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Preparation of 1,2,4-trisubstituted imidazoles by ammonolysis of *N*-(2-oxoalkyl)oxazolinium salts

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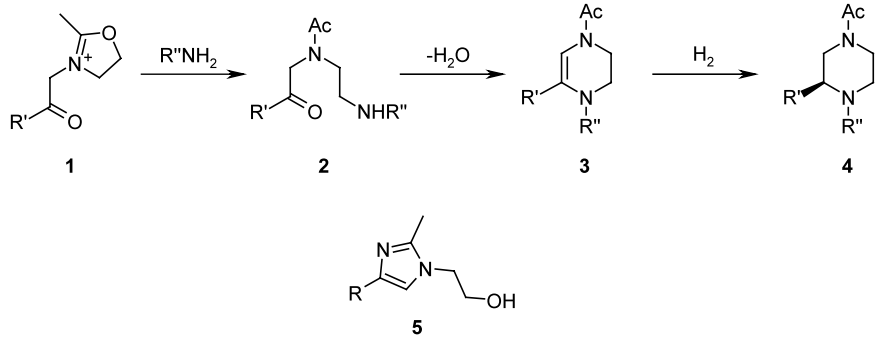
Abstract—A variety of aryl and alkyl substituted imidazoles have been prepared by the ring opening of *N*-(2-oxoalkyl)-oxazolinium salts with ammonia.

We have recently been interested in the synthesis of differentially protected enantiopure piperazines **4** for incorporation into new drug candidates. Our proposed synthesis of **4** is depicted in Scheme 1 and relies upon the catalytic asymmetric hydrogenation[1] of the tetrahydropyrazine **3** in order to provide a flexible route to both antipodes of **4**. We anticipated that ring opening[2] of the *N*-(2-oxoalkyl)oxazolinium salt **1** with a primary amine would deliver the amino ketone **2** which could then undergo spontaneous intramolecular enamine formation to give the hydrogenation precursor **3**. However, during the course of our investigations we observed interesting reactivity of the intermediate *N*-(2-oxoalkyl)oxazolinium salts **1** with ammonia and, in this paper, we disclose a novel two step preparation of 1,2,4-trisubstituted imidazoles **5**.

Initially, we decided to probe the reactivity of the *p*-tolyl substituted oxazolinium salt **7** (R = *p*-tolyl). Thus, following literature precedent[3] the salt was prepared by alkylation of 2-methyloxazoline with *p*-methylphenacyl bromide (Scheme 2)[4] in isopropyl acetate. Conveniently, the salt could be isolated directly by filtration of the reaction mixture and was found to exist in DMSO solution entirely as the enol rather than the keto tautomer.[5] On storage at room temperature this *p*-tolyl substituted oxazolinium salt **7** slowly underwent hydrolytic ring opening to afford the acetate **8** as its hydrobromide salt.

On treatment with an excess of methanolic ammonia, **7** was rapidly consumed to generate a crystalline product



Scheme 1.

Keywords: imidazole; oxazolinium salts; ammonia.

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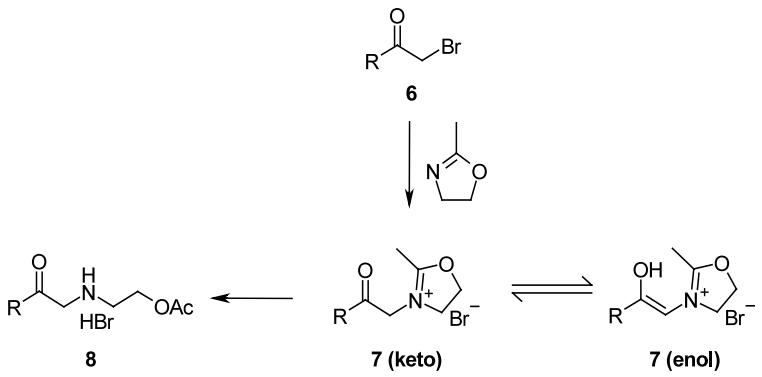


Scheme 2.

which demonstrated ^{1}H NMR and IR spectra that were consistent with the imidazole **5** rather than the desired dehydropiperazine **10** (Scheme 3).[4] Presumably, contrary to significant precedent,[2] the nucleophile had added to the C=N double bond and, following ring scission, the resulting amidine cyclised spontaneously to give the imidazole **5** (path b).

To examine the scope and generality of this approach towards 1,2,4-trisubstituted imidazoles a number of commercially available α-bromoketones **6** were converted to their corresponding oxazolinium salts **7** under analogous conditions. It was found that a number of these salts, unlike the *p*-nitrophenyl derivative, existed as a mixture of keto and enol tautomers and indeed the *p*-methoxyphenyl derivative favoured the former completely. As before, exposure of the salts to methanolic ammonia served to cleanly provide their respective imidazole frameworks in reasonable to good yield.[6] Furthermore, the procedure could be extended to the preparation of 4-alkylimidazoles by performing both the alkylation and ammonolysis steps using THF as the solvent which obviated the need to isolate the labile alkyl substituted oxazolinium salts.[7] The unoptimised yields quoted are for the two step conversion of the bromoketones **6** to the imidazoles **5**.[4] In order to obtain a definitive structural assignment for this class of compounds the imidazoles **5d**, **5e** and **5n** were recrystallised and subjected to single crystal X-ray diffraction analysis—the 50% thermal ellipsoid plot for imidazole **5n** is depicted in Fig. 1.[8]

In an attempt to alter the regioselectivity of the ammonia addition we examined the use of more sterically

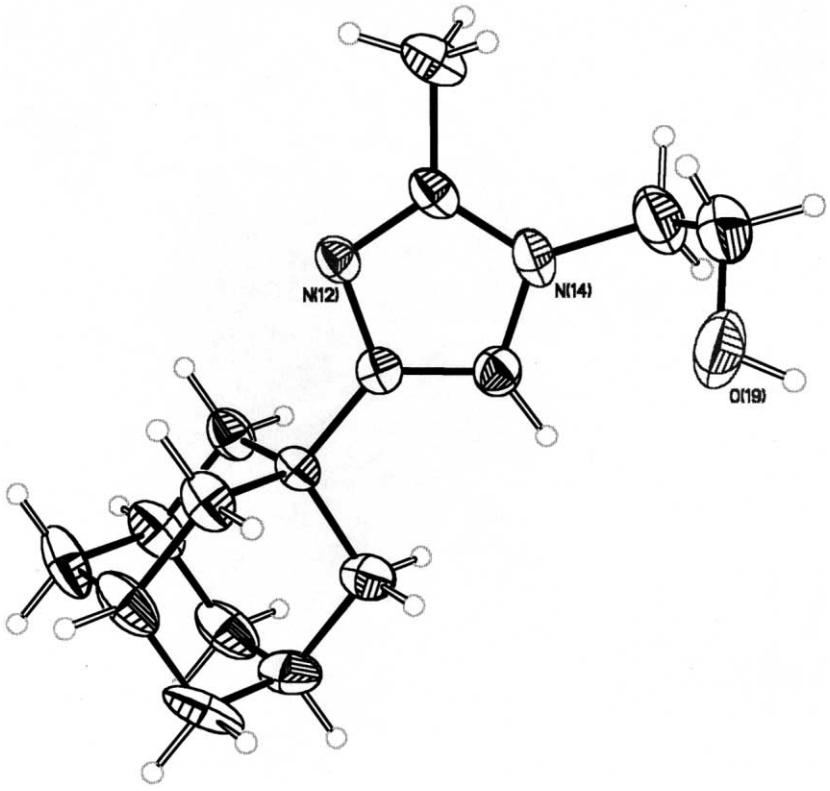
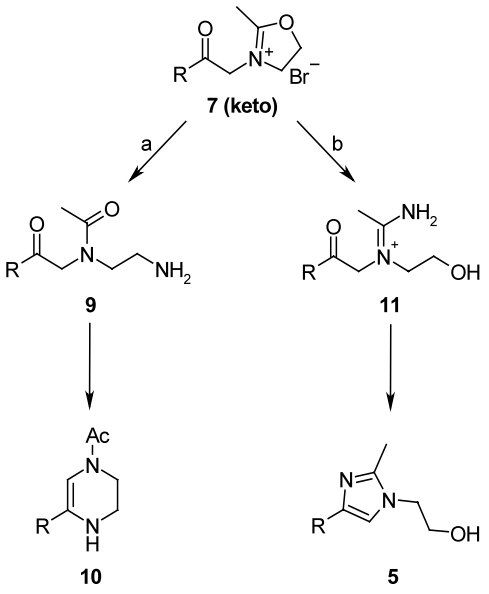


Figure 1. 50% thermal ellipsoid plot of imidazole **5n**.



Scheme 3.

hindered amines such as α-methylbenzylamine and hexamethyldisilazane but disappointingly these reactions proved unsuccessful.

In conclusion, a facile preparation of a variety of 1,2,4-trisubstituted imidazoles from α-bromo ketones has been demonstrated. Further investigations directed towards the modification of the reaction pathway and to elucidate the mechanism of imidazole formation are currently underway.

Acknowledgements

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2. (a) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Org. Chem*. **1996**, *61*, 10–11; (b) Brunel, S.; Chevalier, Y.; Le Perchec, P. *Tetrahedron* **1989**, *45*, 3363–3370; (c) Forestiere, A.; Sillion, B. *J. Heterocyclic Chem*. **1980**, *17*, 1381–1383.
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4. The nature of R is denoted by the following letters: **a**, *p*-MeC_6H_4 (48%); **b**, *p*-$NO_2C_6H_4$ (57%); **c**, *o*-FC_6H_3 (49%); **d**, *p*-ClC_6H_4 (36%); **e**, *p*-$CH_3OC_6H_4$ (33%); **f**, *p*-FC_6H_4 (61%); **g**, *p*-BrC_6H_4 (55%); **h**, *m*,*p*-$Cl_2C_6H_3$ (63%); **i**, 2-naphthyl (34%); **j**, *p*-$C_6H_5C_6H_4$ (19%); **k**, *p*-NCC_6H_4 (65%); **l**, *m*-FC_6H_4 (19%); **m**, *m*-$NO_2C_6H_4$ (29%); **n**, 1-adamantyl (36%); **o**, *m*-CH_3, *p*-ClC_6H_3 (19%); **p**, 3-benzothienyl (40%).
5. Bansal, R. K.; Gupta, N.; Kabra, V.; Jain, C. B.; Karaghiosoff, K.; Schmidpeter, A. *Phosphorus Sulfur Silicon Relat. Elem*. **1994**, *86*, 139–143.
6. All new compounds were fully characterised by ^1H NMR, ^{13}C NMR, high-resolution MS and IR.
7. **Typical experimental conditions**: 2-[4-(4-Fluorophenyl)-2-methylimidazol-1-yl]ethanol (**5f**): 2-Methyl-2-oxazoline (0.39 g, 4.61 mmol) was added to a stirred solution of 4-fluorophenacyl bromide (1.00 g, 4.61 mmol) in tetrahydrofuran (4 ml) at room temperature. The mixture was stirred for 16 h, then treated with ammonia (7 M in methanol, 1.97 ml, 13.82 mmol) and stirred for a further 16 h. The solvent was removed under reduced pressure and the residue was partitioned between water (5 ml) and methyl acetate (5 ml). The organic layer was separated and the aqueous layer was extracted with methyl acetate (2×5 ml), then the organic extracts were washed with brine (10 ml), dried ($MgSO_4$) and concentrated in vacuo to leave the imidazole (0.62 g, 61%) as an off-white solid; ν_{max}/cm^{-1} (solid phase) 3256, 2877, 2813, 2423, 2188; δ_H (400 MHz, CD_3OD) 7.71–7.65 (2H, m, *Ar*), 7.39 (1H, s, NC=C*H*N), 7.13–7.06 (2H, m, *Ar*), 4.04 (2H, t, $J=5.1$, NCH_2CH_2OH), 3.85 (2H, t, $J=5.4$, NCH_2CH_2OH), 2.45 (3H, s, CCH_3); δ_C (100 MHz, CD_3OD) 163.7 (d, $J=244.4$), 147.6, 139.1, 131.4 (d, $J=3.2$), 128.0 (d, $J=8.0$), 117.7, 116.8 (d, $J=21.8$), 62.6, 50.3, 13.0; *m*/*z* (ES^+) 221.1084 ($M+H^+$), $C_{12}H_{14}FN_2O$ requires 221.1090.
8. The crystallographic data has been deposited at the Cambridge Crystallographic Data Centre with deposition number CCDC 189970. Chemical formula = $C_{26}H_{24}N_2O$; formula weight = 260.37; crystal system: monoclinic; space group $P2_1$; $a=7.2591(9)$, $b=7.1821(9)$, $c=13.7076(17)$ Å; $\beta=91.929(2)°$; $V=714.25(15)$ $Å^3$; data collection temp. 160(2) K; radiation: Mo Kα ($\lambda=0.71073$ Å).