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 SYSTEMS[1]

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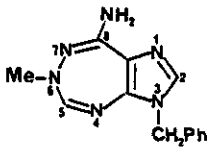
Abstract - A novel rearrangement which involves the potential intermediacy of an imidazo[4,5-e]- or a pyrazolo[3,4-e][1,3,4]triazepine is reported.

As part of our continuing program directed at the synthesis of 5:7-fused heterocycles[2] 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.



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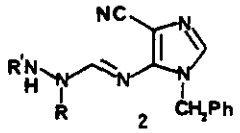
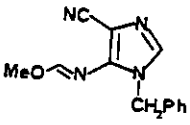


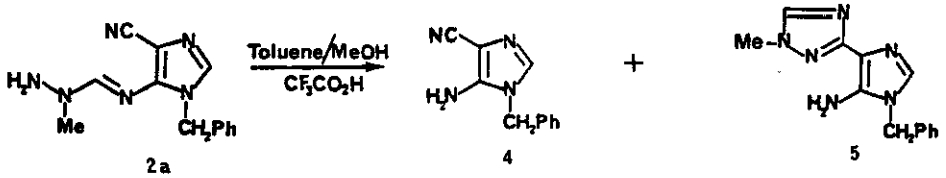
a; R = Me, R' = H
b; R = H, R' = Me

2



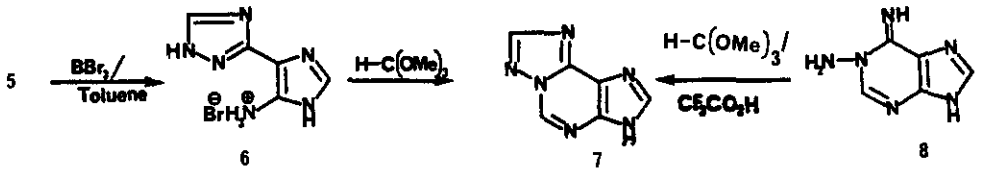
3

The structure **2a** was distinguished from the alternative **2b** by the ^1H nmr spectrum which exhibited singlets for both N-Me and NH_2. 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 ≥90%) of 4[8] and 5 [mp 254-255°C (decomp.); ^1H nmr (Me_2SO-d_6) δ 3.82 (s, 3, CH_3), 5.09 (s, 2, CH_2), 5.41 (s, 2, NH_2, exchangeable with D_2O), 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^+-CH_2Ph);



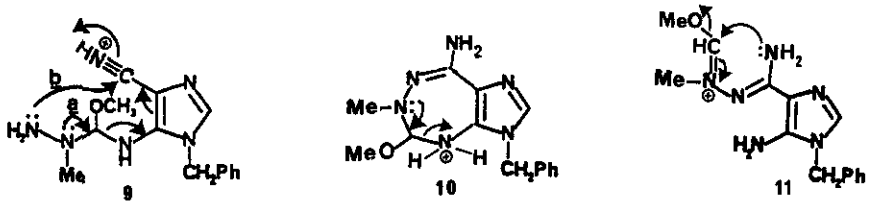
2a 4 5

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]



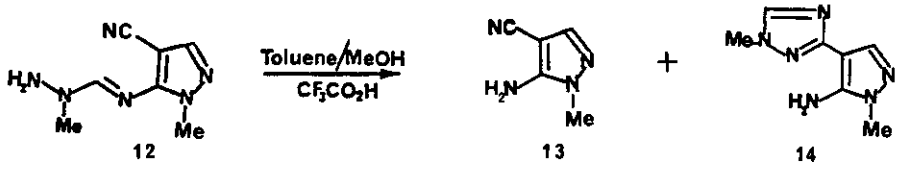
6 7 8

In speculating about a mechanism for the conversion **2a** ⟶ **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** ⟶ **10**), ring-opening (**10** ⟶ **11**), and ring-closure, followed by elimination of methanol (**11** ⟶ **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 proposed[12] 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** ⟶ **4** + **5**.



9 10 11

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 **13**[13] (48%) and **14** [43%; mp 177-179°C; ^{1}H nmr (Me_2SO-d_6) δ 3.58 (s, 3, pyrazole CH_3), 3.84 (s, 3, triazole CH_3), 5.75 (br s, 2, NH_2, exchangeable with D_2O), 7.47 (s, 1, pyrazole CH), 8.36 (s, 1, triazole CH); mass spectrum (70 eV) 178 (M^+), 163 (M^+-CH_3); uv λ_{max} (EtOH) 239 nm; (pH 13) 237; (pH 0.1) 231, 262; Anal.[9] C, H, N].



12 **13** **14**

The conversion described above represents a novel "translocative" rearrangement[14] involving the transfer of an H_2N-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

1. This paper is dedicated to Professor Nelson J. Leonard of the University of Illinois, Urbana, on the occasion of his 70th birthday.
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