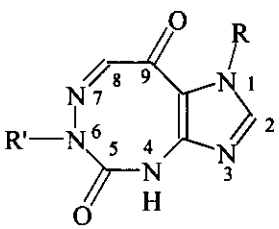
IMIDAZO[4,5-*e*][1,2,4]TRIAZOCINE: A NOVEL 5:8-FUSED RING SYSTEM RIDDLED WITH REARRANGEMENTS

Friedrick N. Burnett and Ramachandra S. Hosmane*

Laboratory for Drug Design and Synthesis
Department of Chemistry and Biochemistry
University of Maryland Baltimore County
Baltimore, Maryland 21228, USA

Abstract - Attempts to synthesize the title 5:8-fused heterocyclic ring system resulted in a number of novel opportunistic rearrangements and transformations. There is, however, some evidence to believe that one of these rearrangements might proceed through the transient intermediacy of this ring system.



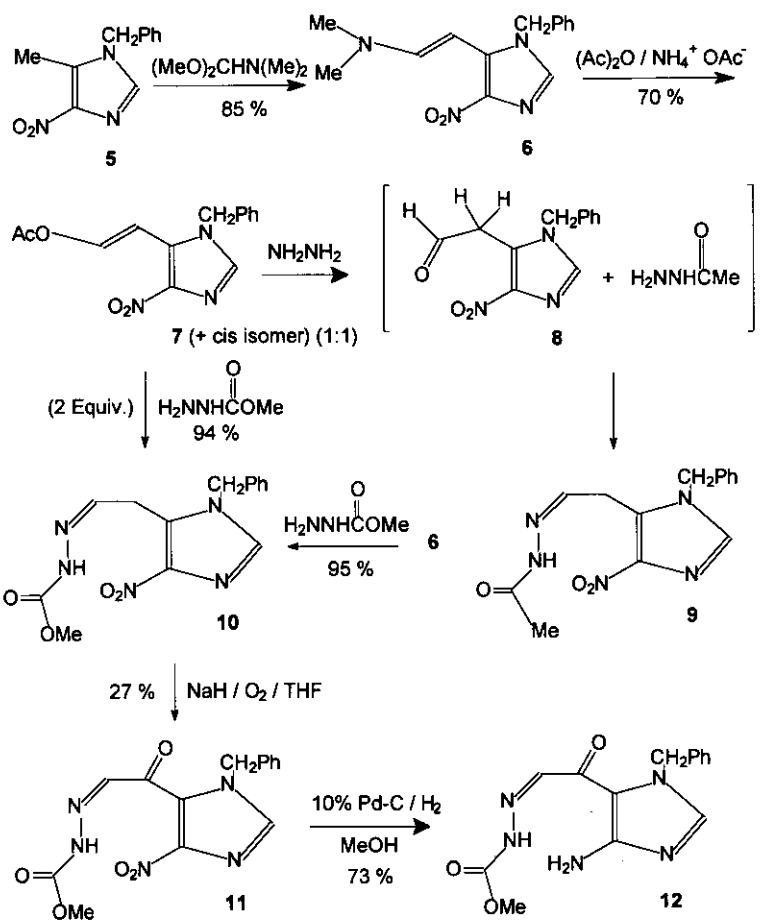
1; R = R' = H
2; R = R' = CH_2Ph
3; R = CH_2Ph, R' = H
4; R = H, R' = CH_2Ph

Heterocycles with structural features that resemble ring-expanded purines are of chemical, biochemical, biophysical, as well as medicinal interest. In this regard, while several 5:7-fused heterocyclic ring-systems containing both imidazodi- and -triazepine nuclei have been extensively explored, both in this laboratory[1] and elsewhere,[2] as ring-expanded purine bases, nucleosides, and nucleotides, little is documented on the related 5:8-fused systems. Large ring heterocycles pose considerable synthetic challenge, especially when dealing with antiaromatic ring systems, which are often plagued with undesired, opportunistic rearrangements. We have indeed uncovered a few such rearrangements during the synthesis of heterocycles containing the 5:7-fused imidazo[4,5-*e*][1,2,4]triazepine ring skeleton,[3] although most of the target compounds were later found to be remarkably stable when once synthesized. Reported herein are our synthetic endeavors on the larger 5:8-fused imidazo[4,5-*e*][1,2,4]triazocine ring system (**1**-**4**). As delineated, while there is some evidence for the existence of such a ring system as a transient intermediate, all our efforts thus far to isolate a representative member of this class of compounds have only led to products resulting from a variety of opportunistic, nonetheless interesting, rearrangements and transformations.

As an initial synthetic target, we chose **1**--a ring-expanded analogue of xanthine--as it could later be conveniently converted into the corresponding adenine and guanine analogues. Our synthesis commenced with 1-benzyl-5-methyl-4-nitroimidazole (**5**)[4] (**Scheme I**), which was treated with dimethylformamide

dimethyl acetal, catalyzed by trifluoroacetic acid, to form 1-benzyl-5-[β-(*N,N*-dimethylamino)ethylene]-4-nitroimidazole, mostly as a *trans* isomer (**6**, mp 148-149 °C, ^{1}H NMR, MS, Anal. C,H,N)[5] in 85% yield. The enamine (**6**) was converted to the corresponding enol-acetate (**7**) as a mixture of *cis* and *trans* isomers in a 1:1 ratio (mp *cis* 82-84 °C, *trans* 129-130 °C, ^{1}H NMR, MS, Anal. C,H,N)[5] in 70% yield by reaction with acetic anhydride/ ammonium acetate. When **7** was treated with an equivalent of hydrazine, the sole product isolated was the acetylhydrazone (**9**) (mp 168-169 °C, ^{1}H NMR, MS, Anal. C,H,N).[5] Apparently, **7** undergoes initial deacylation to form the intermediate aldehyde (**8**) and acetylhydrazine, which further react to form **9**. Based upon this result, the desired **10** (foam, ^{1}H NMR, IR, Anal. C,H,N)[5] was prepared from **7** in 94% yield by reaction with two equivalents or more of methyl-carbazate. It was later discovered that **10** could also be prepared directly from **6** and methyl carbazate in 95% yield, although our earlier attempts of enamine exchange reactions of **6** with a variety of simple primary amines had failed. The 5-methylene group of **10** was oxidized to the corresponding keto group of **11** (mp 161-162 °C, ^{1}H NMR, MS, Anal. C,H,N)[5] by treatment with sodium hydride in the presence of molecular oxygen in 27% yield. The structure of **11** was confirmed by single-crystal X-ray diffraction analysis.[6] The nitro group of **11** was reduced by hydrogenation over 10% Pd-C to obtain the amino compound (**12**) (mp 193.5-195 °C, ^{1}H NMR, MS, UV, Anal. C,H,N)[5] in 73% yield. Compound (**12**) is the required precursor for the final ring-closure to form the target ring system.

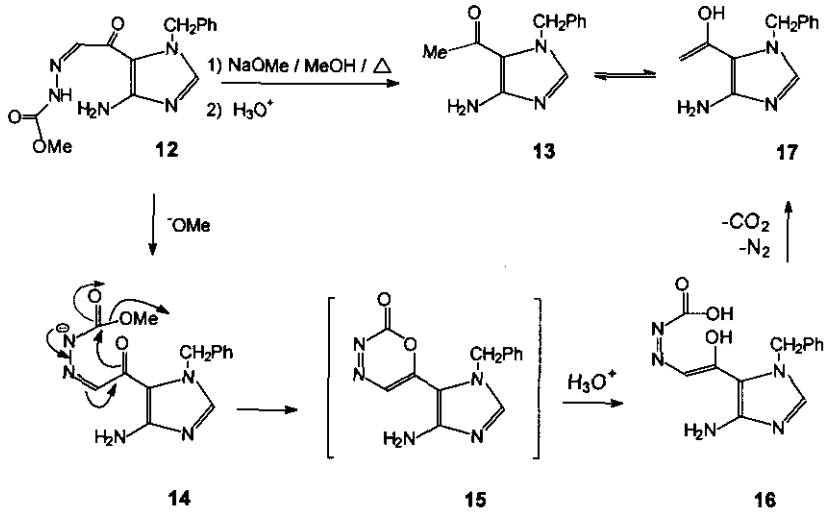
Scheme I



The attempted ring-closure of **12** to **3** with sodium methoxide/ methanol, followed by acid work-up, however, produced only the degradation product, 5-acetyl-4-amino-1-benzylimidazole (**13**) (88%, mp 161-163 °C, ^{1}H

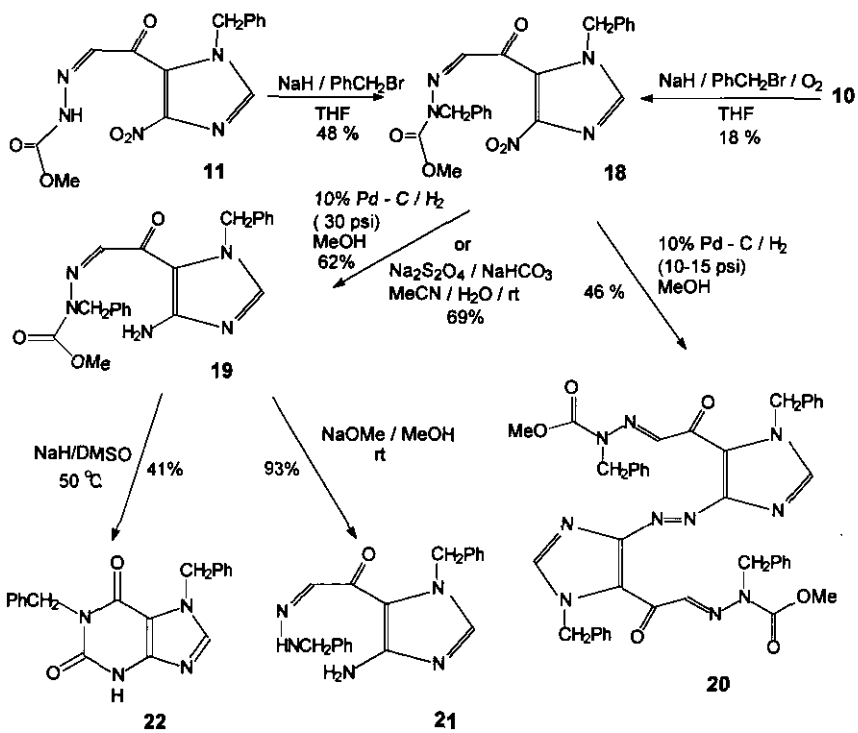
NMR, IR, MS).[5] A tentative mechanism (**Scheme II**) for the formation of **13** involves the initial generation of the anion (**14**) which undergoes ring-closure to the oxadiazinone (**15**), which upon acid work-up ring opens to form **16**. Facile ring-opening reactions of oxadiazinones with nucleophiles are well documented.[7] Intermediate (**16**) readily loses carbon dioxide and nitrogen gases to yield **17**. Finally tautomerization of **17** produces **13**.

Scheme II



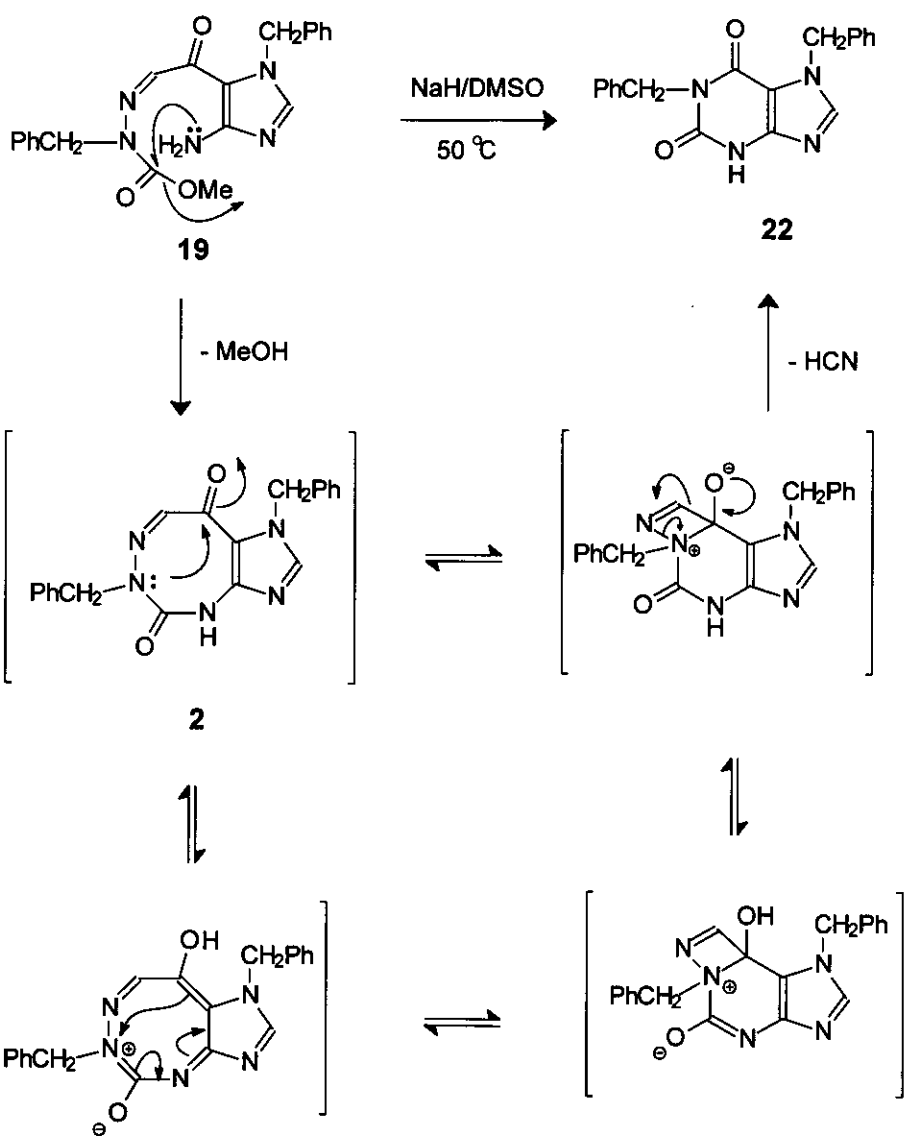
In order to avoid the above undesired ring-closure, the anion-forming α-NH of the side-chain carbazate moiety was protected by benzylation. The dibenzyl product (**18**) (mp 128-130 °C, ^{1}H NMR, IR, MS, Anal. C,H,N)[5] (**Scheme III**) could be prepared either from **11** using benzyl bromide/ sodium hydride (48% yield) or directly from **10** in a one-pot reaction using the same reagents plus oxygen gas (18%). Catalytic hydrogenation of **18** at 30 psi provided the desired **19** (mp 176-177 °C, ^{1}H NMR, IR, Anal. C,H,N)[5] in 62% yield. However, when the same reaction was carried out under low pressure of hydrogen (10-15 psi), the dimer (**20**) (mp 212-214 °C, ^{1}H NMR, IR, UV, MS, Anal.

Scheme III



C,H,N)[5] was obtained in 46% yield). The structure of **20** was confirmed by single-crystal X-ray diffraction analysis.[6] Apparently, under low pressure of hydrogen, the partially reduced **18** reacts with the unreacted **18** to form **20**. The attempted ring-closure of **19** to **2** with sodium methoxide/methanol only resulted in the production of the decarboxymethylated product **21** (93%). Apparently, methoxide, acting as a nucleophile, attacks the methyl carbazate carbonyl, forming dimethyl carbonate and **21**. The ring-closure of **19** to **2** was, therefore, attempted with a non-nucleophilic base, *i.e.*, sodium hydride in dimethyl sulfoxide at 50-60 °C. However, this reaction gave instead the 5:6-fused 1,7-dibenzylxanthine (**22**) (41%). The structure of **22** was confirmed by single-crystal X-ray diffraction analyses.[6] As outlined in **Scheme IV**, the observed transformation of **19** to **22** might indeed proceed by way of the desired 5:8-fused heterocyclic system **2**.

Scheme IV



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5. The elemental microanalyses, performed by Atlantic Microlab, Inc., were within 0.4% of the calculated values. The spectral data are consistent with the structure assigned.

6. The X-ray diffraction analyses were performed by Dr. Hongming Zhang at the Department of Chemistry, Southern Methodist University, Dallas, Texas.

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