REACTION OF 3,4-DIBENZOYL-1,2,5-THIADIAZOLE WITH ETHYLAMINE DERIVATIVES. FORMATION OF SCHIFF BASES AND THEIR BASE-CATALYZED RING CLOSURE REACTIONS

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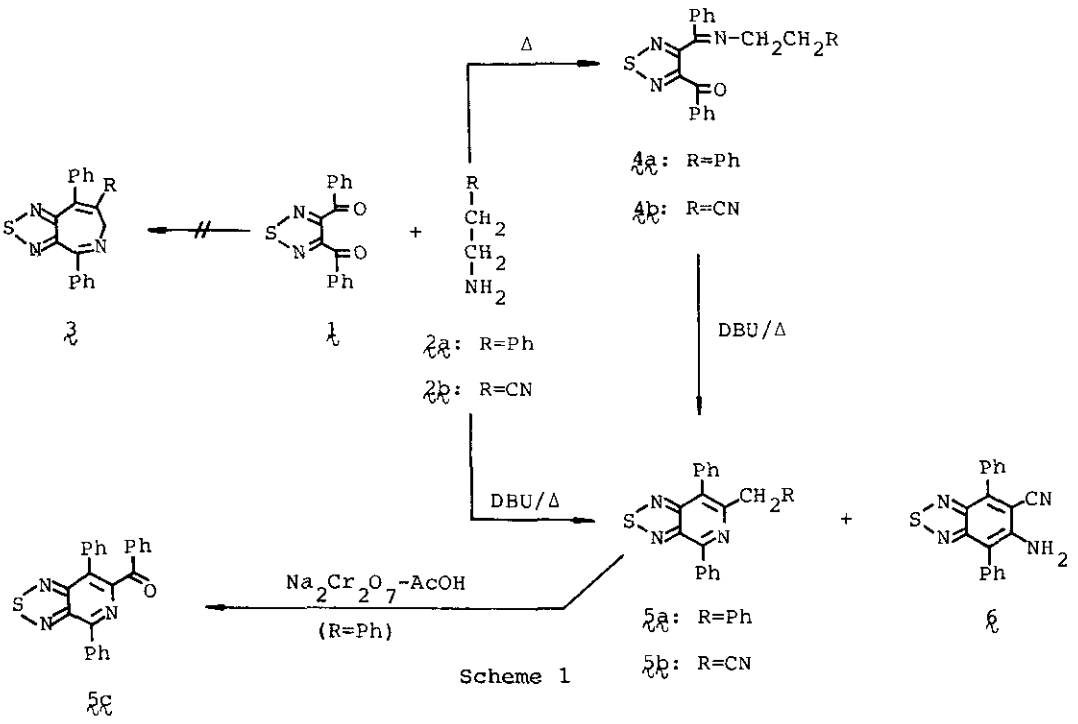
Abstract —— The reaction of 3,4-dibenzoyl-1,2,5-thiadiazole (1) with phenethylamine (2a) and β-aminopropionitrile (2b) gave the corresponding Schiff bases (4a and 4b), which, on treatment with DBU, cyclized into thiadiazolopyridines (5a and 5b). Compound 5a or 5b was directly obtained in the reaction of 1 and 2 in the presence of DBU. The reaction with α,β-diphenylethylamine (2c) gave the triphenylthiadiazolopyridine (5d) in poor yield. The Schiff base (4c) was obtained in the reaction with ethyl β-amino-β-phenylpropionate (2d) and treatment of 4c with a base afforded the pyrrolinyl-1,2,5-thiadiazole (7).

A variety of heterocycle-fused pyridines was prepared by the condensation reaction of dibenzoyl heterocyclic compounds with α-substituted methylamines.[1-4] Expecting the formation of thiadiazoloazepines (3), we investigated the reaction of 3,4-dibenzoyl-1,2,5-thiadiazole (1) with ethylamines (2) bearing an electron-withdrawing group on the β-carbon.

RESULTS AND DISCUSSION

The reaction of 1 with phenethylamine (2a) in refluxing toluene afforded the Schiff base 4a in 32% yield with a recovery of 1 in 38% yield. When 4a was treated with DBU, a cyclized compound 5a was obtained in 44% yield. Compound 5a was also obtained in 70% yield when 1 was heated in an excess of 2a with DBU[5] at 140-150°C for 6 h. However compound 5a was not the expected 3 but was proved to be 6-benzyl-4,7-diphenyl-1,2,5-thiadiazolo[3,4-c]pyridine from its oxidation by sodium dichromate to the 7-benzoyl derivative (5c).[2c]



Scheme 1

Compound 1 reacted with β-aminopropionitrile (2b) in refluxing toluene to give the Schiff base (4b) in 62% yield. On treatment with DBU in toluene under reflux, 4b afforded 6-cyanomethyl-4,7-diphenyl-1,2,5-thiadiazolo[3,4-c]pyridine (5b) in 17% yield. When a mixture of 1 and 2b was treated with DBU,[5] 5b was obtained in 38% yield, accompanied by 6 (1% yield), which might be formed via the initial condensation reaction between the activated β-methylene of 2b and the carbonyl group of 1.

The ^{1}H-nmr spectra of 4a and 4b in deuteriochloroform displayed two kinds of methylene signals. New signals came to appear with time and after 2 days, four kinds of methylene signals with equal intensities were observed as shown in the Figure. The recovered samples were identical with original 4a and 4b in all respects including the ^{1}H-nmr spectra. This suggests that 4 is present in the equilibrium between 4-1 and 4-2 in deuteriochloroform solution.

High field shift of the new β-methylene signal is due to the deshielding effect of the carbonyl group which situates above the β-methylene group in the form of 4-2.

As the expected azepines (3) were not obtained in the reaction of 1 with ethylamines (2a and 2b) having the unsubstituted α-methylene group, we investigated the reaction

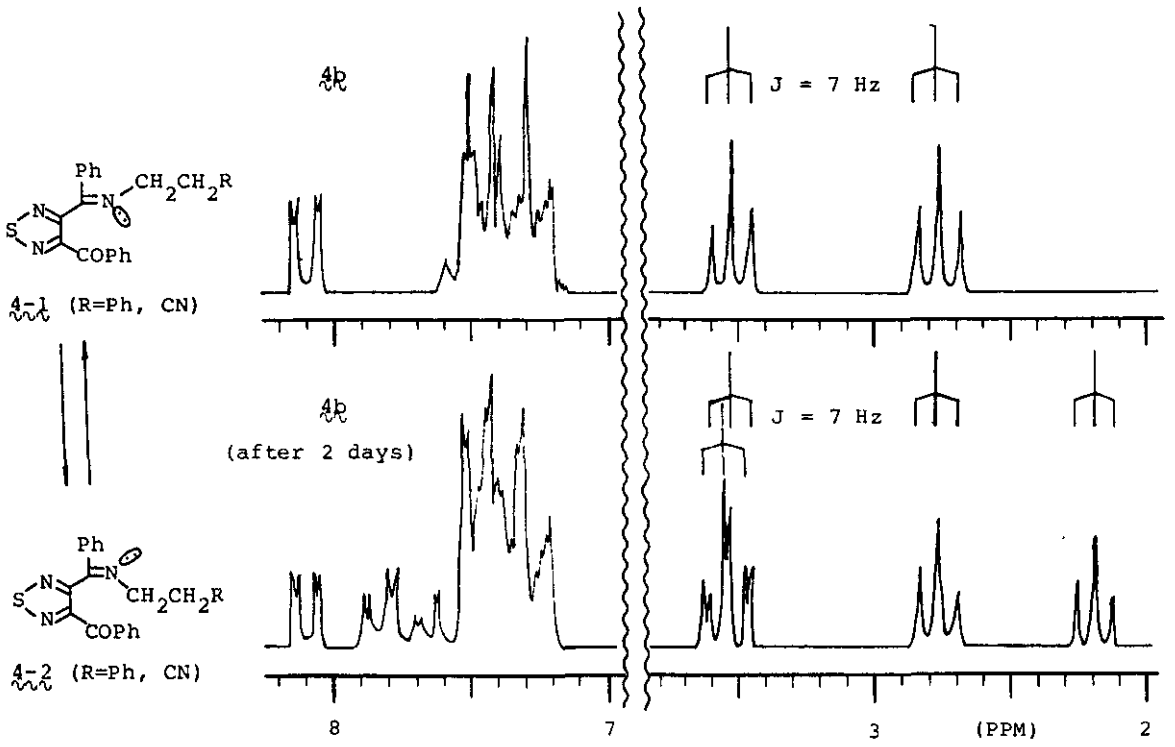
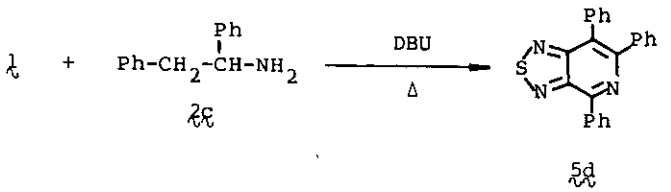


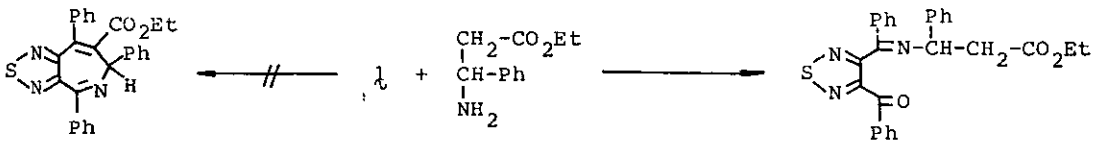
Figure. ^{1}H-nmr spectra of 4b in $CDCl_3$.

with α,β-diphenylethylamine (2c). A large amount of tarry materials was formed and 4,5,7-triphenyl-1,2,5-thiadiazolo[3,4-c]pyridine (5d)[1] was obtained in a poor yield, accompanied by a recovery of 1 in 17% yield.

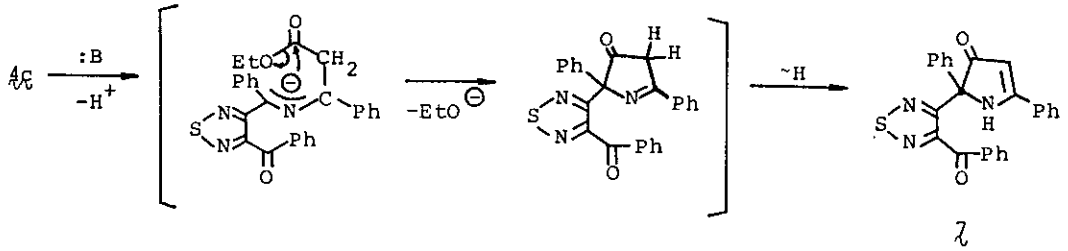


Therefore, we next investigated the reaction of 1 with the ethylamine (2d)[6] having phenyl and the electron-withdrawing ethoxycarbonyl function on the α and β carbons, respectively.

The Schiff base (4c) was obtained in 32% yield when the reaction was carried out in refluxing meta-xylene for 3 h.



Treatment of 4c with many kinds of base did not give the expected azepine and a large amount of resinous material was formed with benzoic acid. Compound 7 was isolated in a poor yield only when 4c was treated with sodium ethoxide or potassium hydroxide in refluxing ethanol. The structure of 7 was elucidated on the basis of analysis and spectral data. A tentative pathway for the formation of 7 is presented.



EXPERIMENTAL

All melting points are uncorrected. Ir spectra were measured on a Nippon Bunko A-102 spectrophotometer as potassium bromide pellets. ^{1}H-nmr spectra were determined at 100 MHz on a Nippon Denshi JEOL FT-100 in deuteriochloroform using TMS as an internal standard. Mass spectra were obtained on a Nippon Denshi JMS-01SG-2 mass spectrometer at 75 eV using a direct inlet system.

Reaction of 1 with 2a

(i) In the absence of DBU. After a mixture of 1 (300 mg) and 2a (370 mg) in toluene (20 ml) was refluxed for 24 h, the reaction mixture was condensed in vacuo and chromatographed on silica gel (Wako gel C-300). From benzene eluent was obtained 115 mg (38%) of unreacted 1 and from $CHCl_3$ eluent 129 mg (32%) of N-[3-(4-benzoyl)-1,2,5-thiadiazolyl]benzylidene-β-phenylethylamine (4a): colorless prisms (hexane) of mp 80-83°C; ir, $\nu_{C=O}$ 1645 cm^{-1}; ms: m/e (relative intensity) 397 (M^+, 6), 306 (M^+ - $PhCH_2$, 52), 105 (100). Anal. Calcd for $C_{24}H_{19}N_3OS$: C, 72.52; H, 4.82; N, 10.57. Found: C, 72.40; H, 4.77; N, 10.29.

(ii) In the presence of DBU. After a mixture of 1 (200 mg) and DBU (0.5 ml) in 2a (10 ml) was heated at 140-150°C for 6 h, it was poured into dilute hydrochloric acid (100 ml) and extracted with chloroform (30 ml × 2). The extract was dried over sodium sulfate and evaporated in vacuo to leave the residue which, on trituration with benzene, afforded 178 mg of 5a: green needles (hexane) of mp 173-174°C; ms: m/e 379 (M^+, 100), 378 (79); ^{1}H-nmr: δ 4.30 (s, 2H), 7.22 (br s, 5H), 7.33-7.61

(m, 8H), 8.56-8.68 (m, 2H) ppm. Anal. Calcd for $C_{24}H_{17}N_3S$: C, 75.96; H, 4.52; N, 11.07. Found: C, 75.58; H, 4.49; N, 10.72.

Reaction of 1 with 2b.

(i) In the absence of DBU. A mixture of 1 (300 mg) and 2b (714 mg) in toluene was heated under reflux for 1 h and treated as described above. From benzene eluent was obtained 219 mg (62%) of N-[3-(4-benzoyl)-1,2,5-thiadiazolyl]benzylidene-β-cyanoethylamine (4b): colorless prisms (ethanol) of mp 120-121°C; ir, ν_{CN} 2245, $\nu_{C=O}$ 1660 cm^{-1}. Anal. Calcd for $C_{19}H_{14}N_4OS$: C, 65.88; H, 4.07; N, 16.17. Found: C, 65.82; H, 4.06; N, 15.98.

(ii) In the presence of DBU. A mixture of 1 (1000 mg), 2b (714 mg) and DBU (155 mg) in toluene (30 ml) was heated under reflux for 1 h and treated as described above. Unreacted 1 (15 mg) was eluted with a 1:1-mixture of benzene and hexane and 6-cyanomethyl-4,7-diphenyl-1,2,5-thiadiazolo[3,4-c]pyridine(5b) (419 mg, 38%) was eluted with benzene: pale green prisms (hexane) of mp 178-180°C; ir, ν_{CN} 2240 cm^{-1}; ms: m/e (relative intensity), 328 (M^+, 100), 302 (M^+-CN, 5), 77 (11); ^{1}H-nmr: δ 4.02 (s, 2H), 7.48-7.63 (m, 8H), 8.64-8.76 (m, 2H) ppm. Anal. Calcd for $C_{19}H_{12}N_4S$: C, 69.49; H, 3.68; N, 17.06. Found: C, 69.11; H, 3.67; N, 16.91.
Finally, 5-amino-6-cyanobenzo-2,1,3-thiadiazole (6) (10 mg, 1%) was eluted with chloroform: orange needles (hexane) of mp 204-206°C; ir, ν_{NH} 3440, 3340, ν_{CN} 2200 cm^{-1}; ms: m/e (relative intensity) 328 (M^+, 100), 77 (80); ^{1}H-nmr: δ 4.75 (br s, 2H, disappeared with D_2O), 7.30-7.82 (m, 10H) ppm. Anal. Calcd for $C_{19}H_{12}N_3S$: C, 69.49; H, 3.68; N, 17.06. Found: C, 69.34; H, 3.88; N, 16.63.

Conversion of 4a into 5a.

A mixture of 4a (50 mg) and DBU (0.3 ml) in toluene was heated under reflux for 4 h and evaporated in vacuo to leave the residue, which was chromatographed on silica gel to give 21 mg (44%) of 5a.

Oxidation of 5a.

After a mixture of 5a (50 mg) and sodium dichromate (120 mg) in acetic acid (10 ml) was heated under reflux for 20 h, it was poured into water (100 ml) and extracted with benzene (30 ml × 2). Evaporation of the extract afforded 21 mg (41%) of 5c.

Conversion of 4b into 5b.

A mixture of 4b (150 mg) and DBU (0.5 ml) in toluene was heated under reflux for 1 h and treated as described above to give 25 mg of 5b (17%).

Reaction of 1 with 2c.

A mixture of 1 (300 mg) and DBU (0.5 ml) in 2c (10 ml) was heated at 130-140°C for 24 h and poured into dilute hydrochloric acid (100 ml). It was extracted with benzene (50 ml) and the extract was evaporated in vacuo to leave the residue, which was chromatographed on silica gel. Unreacted 1 (52 mg) and 5d (6 mg) were eluted with benzene.

Preparation of 2d.

Compound 2d was obtained by the esterification of the acid with concentrated sul-

furic acid. This method is more convenient than the reported one[6] using dry hydrogen chloride.

To a mixture of β-amino-β-phenylpropionic acid (10 g) in ethanol (300 ml) was added concentrated sulfuric acid (20 ml) in small portions and the mixture was stirred at room temperature for overnight. It was poured into crashed ice (500 g), neutralized and extracted with benzene (50 ml × 2). Distillation of the extract afforded 8.7 g (74%) of 2d: bp 99°C/2 mmHg (lit.,[6] 130°C/5 mmHg).

Reaction of 1 with 2d.

After a mixtrue of 1 (1000 mg) and 2d (1000 mg) in meta-xylene (20 ml) was heated under reflux for 3 h, the solvent was evaporated in vacuo and the residue was subjected to chromatography on silica gel. Unreacted 1 (340 mg) and ethyl N-[3-(4-benzoyl)-1,2,5-thiadiazolyl]benzlidene-β-amino-β-phenylpropionate (2d) (512 mg) were eluted with benzene: colorless crystals (a 1:2-mixture of hexane and benzene) of mp 134-135°C; ir, $\nu_{C=O}$ 1725, 1675 cm^{-1}; ms: m/e (relative intensity), 469 (M^+, 26), 382 ($M^+-CH_2CO_2Et$, 36), 105 (88), 77 (100). Anal. Calcd for $C_{27}H_{23}N_3O_3S$: C, 69.06; H, 4.94; N, 8.95. Found: C, 69.08; H, 4.93; N, 8.69.

Reaction of 4c with sodium ethoxide.

Compound 4c (100 mg) was heated for 3 h in refluxing ethanol (20 ml) containing sodium ethoxide (144 mg). It was poured into water (50 ml), extracted with benzene and evaporated in vacuo to leave the residue, which was subjected to chromatography on silica gel to give 3-benzoyl-4-[5-(2,5-diphenyl)-Δ^2-pyrrolin-4-onyl]-1,2,5-thiadiazole (7) (7mg, 8%): colorless prisms (hexane) of mp 179-185°C; ir, ν_{NH} 3350, $\nu_{C=O}$ 1675 cm^{-1}; ms: m/e (relative intensity), 423 (M^+, 49), 278 (M^+-PhC_3NOH, 99), 77 (100); ^{1}H-nmr: δ 5.64, 5.65 (each s, 1H), 6.98-7.86 (m, 15H) ppm. Anal. Calcd for $C_{25}H_{17}N_3O_2S$: C, 70.90; H, 4.05; N, 9.92. Found: C, 70.61; H, 4.09; N, 9.62.

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2) S. Mataka, K. Takahashi, M. Tashiro and Y. Tsuda, ibid., 1980, 842.

3) S. Mataka, K. Takahashi, Y. Tsuda and M. Tashiro, Heterocycles, 1980, 14, 789.

4) S. Mataka, K. Takahashi and M. Tashiro, J. Heterocyclic Chem., 1980, 18, 1073.

5) When the reaction of 1 and 2 was carried out in the presence of DBU, a small amount of green needles (hexane) of mp 178-179°C was isolated. Its molecular formula corresponds to the 1:1-adduct of 1 and DBU with a loss of H_2O, but, structure is not known.

6) E. Fischer, H. Scheibler and R. Groh, Ber., 1910, 43, 2020.

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