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IMIDAZOLE SYNTHESIS ON A SOLID SUPPORT

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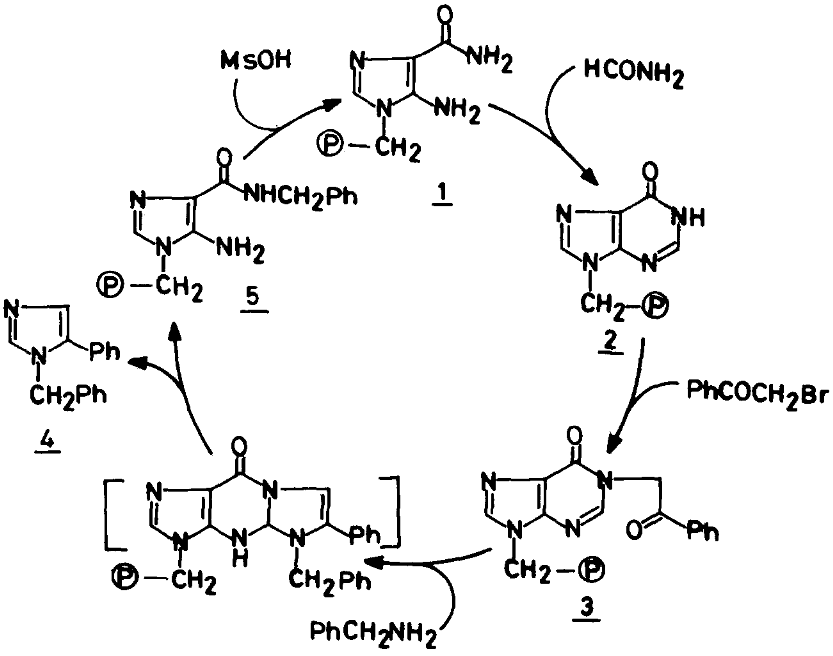
ABSTRACT : Imidazole synthesis has been demonstrated using polymer supported 4-carboxamido -5-aminoimidazole and hypoxanthine.

We report in this communication the structuring of an imidazole producing machine and the demonstration of the ability of such a system to generate derived imidazoles in cyclic operations (Scheme)[1].



Ⓟ= Styrene-divinyl benzene (2 %) copolymer

Macroporous polystyrene (Aldrich) was chloromethylated[2] to yield 66% of the product carrying the functional group. The reaction of the resulting Ⓟ—CH_2Cl (15mmol) with 6-chloropurine (32mmol)and anhyd. K_2CO_3 (36mmol) in dry DMSO (90ml) for 2 d at rt followed by usual work up[3] gave 12 mmol[4] of polymer bound 6-chloropurine which on reflux in IN HCl (170ml) for 18h followed by exhaustive washing[5] gave 9.5 mmol of Ⓟ—CH_2-hypoxanthine (2). Compound 2 (9mmol) was stirred for 2h with 0.5M KOH/MeOH (60ml), admixed gradually with $PhCOCH_2Br$ in absolute MeOH (45mmol, 30ml), the mixture refluxed for 45h and worked up[6] to give 9mmol of 1-phenacyl -Ⓟ—CH_2-hypoxanthine (3). Compound 3 (8.4 mmol) was suspended in dry xylene (80ml), admixed with $PhCH_2NH_2$ (56mmol) and anhyd. p -TsOH (42mmol), refluxed for 35h and the reaction mixture processed[7] to yield 2.5 mmol (30%) of derived product 1-benzyl-5-phenyl imidazole (4) mp 111°C which was identical in all respects with an authentic sample[1], and 6mmol of 4-N-benzylcarboxamido -5-amino Ⓟ—CH_2-imidazole (5). The over all yield of 4 from Ⓟ—CH_2-hypoxanthine, which is more realistic[4], was 24%, which compares very well with the overall yield of 22% that was obtained from the soluble template 9-benzylhypoxanthine[1]. Compound 5 (10.7mmol) was suspended in MsOH (50ml), held at 120-125°C for 30h and processed[8] to give 10.2mmol of 4-carboxamido-5-amino- Ⓟ -CH_2-imidazole (1), which was used to initiate a second cycle.

A suspension of 4.8mmol of 1 in $HCONH_2$ (12ml) was held at 195°C for 1h and worked up[3] to yield 4.7mmol of Ⓟ — CH_2-hypoxanthine (2). The thus Ⓟ— CH_2-hypoxanthine prepared by recycling (4.6mmol) was alkylated with phenacylbromide as described in the original cycle to give 3.7mmol of 3. Compound 3 (3.6mmol) when processed with $PhCH_2NH_2$ and p -TsOH as described earlier for the first cycle gave 0.5mmol (14%, overall yield from Ⓟ—CH_2-hypoxanthine of the second cycle : 12%[4]) of the derived product 1-benzyl-5-phenylimidazole (4), thus demonstrating that 2 can be successfully reused for further production of imidazoles[9].

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REFERENCES AND NOTES

1. The structures proposed for the intermediates 1 , 2 , 3 and 5 are not proven and are based on our earlier observations (D. Ranganathan and F. Farooqui, Tetrahedron Lett., 5701 (1984); D. Ranganathan, F. Farooqui and D. Bhattacharyya, Tetrahedron Lett., 2905 (1985)).
2. J.M.J.Frechet, M.D. de Smet and M.J.Farrall, J.Org.Chem., 44, 1774 (1979).
3. The beads were filtered, washed successively with hot water (2x20ml), dioxan (3x10ml), acetone (3x20ml), ether (3x20ml) and dried.
4. The yields are estimated throughout on the basis of nitrogen analysis of samples dried to constant weight in vacuo at 60°C. The most reliable yields are in step Ⓟ— CH_2Cl→Ⓟ— CH_2 -6-chloropurine (0% Nitrogen→20.7% N per unit) and in the step where crystalline monomer 1-benzyl-5-phenylimidazole is isolated as the derived product. The overall yield of the derived product therefore is more reliable than the yield obtained in the step where it is produced.
5. The Polymer was filtered, washed with water (4x20ml), saturated $NaHCO_3$ (4x20ml), water (2x20ml), MeOH (2x20ml), ether (2x20ml) and dried.
6. The reaction mixture was filtered, washed with ether (2x20ml), MeOH (3x20ml), water (2x20ml), acetone (2x20ml) and MeOH (2x20ml) and dried.
7. The reaction mixture was filtered and the residue washed with EtOAc until no brown filtrate was obtained. The filtrate thus obtained was evaporated in vacuo and the residue chromatographed on silica gel. Elution with PhH : EtOAc :: 1 : 1 gave the derived imidazole 4, mp 111°C. The residual beads were further washed with water (2x20ml), MeOH (2x20ml), ether (2x20ml) and dried.
8. The reaction mixture was cooled, mixed with cold water (50ml), neutralized with NH_4OH, filtered, washed with cold water (3x20ml), MeOH (3x20ml), ether (2x20ml) and dried.
9. We are most grateful to the referees for valuable suggestions.

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