The Rearrangement of 2-Amino-5-benzoyloxazoles with Dimethylamine

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The rearrangement of 2-amino-5-phenacyloxazoles with dimethylamine is described. One such rearrangement provided an unexpected tricyclic product.

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The rearrangement of 5-acetyl-2-aminooxazoles with amines has been previously reported [1,2]. As shown in Equation 1, it was noted that a mixture of products was obtained with R = CH₃. When the rearrangement was extended to include aromatic R groups, we found that instead of favoring, if either product, the imidazole 2b, the pyrimidine 3b became, by far, the predominant product.

In the Table, are summarized the results from the rearrangement of various substituted phenylacyl oxazoles with dimethylamine [3]. It will be noted that the least selective rearrangement occurs with the 4-methoxy derivative (Entry 2). We reason that the electron releasing nature of the 4-methoxy group may be responsible for the decreased selectivity compared to Entry 1, especially since the most selective reactions for pyrimidine formation are those performed on derivatives with electron withdrawing groups on the phenyl ring. A consideration of the mechanism of the rearrangement allows at least a rationalization of these results.

The putative intermediates in these rearrangements are illustrated in Equation 2 [1,4]. An electron withdrawing group R in 4 may result in a favoring of the benzoyl car-

bonyl toward nucleophilic attack, thus leading to a pyrimidine product.

An interesting side reaction was noted in the case of Entry 8 (Table). If the reaction of this derivative is allowed to proceed for four days, neither the expected pyrimidine 14 nor the imidazole product predominates in the reaction. Instead, a different much less polar compound, 7-chloro-2-dimethylamino-benzofuro[3,2-d]pyrimidine 15 was isolated (Eq. 3). This is the product of an unusually mild aromatic substitution reaction and provides a facile entry into this tricyclic series [5].

In an effort to elucidate the mechanism of this cyclization reaction the following facts were gathered by experiment. If 14 is isolated and resubmitted to the reaction con-

Table

H₂N O CH₃)₂NH N CH₃)₂N H N III

Entry	R	Yield [a]		Ratio [b]	Compound	
		II	III	II:III	II	III
1	Н	67	6	11:1	2b	3b
2	4-OMe	51	22	2.3:1	6	7
3	4-Cl	64	20	3.2:1	8	9
4	3-Me	91	0	>20:1	10	-
5	3-F	93	0	> 20:1	11	_
6	3,4-Cl	68	0	>20:1	12	_
7	3-CF	65	0	> 20:1	13	_
8	2,4-Cl	51	0	>20:1	14	_

[a] Yield refers to isolated pure product. [b] Ratios were determined by weighing isolated products. When the ratio is indicated as >20:1, it was determined by nmr analysis of the crude reaction product.

ditions one obtains 15. This reaction requires a base, as in the absence of dimethylamine the reaction does not proceed. However, when sodium hydroxide is substituted for dimethylamine, the reaction yields 15 and 14. The presence of the radical scavenger, 3-t-butyl-4-hydroxy-5-methylphenyl sulfide, does not inhibit the reaction. When the radical initiator azobisisobutyronitrile is added in place of a base, the reaction yields only starting material. While it had been speculated that this ring closure reaction had proceeded by a radical mechanism [6], on the basis of these data, it is concluded that the reaction proceeds by a base-induced addition-elimination reaction.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1420 spectrometer. The pmr spectra were recorded on a Varian XL-300 spectrometer and are reported in the following manner: solvent, chemical shift, multiplicity, coupling constant, integration. Mass spectra were recorded on either a Finnegan 4510 EI/CI spectrometer or AEI MS-30 spectrometer using a direct insertion probe. Column chromatography was performed according to the method of Still, et al [7].

Experimental Procedure.

To a round bottomed flask under nitrogen containing a solution of 2-amino-4-[3,4-dichlorobenzoyl]oxazole (2.0 g, 7.8 mmoles) in t-butyl alcohol (20 ml) was added a 26% aqueous solution of dimethylamine (100 ml). The reaction was stirred at 25° for 4 hours and concentrated on a rotovap. A single product was detected by nmr and tlc analysis. Crystallization afforded 1.5 g of pyrimidine 12, mp 188-189°; nmr (deuteriochloroform): δ 8.23 (d, J = 1.5 Hz, 1), 8.03 (dd, J = 7, 1.5 Hz, 1), 7.90 (s, 1), 7.37 (d, J = 7 Hz, 1), 3.18 (s, 6); ir (potassium bromide): 3440, 2960, 1610, 1550, 1420, 1360, 780 cm⁻¹.

Anal. Calcd. for $C_{12}H_{11}Cl_2N_3O$: C, 50.72; H, 3.90; N, 14.79. Found: C, 50.70; H, 3.86; N, 14.65.

Similarly prepared were the following compounds.

Compound 3b.

This compound had nmr (perdeuteriomethanol): δ 8.18-8.21 (m, 2), 7.99 (s, 1), 7.32-7.44 (m, 3), 4.89 (bs, 1), 3.11 (s, 6); ir (potassium bromide): 3450, 3040, 1600, 1540, 1400 cm⁻¹; ms: p⁺ = 215.

Anal. Calcd. for C₁₂H₁₃N₃O: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.66; H, 6.14; N, 19.48.

Compound 2b.

This compound had nmr (deuteriochloroform): δ 9.70 (bs, 1), 7.32 (s, 1), 7.0-7.2 (m, 5), 3.09 (s, 6); ir (chloroform): 3450, 3260, 2940, 1720, 1630, 1600, 1540 cm⁻¹.

Anal. Calcd. for C₁₂H₁₃N₃O: 215.1058. Found: 215.1067.

Compound 6.

This compound had nmr (perdeuteriomethanol): δ 8.26 (d, J = 4.5 Hz, 2), 7.96 (s, 1), 6.06 (d, J = 4.5 Hz, 2), 4.89 (bs, 1), 3.84 (s, 3), 3.15 (s, 6); ir (potassium bromide): 3450, 2970, 1590, 1410, 1360 cm⁻¹; ms: p⁺ = 245. Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.52; H, 6.06; N, 16.82.

Compound 7.

This compound had nmr (deuteriochloroform): δ 7.79 (d, J=4 Hz, 1), 7.40 (s, 1), 6.91 (d, J=4 Hz, 1), 3.86 (s, 3), 3.10 (s, 6); ir (chloroform): 3450, 3280, 2960, 1720, 1610 cm⁻¹; ms: p* = 245.

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.72; H, 6.05; N, 17.23.

Compound 8.

This compound had nmr (deuteriochloroform, perdeuteriomethanol): δ 8.0 (d, J = 8 Hz, 2), 7.8 (s, 1), 7.25 (d, J = 8 Hz, 2), 4.2 (bs, 1), 3.1 (s, 6); ir: (potassium bromide) 3460, 3060, 1600, 1480, 1420; ms: p* = 249.

Anal. Calcd. for C₁₂H₁₂ClN₃O: C, 57.72; H, 4.84; N, 16.83. Found: C, 57.36; H, 4.85; N, 16.54.

Compound 9.

This compound had nmr (perdeuteriomethanol): δ 7.8-7.9 (m, 3), 7.39-7.5 (m, 2), 3.2 (s, 6).

Anal. Calcd. for C₁₂H₁₂N₃O: 249.0668. Found: 249.0701.

Compound 10

This compound had nmr (deuteriochloroform): δ 8.13 (d, J=4 Hz, 2), 8.0 (s, 1), 7.24 (d, J=4 Hz, 2), 4.90 (bs, 1), 3.16 (s, 6), 2.40 (s, 3); ir (potassium bromide): 3426, 3036, 1596, 1570, 1523, 1406 cm⁻¹.

Compound 11.

This compound had nmr (deuteriochloroform): δ 8.83 (d, J=6 Hz, 1), 8.19 (d, J=6 Hz, 1), 8.05 (s, 1), 7.05 (m, 2), 3.1 (s, 6H); ir (potassium bromide): 3450, 2920, 1600, 1420, 1320 cm⁻¹; ms: p* = 233.

. Anal. Calcd. for C₁₂H₁₂FN₃O: C, 61.79; H, 5.19; N, 18.02. Found: C, 61.56; H, 5.25; N, 17.81.

Compound 12.

This compound had nmr (perdeuteriomethanol): δ 8.56 (s, 1), 8.49 (d, J = 4 Hz, 1), 8.40 (s, 1), 7.52-7.70 (m, 2), 4.86 (bs, 1), 3.12 (s, 6); ir (potassium bromide): 3420, 2950, 1620, 1540, 1430 cm⁻¹; ms: p + 1 = 284.

Anal. Calcd. for $C_{13}H_{12}F_3N_3O$: C, 55.12; H, 4.27; N, 14.83. Found: C, 54.91; H, 4.24; N, 14.80.

Compound 13.

This compound had nmr (deuteriochloroform/perdeuteriomethanol): δ 8.05 (s, 1), 7.5-7.3 (m, 3), 3.1 (s, 6); ir (chloroform): 3560, 3240, 2940, 1600, 1420; ms: $p^* = 283$.

Anal. Calcd. for $C_{12}H_{11}Cl_2N_3O$: C, 50.72; H, 3.90; N, 14.79. Found: C, 50.91; H, 3.95; N, 14.65.

Compound 14.

This compound had nmr (deuteriochloroform): δ 8.48 (s, 1), 7.92 (d, J = 4 Hz, 1), 7.42 (s, 1), 7.24 (d, J = 4 Hz, 1), 3.20 (s, 6); ir (potassium bromide): 1627, 1601, 1563, 1539, 1474 cm⁻¹.

Anal. Calcd. for $C_{12}H_{10}CIN_3O$: C, 58.19; H, 4.07; N, 16.97. Found: C, 58.11; H, 4.05; N, 16.74.

REFERENCES AND NOTES

- [1] J. L. LaMattina and C. J. Mularski, Tetrahedron Letters, 25, 2957 (1984).
- [2] For a recent related report see A. K. Sen, and D. K. Sengupta, Indian J. Chem., 248, 535 (1985).
- [3] These compounds were prepared analogously to those in reference [1].
 - [4] I. J. Turchi and M. J. S. Dewar, Chem. Rev., 75, 389 (1975).
- [5] S. B. Mahajan, S. S. Sangapure, and Y. S. Agasimrundin, *Indian J. Chem.*, 19B, 596 (1980); G. G. DeAngelis and H.-J. Hess, U. S. Patent 3,755,583, 1973.
- [6] For a leading reference on substitution reactions of dichloropyrimidines see H. M. Bell, D. R. Carver, J. S. Hubbard, Y. P. Sachdeva, and J. F. Wolfe, J. Org. Chem., 50, 3442 (1985).
 - [7] W. C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 43, 2923 (1978).