

CHEMISTRY OF THE 5:7-FUSED HETEROAROMATIC SYSTEMS: A NOVEL REARRANGEMENT INVOLVING THE IMIDAZO[4,5-e][1,3,4]TRIAZEPINE AND PYRAZOLO[3,4-e][1,3,4]-TRIAZEPINE SYSTEMS¹

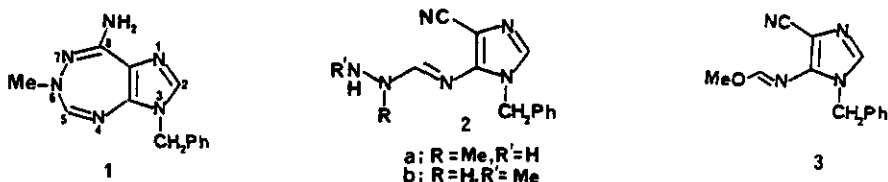
Ramachandra S. Hosmane* and Benjamin B. Lim

Laboratory for Chemical Dynamics, Department of Chemistry

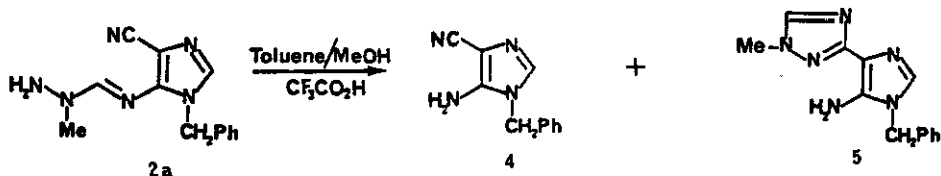
University of Maryland Baltimore County, Catonsville, Maryland 21228, U.S.A.

Abstract - A novel rearrangement which involves the potential intermediacy of an imidazo[4,5-e]- or a pyrazolo[3,4-e][1,3,4]triazepine is reported.

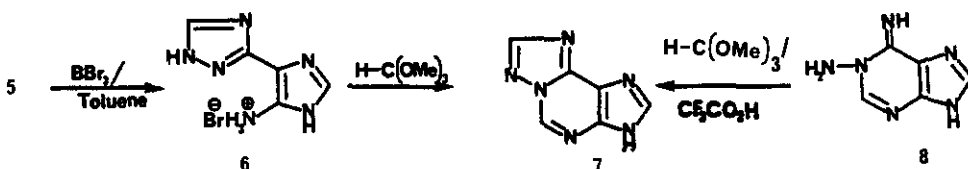
As part of our continuing program directed at the synthesis of 5:7-fused heterocycles² and nucleosides,³ we undertook to prepare 8-amino-3-benzyl-6-methylimidazo[4,5-e][1,3,4]triazepine (1) by ring closure of 2a. Compound 2a was obtained from the reaction of 3^{4,5} with methylhydrazine.



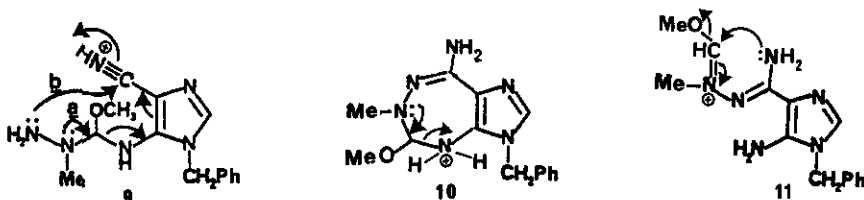
The structure 2a was distinguished from the alternative 2b by the ¹H nmr spectrum which exhibited singlets for both N-Me and NH₂. This assignment was consistent with the known reactivity of methylhydrazine which reacts with electrophiles from its N-methyl end.^{6,7} While the thermolysis of 2a in refluxing toluene-methanol yielded only the starting material, catalysis of the same reaction by trifluoroacetic acid gave a nearly equimolar mixture (total yield $\geq 90\%$) of 4⁸ and 5 [mp 254-255°C (decomp.); ¹H nmr (Me₂SO-d₆) δ 3.82 (s, 3, CH₃), 5.09 (s, 2, CH₂), 5.41 (s, 2, NH₂, exchangeable with D₂O), 7.28 (br s, 6, imidazole CH + Ph), 8.35 (s, 1, triazole CH); uv λ_{max} (EtOH) 258 nm; (pH 13) 258; (pH 1) 246, 276; mass spectrum (70 eV) m/z 254 (M⁺), 163 (M⁺-CH₂Ph);



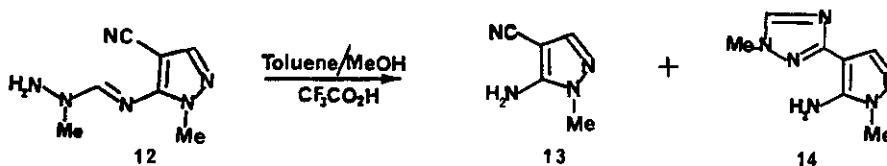
Anal.⁹ C, H, N]. The two compounds were readily separated by differential solubility or by flash chromatography on silica gel. In order to obtain structure proof, compound 5 was dealkylated with boron tribromide in toluene to form 6 which, upon treatment with trimethyl orthoformate, ring-closed to 7.¹⁰ The latter was also obtained by the acid-catalyzed ring-closure of 8^{10a} with trimethyl orthoformate. The observed large NOE (14.9%) between the methyl and the methine protons established the position of the methyl group in the triazole ring as shown in 5. Finally, the structure 5 was confirmed by single crystal x-ray analysis.¹¹



In speculating about a mechanism for the conversion $2a \rightarrow 4 + 5$, it was noted that the reaction failed in the absence of methanol in spite of TFA catalysis. A tentative mechanism for the conversion involves the intermediate 9 which decomposes to 4 via path a or rearranges to 5 via path b upon sequential ring-closure ($9 \rightarrow 10$), ring-opening ($10 \rightarrow 11$), and ring-closure, followed by elimination of methanol ($11 \rightarrow 5$). Another pathway for the formation of 5 would involve the recombination of 4 with the by-product of path a, namely 1-formyl-1-methylhydrazine dimethyl acetal. However, this latter possibility was ruled out by the observed failure of 4 to react with either formylhydrazine or methylhydrazine in a mixture of toluene-methanol at reflux for three days with or without TFA catalysis. It should be pointed out that a seven-membered ring intermediate has been proposed¹² for the base-catalyzed conversion of 1-aminoadenosine or its 9-methyl analogue to the corresponding imidazolyl-1,2,4-triazole derivatives analogous to 5. Furthermore, acid-catalyzed conversion of 6-hydrazinopurine and its derivatives to the respective imidazolyl-1,2,4-triazoles has been documented.^{10b} However, despite careful monitoring at frequent intervals, we have been unable to isolate or detect either 9-benzyl-1-(methylamino)adenine or 9-benzyl-6-(β -methylhydrazino)purine in the reaction, $2a \rightarrow 4 + 5$.



The study of the above rearrangement was extended to the pyrazole system in an attempt to explore its generality. Thus, when the analogous pyrazole-hydrazidine 12 was heated in toluene/methanol/TFA, the product was a mixture of 13¹³ (48%) and 14 [43%; mp 177-179°C; ¹H nmr (Me₂SO-d₆) δ 3.58 (s, 3, pyrazole CH₃), 3.84 (s, 3, triazole CH₃), 5.75 (br s, 2, NH₂, exchangeable with D₂O), 7.47 (s, 1, pyrazole CH), 8.36 (s, 1, triazole CH); mass spectrum (70 eV) 178 (M⁺), 163 (M⁺-CH₃); uv λ_{max} (EtOH) 239 nm; (pH 13) 237; (pH 0.1) 231, 262; Anal.⁹ C, H, N].



The conversion described above represents a novel "translocative" rearrangement¹⁴ involving the transfer of an H₂N-N(Me)-CH= group from a heterocyclic hydrazidine side-chain to the vinylogous nitrile function. Since the by-products 4 and 13 can be easily separated and recycled to 2a and 12, respectively, via the corresponding imidates (e.g. 3), the rearrangement carries useful practical implications in the synthesis of the otherwise not easily accessible heterocycles of potential biological and medicinal significance.¹⁵

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REFERENCES AND NOTES

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