The Use of Enamines in the Synthesis of Heterocycles (1)

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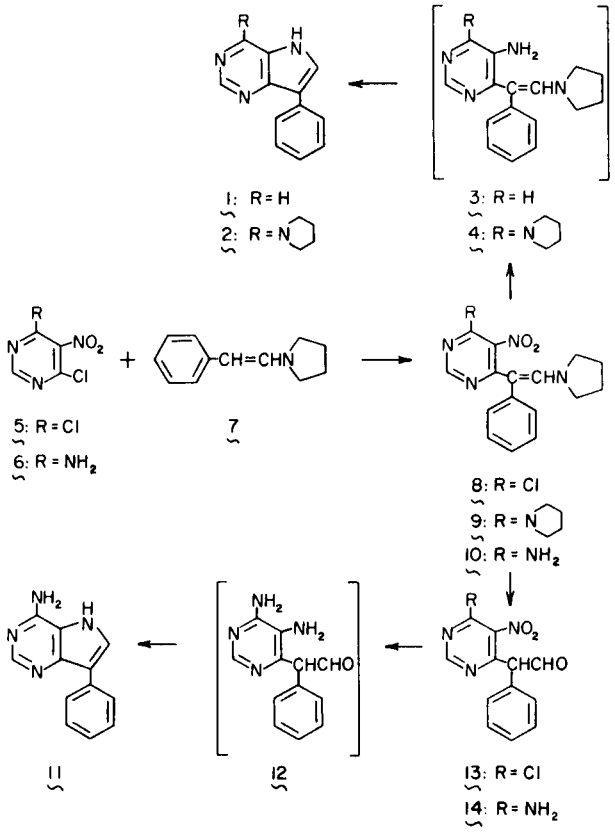
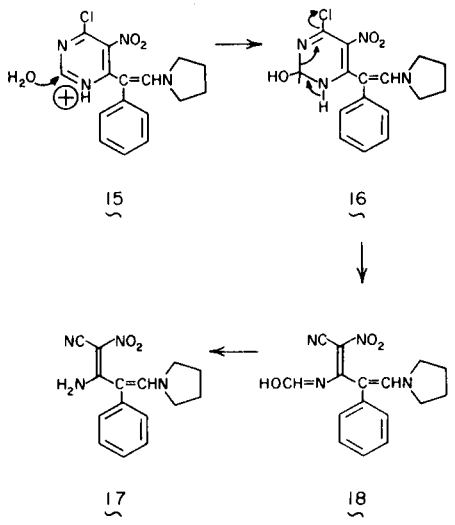
The reaction of the enamine *N*-styryl pyrrolidine with 4,6-dichloro-5-nitropyrimidine and 4-amino-6-chloro-5-nitropyrimidine was investigated. Reduction of resultant compounds was followed by spontaneous ring closure to the pyrrolo[3,2-*d*]pyrimidine ring system. This reaction sequence should provide a general method for the preparation of 4,7-disubstituted pyrrolo[3,2-*d*]-pyrimidines.

Some time ago in this laboratory we developed a synthesis of pyrrolo[3,2-*d*]pyrimidines (9-deazapurines) based on the reaction of 4,6-dichloro-5-nitropyrimidine (**5**) with ketene acetal (2). It occurred to us that a more general synthesis of this ring system, which could in fact lead to the preparation of the *C*-nucleoside 9-deazaadenosine, might be based on the reaction of this reactive chloropyrimidine (**5**) with enamines (3). As a model for this synthetic route, we decided to investigate the reaction of **5** with *N*-styryl pyrrolidine (**7**) (4). Reaction occurred exothermically in dichloromethane using triethylamine as the acid acceptor and gave a 67% yield of 1-(6-chloro-5-nitropyrimidin-4-yl)-2-pyrrolidinylstyrene (**8**) (Scheme 1). Reduction of the nitro group of **8** with Raney nickel proved difficult and very slow, in contrast to the facile reduction of other 4-chloro-5-nitro-6-substituted pyrimidines (5). A large excess of Raney nickel had to be employed and the reduction carried out for two days. Under these conditions reduction of the chloro group also occurred, although the sequence of the reduction is not known and may be mixed. In any event the product isolated was 7-phenylpyrrolo[3,2-*d*]pyrimidine (**1**) contaminated with 7-phenyl-4-pyrrolidinylpyrrolo[3,2-*d*]-pyrimidine (**2**), which presumably arose from the replacement of the chloro group of **8** by pyrrolidine generated



Scheme 1



Scheme 2

in the formation of **1** followed by reduction of the nitro group of **9** and spontaneous ring closure of **4**. It seemed likely that the bulky group at C-6 of **8** interfered with its orientation on the surface of the Raney nickel catalyst causing it to be reduced very slowly. Consequently, acid hydrolysis of the enamine **8** to the aldehyde **13** appeared to be a logical way to circumvent the problem. Acid hydrolysis of **8**, however, proceeded in an unexpected manner to give a product the mass spectrum of which (M^+ = 284) indicated the loss of chlorine and CH from **8**. The pmr spectrum of the product, obtained in 60% crude yield, confirmed its identity as 1-cyano-1-nitro-2-amino-3-phenyl-4-pyrrolidinylbutadiene (**17**). This truly remarkable reaction, considering the normal acid lability of enamines, is envisaged as resulting from the attack of water at C-2 of the protonated pyrimidine ring (**15**) as shown in Scheme 2. A similar ring cleavage has been observed by Clark *et al.* (6). To avoid this reaction we next tried the amination of **8** to the presumably more stable 1-(6-amino-5-nitropyrimidin-4-yl)-2-pyrrolidinylstyrene (**10**). Although mass spectral data and retrospective analysis of chromatographic data indicated that some of the desired product (**10**) was indeed formed, the reaction was a poor one giving a complex mixture of at least four components. We next examined the reaction of *N*-styryl pyrrolidine (**7**) with 4-amino-6-chloro-5-nitropyrimidine (**6**), even though this compound was considered less likely to react well with the enamine, since its chloro group is less reactive than those of 4,6-dichloro-5-nitropyrimidine (**5**) (7). In fact, the reaction of **6** with **7** was slower and yield of desired product (**10**) lower than with **5** but still quite satisfactory. The isolation of **10** by silica gel chromatography was undertaken, since it failed to crystallize, but the instability of **10** was such that the mildly acid silica gel caused hydrolysis of the enamine and the material isolated was 1-(6-amino-5-nitropyrimidin-4-yl)-phenylacetaldehyde (**14**). The contrast in stability of the enamine function of these two closely related compounds (**8** and **10**) bears further study. But the fortuitous hydrolysis of **10** to **14** allowed reduction of the nitro group to proceed in the usually facile manner. The intermediate diaminopyrimidine **12** could not be isolated as such but spontaneously cyclized to the desired 4-amino-7-phenylpyrrolo[3,2-*d*]pyrimidine (**11**). There seem to be no further obstacles to the application of this route to a number of enamines, allowing the preparation of a variety of 9-substituted pyrrolo[3,2-*d*]pyrimidines.

EXPERIMENTAL

Melting points were determined with a Mel-Temp apparatus and are not corrected. The uv spectra were determined in aqueous solution with a Cary Model 17 spectrophotometer. The ir spectra were determined in pressed KBr discs with a Perkin-Elmer Model 621 spectrometer. The pmr spectra were determined in DMSO-d_6 (TMS) with a Varian A-60A spectrometer; chemical shifts quoted for multiplets were measured from the approximate centers. Chromatographic analyses were carried out on tlc plates of silica gel H (Brinkmann). The spots were detected by uv light after spraying with Ultraphor (WT, highly concentrated) or by charring after spraying with aqueous ammonium sulfate.

The Reduction of 1-(6-Chloro-5-nitropyrimidin-4-yl)-2-pyrrolidinylstyrene.

A solution of 1-(6-chloro-5-nitropyrimidin-4-yl)-2-pyrrolidinylstyrene (745 mg., 2.25 mmoles) in ethyl acetate (150 ml.) was hydrogenated in a Parr shaker at room temperature at an initial pressure of 37 psi using Raney nickel (500 mg.) as catalyst. After 24 hours, additional fresh catalyst (1 g.) was added and hydrogenation was continued for another 24 hours. [Hydrogenation at atmospheric pressure required 4 days and a larger excess of catalyst]. The catalyst was removed by filtration through a Celite pad and washed well with ethyl acetate and ethanol; the filtrate and washings were evaporated to dryness. The residue was purified by column chromatography (23" Mallinckrodt SilicAR-TLC-7 pressure column, eluted with 9:1 chloroform methanol). The combined homogeneous fractions (300 mg.) were recrystallized from benzene (15 ml.) to give a cream colored solid (112 mg.) identified as 7-phenylpyrrolo[3,2-*d*]pyrimidine (**1**). λ max in nm: 0.1 *N* hydrochloric acid, *p*H 7-252; 0.1 *N* sodium hydroxide - 271.

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.82; H, 4.65; N, 21.53. Found: C, 73.42; H, 4.95; N, 20.88. Mass spectrum: 195 (M^+), 194 (M^+ -H), 193 (metastable, M^+ -H), 168 (M^+ -HCN), 167 (M^+ -HCN, -H), 144.7 (metastable, M^+ -HCN), 140 (168 -HCN,-H), 117.4 (metastable, 167 -HCN), 114 (168 -2HCN). The mass spectrum revealed a small amount of an impurity identified as 7-phenyl-4-pyrrolidinylpyrrolo[3,2-*d*]pyrimidine: 264 (M^+), 236 (M^+ -C_2H_4), 235 (M^+ -C_2H_5), 234 (metastable, 236 -H), 222 (M^+ -C_3H_6), 209 (236 -HCN), 194 (M^+ -C_4H_8N), 167 (194 -HCN), 140 (167 -HCN). The pmr spectrum confirmed these assignments and showed the ratio of **1** to **2** to be 6:1; δ in ppm (**1**): 7.4 and 8.3 (m, phenyl), 8.4 (d, C_6H), 9.0 (s, C_2H and C_4H), 10.5-12.5 (NH); (**2**): 2 and 3.8 (m, four CH_2), 7.4 and 8.3 (m, phenyl), 7.9 (d, C_6H), 9.0 (C_2H), 10.5-12.5 (NH). NH exchange with deuterium oxide caused the CH doublets at 7.9 and 8.4 to collapse to singlets.

1-(6-Chloro-5-nitropyrimidin-4-yl)-2-pyrrolidinylstyrene (**8**).

To a suspension of 4,6-dichloro-5-nitropyrimidine (970 mg., 5 mmoles) in dichloromethane (10 ml.) under nitrogen, was added, dropwise, a solution of *trans*-β-pyrrolidinostyrene (1) (865 mg., 5 mmoles) and triethylamine (0.69 ml., 5 mmoles) in dichloromethane (5 ml.). The resulting solution was stirred at room temperature for 1 hour, then evaporated to dryness at reduced pressure. The residue was suspended in boiling benzene (50 ml.), cooled and filtered to remove the solid triethylamine hydrochloride. The filtrate was evaporated to dryness at reduced pressure, and trituration of the residue in acetonitrile (3 x 5 ml.) gave the product as a chromatographically homogeneous solid in 41% yield. Two recrystallizations from ethyl acetate gave the analytically pure product, m.p. 146-148° (dec.); λ max in nm (ε x 10^{-3}): *p*H 1 - 251 (6.1), 323 (2.5); *p*H 7 - 286 (6.2), 398 (24.0); *p*H 13 - 295 (11.5) unstable, 345 (9.2), 390 (9.7); ν in cm^{-1}: 2870, 2975 (aliphatic CH); 1595, 1530, 1495 (C=C, C=N); δ in ppm: 1.8 and 3.1 (m, four CH_2), 7.2 (m, phenyl), 8.2 and 8.5 (s, C_2H and =CH-).

Anal. Calcd. for $C_{16}H_{15}ClN_4O_2$: C, 58.10; H, 4.57; N,

16.94. Found: C, 57.78; H, 4.87; N, 16.88.

4-Amino-7-phenylpyrrolo[3,2-*d*]pyrimidine (**11**).

A solution of 1-(6-amino-5-nitropyrimidin-4-yl)phenylacetaldehyde (695 mg., 2.7 mmoles) in ethanol (175 ml.) was hydrogenated at atmospheric pressure using Raney nickel as catalyst. Reduction was complete within 1.5 hours and after removal of the catalyst by filtration through a Celite pad, the solvent was evaporated at reduced pressure. The solid residue was recrystallized from aqueous methanol (1:1): yield 304 mg. (54%), after drying 3 hours at 100° *in vacuo* over phosphorus pentoxide, m.p. 345° (dec.); λ max in nm (ϵ x 10^{-3}): *p*H 1 - 252 (26.5); *p*H 7 - 252 (28.9); *p*H 13 - 265 (27.9); ν in cm^{-1}: 3420, 3300 (NH_2); 3110-3010 broad (aromatic CH); 1640 (NH_2); 1600, 1580, 1535, 1520 (C=C, C=N); δ in ppm: 6.8 (s, NH_2), 7.3 and 8.1 (m, phenyl), 8.0 (s, C_6H), 8.2 (s, C_2H).

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.44; H, 4.77; N, 26.58.

1-(6-Amino-5-nitropyrimidin-4-yl)phenylacetaldehyde (**14**).

To a suspension of 4-amino-6-chloro-5-nitropyrimidine (873 mg., 5 mmoles) in dichloromethane (10 ml.) under nitrogen, was added, dropwise, a solution of *trans*-β-pyrrolidinostyrene (865 mg., 5 mmoles) and triethylamine (0.69 ml., 5 mmoles) in dichloromethane (5 ml.). The resulting dark red mixture was stirred at room temperature for 1 hour, then evaporated to dryness at reduced pressure. The residue was suspended in boiling benzene (50 ml.), cooled and filtered to remove the solid triethylamine hydrochloride. The filtrate was evaporated to dryness at reduced pressure, and the oil residue was purified by column chromatography (350 g., 30/60 mesh silica gel–Applied Science Laboratories, Inc.–eluted with 2:1 benzene ethyl acetate). The product (732 mg., 56%) was recrystallized from benzene; m.p. 181° dec.; λ max in nm (ϵ x 10^{-3}): *p*H 1 - 250 (16.0), 307 (5.3); *p*H 7 - 217 (19.3), 250 sh (9.0), 326 (8.4); *p*H 13 - 250 (10.5), 277 (10.0), 325 (9.3); ν in cm^{-1}: 3390, 3285 (NH_2); 3090, 3025 (aromatic CH); 1645 (CHO), 1605 (NH_2); 1580, 1575, 1550, 1540, 1515 (C=C, C=N, NO_2); δ in ppm: 7.1 (m, CH and phenyl), 7.7 (s, CHO), 7.8 (broad, NH_2), 8.3 (s, C_2H).

Anal. Calcd. for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 56.11; H, 4.02; N, 21.52.

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