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SYNTHESIS ON TEMPLATES II : DIRECTED SYNTHESIS OF IMIDAZOLES FROM ADENINE

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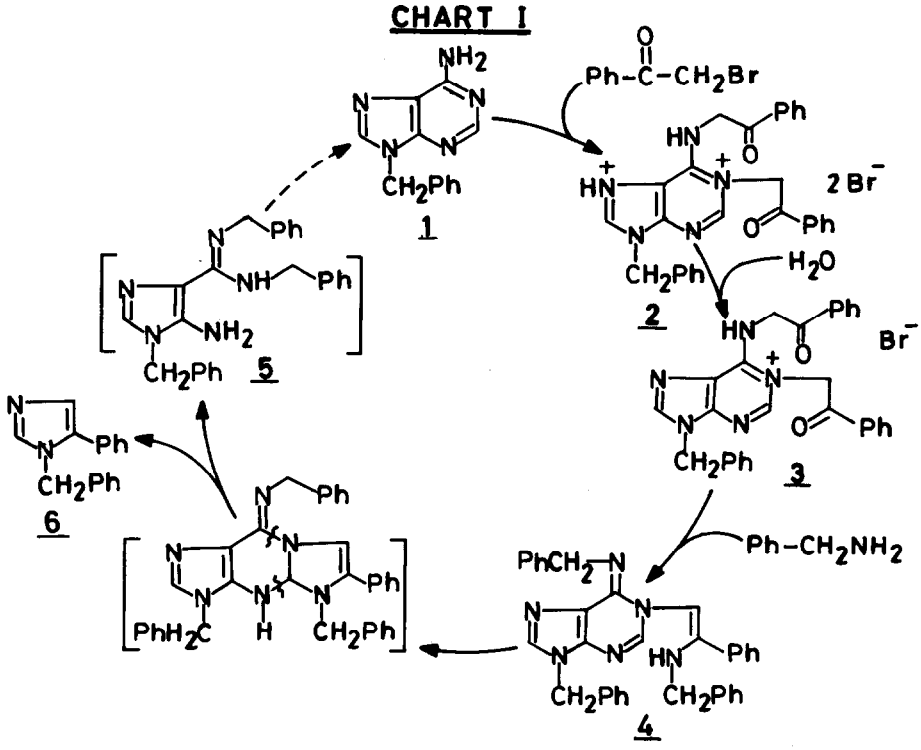
ABSTRACT: Adenine has been used as the template for the directed synthesis of 5-substituted imidazoles. A Novel intermediate involved in the cyclic operation has been characterised.

We have recently[1] been successful in the chemical simulation of the salient features of the "ATP-Imidazole" cycle- related to the biosynthesis of histidine, ATP and GTP - wherein an imidazole is derived from an imidazole template. The crucial nitrogen alkylation was, in this effort, carried out on hypoxanthine. In Nature's cycle however, although hypoxanthine is an integral part, the required alkylation takes place on an adenine. The present communication reports the completion of the ATP-Imidazole cycle with the significantly more reactive adenine as the precursor to the key alkylation (CHART I). An unexpected present finding is that whilst both 9-N protected hypoxanthine and adenine are part of Nature's ATP-Imidazole cycle and can indeed be chemically induced to produce derived imidazoles, for the template operation, only in the former case the nonfunctional ring, namely, the N-protected imidazole, can be replaced. Thus, whereas 4-oxoquinazoline is a superior template compared to hypoxanthine, 4-aminoquinazoline fails.

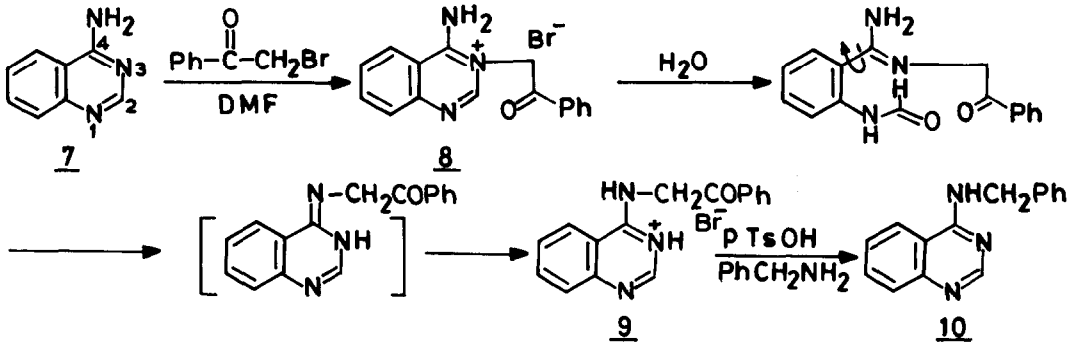
The reaction of 9-benzyl adenine[2] (1) with $PhCOCH_2Br$ (1.5 eq) in dry DMF at rt. overnight followed by evaporation *in vacuo* and crystallisation from absolute methanol gave the bis-salt 2 mp 219-223°C (35%)[3,4,5] which on treatment with hot water gave the bisalkylated monohydrobromide 3, mp 225-228°C (94%)[4,6,7]. Compound 3 on reflux for 4h in dry xylene with $PhCH_2NH_2$ (4 eq) followed by evaporation of solvents, chromatography on silica gel and elution with PhH:EtOAc :: 65 : 35 gave 28% of the novel enamine 4, mp 136-138°C[4,8] and upon further elution with PhH:EtOAc :: 55:45, 38% of the derived product 1-benzyl-5-phenyl imidazole (6), mp 111°C identical to an authentic sample[1]. Compound 4 on reflux in xylene with $PhCH_2NH_2$ (4 eq) and p TsOH (1 eq) for 12h gave the template product 6, in 88% yield, thus demonstrating that the earlier[1] conjecture to the effect that such template processes proceed via key Schiff base/enamine intermediate has much substance[9]. In practice, the intermediate 4 can



be bypassed by treatment of 3 with benzylamine and p TsOH in refluxing xylene leading directly to derived imidazoles[10]. Thus, 3 on reflux in dry xylene with $PhCH_2NH_2$ (4 eq) and p TsOH (2 eq) for 12h followed by work up[1] gave 71% of the derived product 6; with cyclohexylamine, under the same conditions, 1-cyclohexyl-5-phenyl imidazole — identical to an authentic sample[1] — was obtained in 50% yields. It appears therefore that whilst p TsOH is not critical to the formation of the enamine intermediate, its involvement is required in subsequent reactions[11].

Unlike 9-benzyl adenine (1), the related 4-amino quinazoline (7) failed totally to yield an imidazole derivative (vide supra). Treatment of 4-amino quinazoline (7)[12] with phenacyl bromide (1.5 eq) in dry DMF at room temperature and work up as described for 2, gave the 3-N-monoalkylated salt 8, mp 283-288°C , in 68% yields[4,13] (CHART II).

CHART II



The use of 8 as a template for imidazoles failed because of preference for Dimroth rearrangement[14] giving rise to 9, mp 306-311°C in 77% yields[4,15] (CHART II). The reaction of 9 with benzylamine (4 eq) and p TsOH (2 eq) in refluxing xylene for 12 h gave 4-benzylaminoquinazoline (10) mp 172-173°C in 56% yields[4,16]. Treatment of 8 with $PhCH_2NH_2$ and p TsOH in hot xylene gave none of the expected derived imidazoles. This failure is attributed to the ready base induced 2-3 bond rupture which would make imidazole formation impossible[17,18].

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References and Notes

1. D. Ranganathan and F.Farooqui, Tetrahedron Lett., 5701 (1984).
2. K.L. Carraway, P.C. Huang and T.G. Scott, Synthetic Procedures in Nucleic Acid Chemistry, Interscience, 1968, Vol.I, p.3.
3. The alkylation of 1 with 1 eq $PhCOCH_2Br$ failed; with more than 1.5 eq it was found difficult to isolate 2. The reaction of 1 with $PhCH_2Br$, under a variety of reaction conditions gave 6-imino-1,9-dibenzyl purine (K.Kesavan, Ph.D. Thesis, IITK, 1983).
4. Elemental analysis for this compound was in complete agreement with the expected values.
5. 2 :mp 219-223°C; IR (KBr) : 3420, 3060, 1690, 1630, 1600 cm^{-1}.
6. It was anticipated that treatment of 2 with water would give neutral product. Adenine and related compounds possessing a number of basic sites could give a series of salts with acids. The condition that would give rise to a particular salt is very much related to the substrate, the reagent and the reaction conditions (ref. 3).

7. 3 : mp 225-228°C; IR (KBr) : 3460, 3020, 1710, 1660, 1600 cm^{-1}.
8. 4 : mp 136-138°C; IR (KBr) : 3240, 1630 cm^{-1}; NMR : δ ($CDCl_3$) 3.6 (dd,2H), 4.25 (s,2H), 4.75 (d, $+D_2O$(s), 2H), 5.2 (d,1H), 7.2-8.0 (m, 23H); m/e : 522 (M^+).
9. Compound 4 on reflux in xylene with only p TsOH failed to give derived imidazole.
10. The bis-salt 2 under similar conditions gave no derived products.
11. An aspect that has thus far eluded solution is the characterisation of the compound arising from separation of the derived imidazole. In the case of the earlier cycles (ref. 1) this was not a problem. The envisaged compound here (CHART I) is endowed with so many basic and reactive nitrogens. It is not surprising therefore that the fraction after separation of the template product was found to be quite complex! We are hopeful however to sort out this problem eventually. Work is in progress towards this end.
12. J.S. Morley and J.C.E. Simpson, J. Chem. Soc., 1354 (1949).
13. 8 : mp 283-288°C; IR (KBr) : 3360, 3260, 3060, 1695, 1675 cm^{-1}.
14. D.J. Brown in Mechanisms of Molecular Migrations, Ed. B.S. Thyagarajan, Wiley New York, 1968, Vol.1, p.209; M. Wahren, Z. Chem., 9, 241 (1969).
15. 9 : mp 306-311°C; IR (KBr) : 3260, 3060, 1690, 1675 cm^{-1}; m/e: 263 (M^+ - HBr).
16. 10 : mp 172-173°C; IR (KBr) : 3240 cm^{-1}; NMR : δ ($CDCl_3$) 4.87 (d, $+D_2O$(s), 2H), 6.47 (br, 1H), 7.12-7.97 (m, 9H, aromatic), 8.64 (s, 1H); m/e : 235 (M^+). 10 was found identical to an authentic sample prepared by treatment of 4-chloroquinazoline with benzylamine.
17. The charged 3- nitrogen in the alkylated 4-amino quinazoline should account for the ready 2-3 bond rupture. This situation does not exist in the case of 3-N alkylated 4-oxoquinazolines which readily give the template products (ref. 1).
18. 4-Aminoquinazoline offers three sites for alkylation with $PhCOCH_2Br$. Compounds 8 and 9 represent two of the possibilities. Interestingly, alkylation at the third site, namely, N-1, was observed when 7 was either treated with 1.5 equivalents of the reagent in DMF at rt. for 8d or with 4 eq under the same conditions for 2d; yield 48%[4]; mp 310°C; IR (KBr) : 3360, 3250, 3060, 1685, 1665, 1610 cm^{-1}; m/e : 263 (M^+ - HBr). Either this or its isomeric salt arising from water treatment gave with $PhCH_2NH_2$/p TsOH in hot xylene, complex mixtures containing none of the derived products.

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