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SYNTHESIS ON TEMPLATES : REGIOSPECIFIC SYNTHESIS OF IMIDAZOLES

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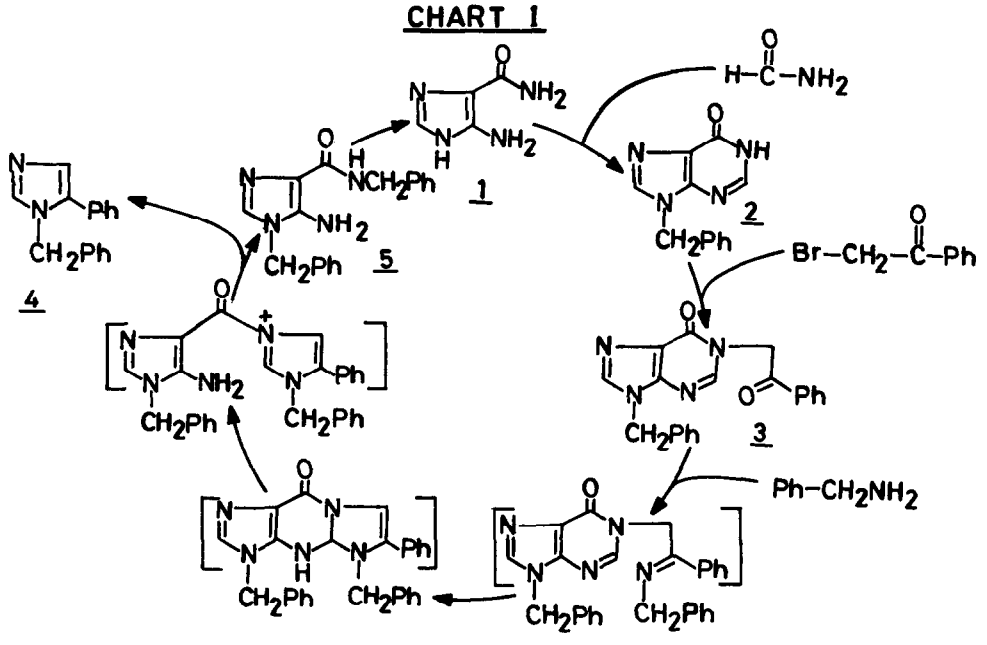
SUMMARY: A new, biomimetic template operated strategy has been developed leading to regiospecific synthesis of imidazoles (CHARTS I & II).

For a number of years we have been interested in developing a biomimetic synthesis of histidine via chemically simulating the salient features of ATP-Imidazole cycle[1,11]. Histidine is synthesized in Nature using a unique template operation where a parent monomeric imidazole acts as a template[2] on which a daughter imidazole is grown. We report here the first successful template operation for the construction of N-protected 5-substituted imidazoles (CHART I)[3].

CHART I



5-Aminoimidazole-4-carboxamide (1)[4], which initiates the ATP-Imidazole cycle was transformed to 9-benzyl-6-chloropurine (a. $HCONH_2$ b. $POCl_3$-$PhN(Me)_2$ c. $PhCH_2Cl$-K_2CO_3), which, on careful treatment with 1N HCl, gave 9-benzylhypoxanthine (2) in 76% yields[5,6]. Specific N-1 alkylation of 2[7] was achieved, by treatment of the potassium salt-generated with KOH (1 eq) - with $PhCOCH_2Br$ in ethanol, leading to 1-phenacyl-9-benzyl hypoxanthine (3)[8,9], mp. 201° in 82% yields. Compound 3 on reflux in xylene for 12 hr with $PhCH_2NH_2$(4 eq) and

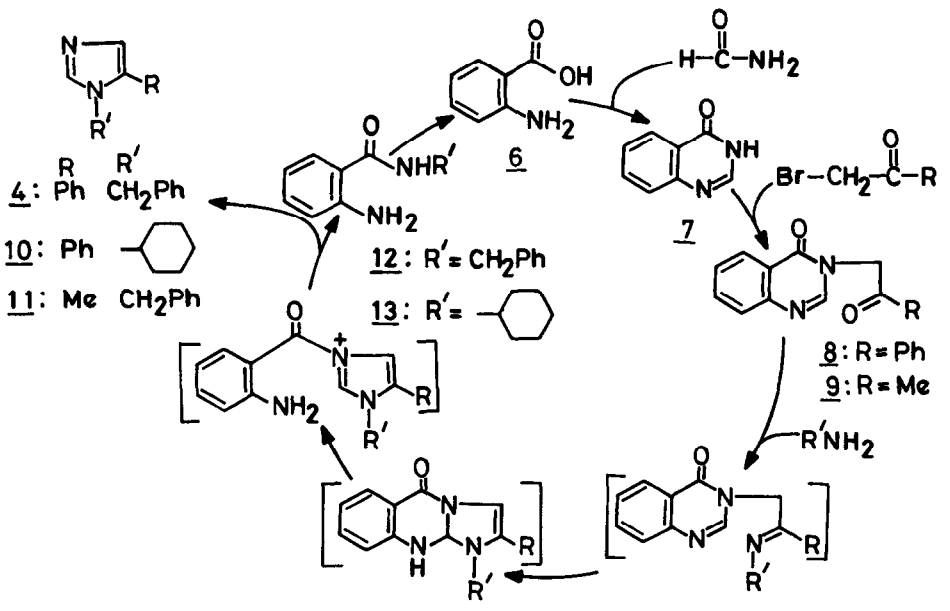
anhydrous p TsOH (3 eq), followed by evaporation of solvents, chromatography on silica gel and elution with PhH: EtOAc::1:1 gave 36% of the daughter product 1-benzyl-5-phenyl imidazole (4)[9] mp.111° and upon further elution with PhH:EtOAc::2:3, 33% of 1-benzyl-5-aminoimidazole-4-benzylamide (5)[9,10] mp. 162°, which is directly related to the parent imidazole 1 (CHART I).

In principle, the novel strategy for the synthesis of 5-substituted imidazoles described above (CHART I), can be transplanted to more adaptive, in vitro templates by incorporation of the operating segment of the cycle, namely, the vicinal disposition of an amino and carboxyl functions, on a rigid, unreactive anchor. The logical choice for such a template would be anthranilic acid (6) and we have been able to demonstrate here, after diverse infructuous approaches[11] that it is effective as an excellent mimic of the ATP-Imidazole cycle.

Anthranilic acid (6) was transformed to 4-quinazolone (7) and regiospecifically alkylated[12] with $PhCOCH_2Br$ and $MeCOCH_2Br$ - under conditions defined for 9-benzyl hypoxanthine- leading to, respectively, 3-phenacyl-4-quinazolone (8, 40%, mp. 159°)[13] and 3-acetonyl-4-quinazolone (9, 50%, mp. 158°)[13] (lit. mp. 159°)[14]. Compound 8 proceeded through the cycle on reflux in xylene for 12 hr with $PhCH_2NH_2$ (4 eq) and anhydrous p TsOH (2 eq) and gave on chromatography on silica gel, 71% of anthranilic acid benzylamide (12, PhH:EtOAc::4:1, mp. 123°)[13] (lit. mp. 123°)[15] and 69% of the template product 4 (PhH:EtOAc::3:2). Compound 12 could be readily transformed, to the template 6, with acids. Similarly, the compound 8 on reflux in benzene with cyclohexylamine gave 65% anthranilic acid cyclohexylamide (13, mp. 154°)[13] (lit. mp. 156°)[15], and 70% of 1-cyclohexyl-5-phenyl imidazole (10, bp. 180°/0.1 torr)[13]. Finally, the acetonyl compound 9 when processed through the cycle on reflux in xylene with $PhCH_2NH_2$, gave 45% of 12 and 55% of the template product, 1-benzyl-5-methyl imidazole (11, PhH:EtOAc ::2:3, mp. 99°)[13] (CHART II)[16], whose structure was confirmed by comparison with an authentic sample prepared via the lengthy sequence: D-fructose→4-hydroxymethyl imidazole+5-hydroxymethyl imidazole → 1-benzyl-4-hydroxymethyl imidazole+1-benzyl-5-hydroxymethyl imidazole, chromatographic separation of the desired 5-isomer, halogenation ($SOCl_2$) and reduction ($Pd/C/H_2$)[17]. The daughter product, 1-benzyl-5-methyl imidazole (11) on treatment with SeO_2 followed by $NaBH_4$, gave 1-benzyl-5-hydroxymethyl imidazole, which on de-protection ($Pd/C/H_2$), reaction with $SOCl_2$ followed by alkylation with $NaCX(COOEt)_2$ and hydrolysis gave dl-histidine (X=NHAc).

The three crucial operations involved in the realization of ATP-Imidazole cycle are, specific N-alkylation, cyclization and cleavage. Whilst, we have been able to prepare a variety of specifically N-alkylated hypoxanthines and quinazolones, the later events take place only when the substituent carries an enamine type unit[11]. Indeed, the first successful simulation was achieved with 3-o-aminophenyl-4-quinazolone (mp. 140°), which was prepared from 4-quinazolone and o-phenylenediamine. This, on reflux in aqueous 1N NaOH for 1.5 hr gave 73% benzimidazole and 79% anthranilic acid. Since the cyclization step can be expected to be reversible, the crucial stage is the irreversible separation of the daughter heterocycle. It appears that the enamine unit provides the needed incentive in the sense that the addition as well as the separation steps are made favourable. Provided that the above mentioned conditions are satisfied, this cyclic strategy can be used to prepare a variety

CHART II



of heterocycles. Studies in this area will be reported in future publications.

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References and Notes

1. D.M.Greenberg, Metabolic Pathways, Vol.III, p.268, Academic Press, 1969; D.Ranganathan and S.Ranganathan, Art in Biosynthesis p.82, Academic Press, 1976; K.Kesavan, Ph.D.Thesis, IITK, 1983.
2. In microscopic terms a template can be defined as a molecular mould for the synthesis of another molecule (J.D.Watson, Molecular Biology of the Gene. 3rd Edn., Benjamin Inc., 1976).
3. In spite of the continuing interest in imidazoles (see M.R.Grimmett in Advances in Heterocyclic Chemistry, Ed. A.R.Katritzky and A.J.Boulton, Vol.27, p.242, Academic Press, 1980), the procedures for the synthesis of N-protected 5-substituted imidazoles are scarce and the pathways cumbersome. Therefore, the strategy outlined in this paper, to the best of our knowledge offers the best procedure for the synthesis of a variety of N-protected 5-substituted imidazoles.
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6. J.A.Montgomery and C.Temple, J.Am.Chem.Soc., 79, 5238 (1957); 83, 630 (1961).
7. The regio-selectivity in the alkylation has been rigorously established by correlation of the product arising from (3,3) shift of 9-benzyl-6-allyloxy purine with that obtained by the direct allylation of the 9-benzyl hypoxanthine conjugate base with allybromide.
8. All new compounds gave satisfactory elemental analysis.
9. 3: IR(KBr) : 1700,1610,1590 cm^{-1}; NMR: δ ($CDCl_3$) 5.3 (s,2H),5.5(s,2H), 7.2-8.2 (m,12H); m/e: 344 (M^+), 239 (M^+-PhCO). 4: NMR: δ ($CDCl_3$) 5.1 (s,2H), 6.7-7.9 (m,12H); m/e; 234 (M^+). 5: IR (KBr) : 3400,3300,1630 cm^{-1}; NMR; δ ($CDCl_3$) 4.45 (d,2H), 4.8 (s,2H), 6.8-7.7 (m,12H); m/e: 306 (M^+).
10. Blank experiments have established that 5 does not arise by a trivial fragmentation of 3 with $PhCH_2NH_2$.

11. The diverse strategies pertaining to the realization of the cycle were invariably tried out on the model template, namely, anthranilic acid, which incorporates the operating part of the ATP-Imidazole cycle (see text).

Strategy I: Cyclisation of specifically 3N-substituted 4-quinazolones (Q-R) to tricyclic systems and their further hydrolysis to daughter products: a range of Q-R (R = CH_2-CH_2X, X = OH, NH_2,NHPh; - CH_2-CH = Y,Y = CH_2, O, NOH; -Z-COPh, Z = NH, CH_2) were prepared. Their cyclisation under a variety of conditions failed. It was established that in several cases the failure was as a result of competing 2-3 bond cleavage.

Strategy II: Selective 3-4 hydrolytic cleavage followed by cyclisation to the 1-2 bond and rupture to daughter products: Every attempt to effect the 3-4 bond cleavage of Q-R failed. With dil. alkali, the 2-3 bond was ruptured and the 2-carbon lost as formic acid. To prevent 2-3 cleavage, the 2-location was blocked by Ph and Me. In these cases, the expected 3-4 cleavage with alkali took place, but the resulting products cyclised involving the 1-N to give o-carboxyphenyl, imidazoles (R = CH_2-COPh) and triazoles (R = NH-COPh).

Strategy III: Synthesis of tricyclic systems followed by rupture to daughter products: The tricyclic system 1,2,3,5-tetrahydro-5-oxo-1-phenyl imidazo-(2,1-b) quinazoline was prepared by an interesting sequence from anthranilic acid. All efforts to reduce the electron rich Q-1-2 bond, a pre-requisite for daughter separation, failed.

Strategy IV:3,3-Shift followed by cyclisation and rupture: Endeavours to effect the entire sequence of changes in one reaction with 4-quinazolyl acetone oxime ether and acetone hydrazone resulted in deep seated re-arrangements.

These experiments above all demonstrated the unique nature of the ATP-Imidazole cycle and led to the identification of enamino unit as crucial to success.

12. The regio-selectivity in alkylations of 4-quinazolones has been rigorously established by direct correlation of 3-N substituted 2'-oxoethyl, 2'-oximinoethyl and 2'hydroxyethyl 4-quinazolones resulting from alkylation of 4-quinazolone congugate base with $BrCH_2CH(OEt)_2$. Thus, 4-O-allyl quinazoline underwent smooth Claisen re-arrangement to 3-N-allyl-4-quinazolone. The latter on OsO_4- periodate degradation gave 3-(2'-oxoethyl) and subsequently, 3-(2' oximinoethyl) and 3-(2' hydroxyethyl) 4-quinazolones identical to those obtained by direct alkylation.

13. 8: IR(KBr): 1690,1665 cm^{-1}; NMR: δ ($CDCl_3$) 5.45 (s,2H), 7.35-8.45 (m,10H); m/e: 264(M^+), 159(M^+ - PhCO). 9: IR(KBr): 1720,1675 cm^{-1}; NMR: δ ($CDCl_3$) 2.35 (s,3H), 4.85 (s,2H), 7.3-8.4 (m,5H); m/e: 202(M^+), 159(M^+ - $COCH_3$). 10: Colourless thick liquid; NMR: δ ($CDCl_3$) 1-2.35 (m,10H), 3.85 (br,1H), 7.85 (brs,7H); m/e: 226 (M^+). 11: NMR: δ($CDCl_3$) 2.1 (s,3H), 5.05 (s,2H), 6.85 - 8.2 (m,7H); m/e: 172 (M^+). 12. IR(KBr): 3480,3360,3310,1630 cm^{-1}; NMR: δ($CDCl_3$) 4.55 (d,2H), 5.25 (br,2H), 6.5-7.5 (m,10H). 13: IR(KBr): 3470,3360,3290, 1620 cm^{-1}; NMR δ($CDCl_3$) 0.6 - 2.3 (m,10H), 3.85 (br,1H), 5.5 (Br,2H), 5.9 (Br,1H), 6.4 - 7.3 (m, 4H).

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16. The absence of reaction on treatment N-alkyl or benzyl systems related to 7 with $PhCH_2NH_2$ in sharp contrast to 8 and 9 shows that neither the oxo-grouping nor the ring is affected at this stage. We believe that the initially formed Schiff's base undergoes cyclisation and the resulting tricyclic system is transformed to a highly activated carbonyl which suffers ready cleavage with $PhCH_2NH_2$.
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