed on treatment with hydrazine hydrate, thiosemicarbazide, and 2-pyridine-carboxamidrazone, respectively. Formation of 4 and 5 could be explained by assuming cyanoformamides 3 as the intermediates. In fact, cyanoformamide 6 corresponding to the intermediates 3 was isolated in 64% yield from the reaction mixture of 2 and benzamidoxime in chloroform, and attempted recrystallization of 6 from ethanol afforded urethane 7. The tendency of ready elimination of hydrogen cyanide from 3 seems to be different from simple cyanoformamide reported recently as a good precursor for heterocycles.[11]

These results suggest that 1,3,4-benzotriazepine-2,5-diones would be obtained through the intermediates 8 by the use of 1,2-disubstituted hydrazines as nucleophiles (Scheme 2). When a mixture of 2 and 1,2-dimethylhydrazine hydrochloride in pyridine in the presence of triethylamine was stirred at room temperature for 2 h, 3,4-dimethyl-3,4-dihydro-1H-1,3,4-benzotriazepine-2,5-dione (9a)[10] was obtained in 62% yield. Other triazepines 9b (46%) and 9c (19%) were also prepared in a similar manner. Our attempt to synthesize 9 directly from 1 and 1,2-dialkylhydrazines resulted in the formation of untractable materials, although 4-methyl-3,4-dihydro-1H-1,3,4-benzotriazepine-2,5-dione was reported[10] to be obtained from 1 and methylhydrazine only in 14.4% yield. Concerning a ring transformation of 3,1-benzoxazines to 1,3,4-benzotriazepines Bitter et al.[12] have reported that 2-dimethylamino-4H-3,1-benzoxazin-4-one hydrochloride reacted with methylhydrazine to give 4-methyl-3,4-dihydro-1H-1,3,4-benzotriazepine-2,5-dione, while hydrazine and phenylhydrazine took a different course to yield 3-amino-

quinazoline-2,4-diones. Our method described here would be a more general route from 3,1-benzoxazines to 1,3,4-benzotriazepines.

Since little is known about the derivatives and reactivities of 1,3,4-benzotriazepine-2,5-diones,[13] halogenation of 9 has been undertaken. The C-7 and C-9 positions of 9 appear to be the active sites as a result of orientation effect of both an amide moiety at the C-5a position and an amine one at the C-9a position. Chlorination of 9a in carbon tetrachloride by passing chlorine in the presence of iodine as a catalyst[14] gave 7-chloro-3,4-dihydro-1H-1,3,4-benzotriazepine-2,5-dione (10a)[10] in 65% yield. Bromination of 9a with bromine in carbon tetrachloride at room temperature yielded 7-bromo derivative 10c in 76% yield. Other products 10b (71%) and 10d (83%) were similarly prepared and all the proton resonances in the region of aromatic protons in the ^{1}H-nmr spectra of 10a-d showed the same coupling patterns, indicating that halogenation occurred selectively at the C-7 position.



2 8

9a: R=Me
b: R=Et
c: R=iso-Pr

10a: X=Cl R=Me
b: R=Cl R=Et
c: X=Br R=Me
d: R=Br R=Et

Scheme 2

EXPERIMENTAL

4-Oxo-4H-3,1-benzoxazine-2-carbonitrile (2)

A mixture of 1[9] (182 mg, 1.0 mmol) and cyanotrimethylsilane (298 mg, 3.0 mmol) in $CHCl_3$ (5 ml) was refluxed under nitrogen atmosphere for 10 h. After evaporation of the solvent, water was added to the residue and the mixture was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and the solvent was removed to give a residue, which was pulverized and extracted with hot hexane. Concentration followed by cooling of the extract yielded precipitates, which were collected by filtration to give 2 (93 mg, 54%). Recrystallization from benzene gave white needles, mp 125-126°C (lit.[6] mp 123°C). Ms: m/z 172 (M^+). Ir (KBr): 2250, 1780, 1620, 1600, 1475, 1460 cm^{-1}.

N-(2,4-Dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)thiourea (5b)

Thiourea 5b (134 mg, 57%) was prepared by refluxing a mixture of 2 (172 mg, 1.0 mmol) and thiosemicarbazide (91 mg, 1.0 mmol) in EtOH (5 ml) for 1.5 h. Mp 242-243°C (MeOH). Ir (KBr): 3360-2850, 1715, 1665, 1615, 1595, 1515, 1480, 1435 cm^{-1}.

Ms: m/z 236 (M^+). Anal. Calcd for $C_9H_8N_4O_2S$: C, 45.76; H, 3.41. Found: C, 45.66; H, 3.61.

N-(2,4-Dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)-2-pyridinecarboxamidine (5c)

Amidine 5c (176 mg, 61%) was prepared by stirring a mixture of 2 (172 mg, 1.0 mmol) and 2-pyridinecarboxamidrazone[15] (136 mg, 1.0 mmol) in $CHCl_3$ (5 ml) for 1 h at room temperature. Mp 272-275°C (MeOH). Ir (KBr): 3420-2930, 1715, 1650, 1625, 1580, 1560, 1490, 1440 cm^{-1}. Ms: m/z 281 (M^+). Anal. Calcd for $C_{14}H_{11}N_5O_2 \cdot 1/2 H_2O$: C, 57.92; H, 4.17. Found: C, 57.85; H, 4.00.

N-[o-(Cyanoformamido)benzoyl]benzamidoxime (6)

A mixture of 2 (172 mg, 1.0 mmol) and benzamidoxime (136 mg, 1.0 mmol) in $CHCl_3$ (10 ml) was stirred for 30 min at room temperature. The precipitates formed were filtered off and recrystallized from $CHCl_3$ to give 6 (198 mg, 64%), mp 157-166°C. Ir (KBr): 3470-3100, 2230, 1710, 1605, 1590, 1525, 1450 cm^{-1}. Ms: m/z 281 (M^+-HCN). Anal. Calcd for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92. Found C, 61.92; H, 4.07.

N-[o-(Ethoxycarbamoyl)benzoyl]benzamidoxime (7)

Attempted recrystallization of 6 (263 mg) from EtOH gave white needles (120 mg, 43 %), mp 164-166°C. Ir (KBr): 3480, 3300, 1725, 1700, 1615, 1585, 1525, 1445 cm^{-1}. Nmr (DMSO-d_6): δ1.27 (t, J=7 Hz, 3H), 4.14 (q, J=7 Hz, 2H), 7.22-8.32 (m, 11H), 10.27 (s, 1H). Ms: 327 (M^+). Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.37; H, 5.24. Found: C, 62.48; H, 5.29.

3,4-Dimethyl-3,4-dihydro-1H-1,3,4-benzotriazepine-2,5-dione (9a)

A mixture of 2 (172 mg, 1.0 mmol), 1,2-dimethylhydrazine hydrochloride (133 mg, 1.0 mmol), and triethylamine (202 mg, 2.0 mmol) in pyridine (10 ml) was stirred at room temperature for 2 h. After evaporation of the solvent water was added to the residue and the aqueous mixture was extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to give a solid, which was recrystallized from CCl_4 to afford white powders (125 mg, 62%), mp 188-189°C (lit.[10] mp 185-188°C). Compounds 9b and c were prepared in a similar manner and purified by recrystallization.

3,4-Diethyl-3,4-dihydro-1H-1,3,4-benzotriazepine-2,5-dione (9b)

46% Yield. Mp 188-189°C (hexane-$CHCl_3$). Ir (KBr): 3250, 2970, 1690, 1615, 1480, 1440 cm^{-1}. Nmr (DMSO-d_6): δ0.90 (t, J=7 Hz, 3H), 1.10 (t, J=7 Hz, 3H), 2.93-4.33 (m, 4H), 6.97-7.73 (m, 4H), 9.25 (s, 1H). Ms: m/z 233 (M^+). Anal. Calcd for $C_{12}H_{15}N_3O_2 \cdot 1/2H_2O$: C, 59.49; H, 6.24. Found: C, 59.50; H, 6.23.

3,4-Diisopropyl-3,4-dihydro-1H-1,3,4-benzotriazepine-2,5-dione (9c)

19% Yield. Mp 73-76°C (hexane). Ir (KBr): 3500, 3200, 2980, 1680, 1620, 1445, 1405 cm^{-1}. Nmr (acetone-d_6): δ1.05-1.47 (m, 12H), 3.50-4.41 (m, 2H), 6.96-7.78 (m, 4H), 8.21 (s, 1H). Ms: m/z 261 (M^+). Anal. Calcd for $C_{14}H_{19}N_3O_2 \cdot H_2O$: C, 60.19; H, 7.58. Found: C, 60.26; H, 7.70.

7-Chloro-3,4-dimethyl-3,4-dihydro-1H-1,3,4-benzotriazepine-2,5-dione (10a)

Into a stirred solution of 9a (214 mg, 1.0 mmol) in CCl_4 (10 ml) chlorine gas was passed slowly at room temperature for 5 min. To this mixture a solution of iodine (20 mg) in CCl_4 (5 ml) was added and chlorine was further passed for additional 10 min (total amount of chlorine 1.5 g). After evaporation of the solvent water was added to the residue and the aqueous mixture was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and evaporated to give a solid, which was recrystallized from CH_2Cl_2-EtOH to afford white powders (165 mg, 65%), mp 219-221°C (lit.[10] mp 218-220°C). Ir (KBr): 3230, 3150, 2920, 1700, 1620, 1485, 1450 cm^{-1}. Nmr (DMSO-d_6): δ2.92 (s, 3H), 3.18 (s, 3H), 7.06 (d, J=8 Hz, H_9), 7.46 (dd, J=2 and 8 Hz, H_8), 7.59 (d, J=2 Hz, H_6), 9.53 (s, 1H).

7-Chloro-3,4-diethyl-3,4-dihydro-1H-1,3,4-benzotriazepine-2,5-dione (10b)

The compound 10b was prepared according to the same method as mentioned above. 71% Yield. Mp 236-238°C (CH_2Cl_2-EtOH). Ir (KBr): 3240, 3160, 2980, 1695, 1625, 1480, 1450 cm^{-1}. Nmr (DMSO-d_6): δ0.88 (t, J=7 Hz, 3H), 1.09 (t, J=7 Hz, 3H), 2.92-4.31 (m, 4H), 7.03 (d, J=8 Hz, H_9), 7.45 (dd, J=2 and 8 Hz, H_8), 7.61 (d, J=2 Hz, H_6), 9.43 (s, 1H). Ms: m/z 267 (M^+). Anal. Calcd for $C_{12}H_{14}ClN_3O_2$: C, 53.84; H, 5.27. Found: C, 53.30; H, 5.25.

7-Bromo-3,4-dimethyl-3,4-dihydro-1H-1,3,4-benzotriazepine-2,5-dione (10c)

To a stirred solution of 9a (214 mg, 1.0 mmol) in CCl_4 (10 ml) a solution of bromine (0.1 ml) in CCl_4 (5 ml) was added and the mixture was stirred at room temperature for 5 h. After evaporation of the solvent, water was added to the residue and the aqueous mixture was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and evaporated to give a solid, which was recrystallized from CH_2Cl_2-EtOH to give white powders (215 mg, 76%), mp 241-245°C. Ir (KBr): 3230, 3150, 2920, 1695, 1480, 1450 cm^{-1}. Nmr (DMSO-d_6): δ2.89 (s, 3H), 3.16 (s, 3H), 7.03 (d, J=8 Hz, H_9), 7.56 (dd, J=2 and 8 Hz, H_8), 7.71 (d, J=2 Hz, H_6), 9.55 (s, 1H). Ms: m/z 283 (M^+). Anal. Calcd for $C_{10}H_{10}BrN_3O_2$: C, 42.28; H, 3.55. Found: C, 42.48; H, 3.60.

7-Bromo-3,4-diethyl-3,4-dihydro-1H-1,3,4-benzotriazepine-2,5-dione (10d)

The compound 10d was prepared according to the same method as mentioned above.

83% Yield. Mp 255-257°C (CH_2Cl_2-EtOH). Ir (KBr): 3230, 3150, 2970, 1695, 1620, 1480, 1450 cm^{-1}. Nmr (DMSO-d_6): δ 0.91 (t, J=7 Hz, 3H), 1.10 (t, J=7 Hz, 3H), 2.94-4.34 (m, 4H), 7.03 (d, J=8 Hz, H_9), 7.57 (dd, J=2 and 8 Hz, H_8), 7.75 (d, J= 2 Hz, H_6), 9.47 (s, 1H). Ms: m/z 311 (M^+). Anal. Calcd for $C_{12}H_{14}BrN_3O_2$: C, 46.17; H, 4.52. Found: C, 45.96; H, 4.51.

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