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REGIOSELECTIVE N-ALKYLATION OF 4-FORMYLIMIDAZOLE

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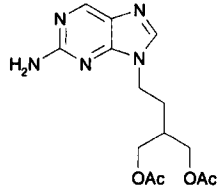
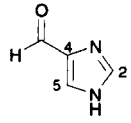
ABSTRACT: We describe here a high yield and highly regioselective N-alkylation of 4-formylimidazole *via* reversible Michael Reaction.

During our search for a concise and cost-effective synthetic route to famciclovir (BRL-42810), the active ingredient in the antiviral drug **Famvir®**, we required a regioselective N-alkylation of 4-formylimidazole (**1**) to form a 1,4-disubstituted imidazole for use in one of our proposed syntheses.



Famciclovir (BRL-42810)



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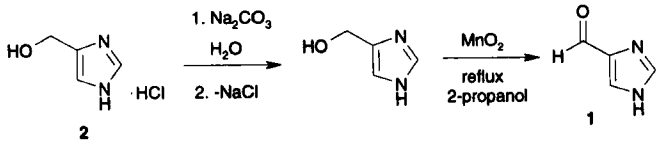
N-Alkylation of asymmetrically substituted imidazoles usually leads to formation of 1,4- and 3,4- regioisomeric mixtures.[1] Direct N-alkylations of imidazole-4-carboxylic acid derivatives were reported in a few cases.[1] Among them, high regioselectivity was reported only on imidazole-4-carboxamide, with simple alkylating reagents.[1b-1d] The 1,4-substituted product is favored by intramolecular hydrogen bonding, as well as for steric reasons.[1d] N-alkylation of 4-formylimidazole (**1**) was reported only with triphenylmethyl chloride, yielding 74% of the 1,4-disubstituted imidazole.[2] The regioselectivity resulted from the steric bulk of the triphenylmethyl group.

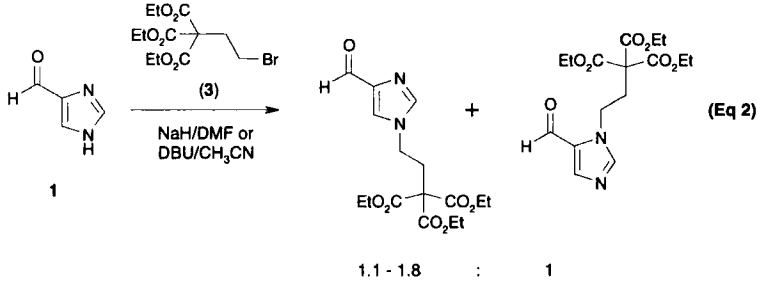
Compound **1** was synthesized in 77% yield from 4-(hydroxymethyl)imidazole hydrochloride (**2**) by following a two-step literature procedure with slight modification, using 2-propanol as the solvent for the oxidation step.[3] Attempts to synthesize **1** directly from the hydrochloride salt **2** with MnO_2, or, to do neutralization and oxidation in one pot gave low yield of product contaminated with a black powder that could not be completely removed. This was probably caused by the poor solubility of the hydrochloride salt **2** in the reaction solvent, and by the reaction between Cl^- and MnO_2.[4]

Initially, we tried the alkylation of **1** with triethyl 3-bromopropane-1,1,1-tricarboxylate (**3**). No reaction was observed with NaOEt/EtOH. Addition of a

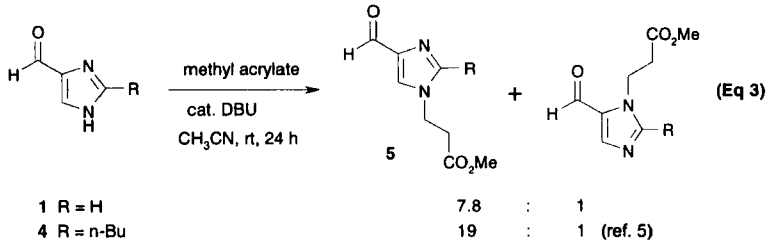


(Eq 1)

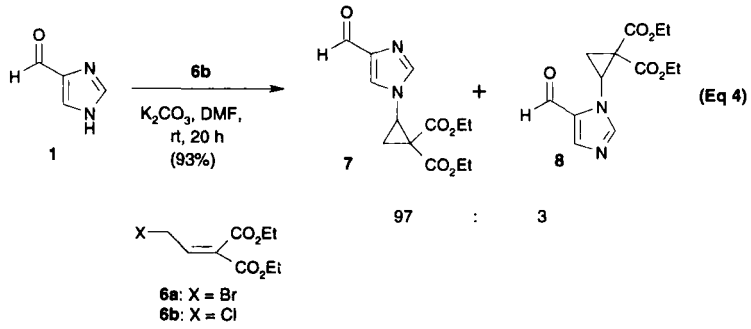
DMF solution of **1** and bromide **3** to NaH/THF at room temperature gave a large amount of polar material. Using Et_3N as the base lead to mainly an unidentified product. With powdered KOH in CH_3CN/H_2O and in the presence of phase transfer catalyst Bu_4NBr, a mixture of the alkylated products and starting material, along with an impurity, was obtained. Poor regioselectivities and less than a 20% yield of alkylation products were obtained with either NaH/DMF or DBU/CH_3CN at room temperature (eq 2). In light of the poor results obtained by simple S_N1 alkylation, we turned to a different alkylation strategy.



The Michael reaction between 2-butyl-4-formylimidazole (**4**) and α,β-unsaturated esters has been shown to lead to highly regioselective N-alkylation.[5] We wondered whether **1**, lacking the steric bulk provided by a 2-substituent, could approach the 19 : 1 selectivity of the DBU-catalyzed reaction of **4** with methyl acrylate. When we tested the alkylation of **1** by this protocol, the reaction was complete in 3 hours, with a ratio of 7.3 : 1. After stirring 24 hours, the ratio had increased only slightly, to 7.8 : 1. The 1-alkyl-4-formylimidazole **5** was obtained as the thermodynamically favored isomer in a 59% isolated yield (eq 3).



Encouraged by this modest selectivity, we turned to an alkylating agent that could be readily converted to the famciclovir sidechain. Diethyl bromo- and chloroethylidene malonate (**6a** & **6b**) have been reported to give good to excellent selectivities in their reaction with 2-amino-6-chloropurine.[6] The reaction mechanism involves a reversible Michael addition followed by an irreversible ring closure. Reaction of **1** with bromide **6a** and a catalytic amount of DBU in acetonitrile gave only a 4 : 1 isomer ratio after stirring for 24 hours, but the results with the chloroethylidene malonate (**6b**) were slightly better (6-8 : 1 ratio). This is consistent with what was described in the literature report,[6] where the increased ratio could be explained by the poorer leaving group (Cl vs. Br) allowing the reversible Michael addition to proceed more towards the thermodynamically favored isomer before the irreversible ring closure takes place. Dramatically better results were obtained when we switched the reaction conditions from DBU/MeCN to K_2CO_3/DMF. After stirring the reaction for 20 hours at room temperature we obtained, following purification, a 93% yield of the alkylation products as an inseparable mixture. LC-MS analysis indicated 97 : 3 ratio of the two isomers. The major isomer was confirmed by NOE experiments as the desired 1-alkyl-4-formylimidazole **7** (Eq. 4).



In summary, a high yield and highly regioselective N-alkylation of 4-formylimidazole was achieved *via* reversible Michael addition to give the thermodynamically favored 1-alkyl-4-formylimidazole. Michael reaction is a potentially good method for making the thermodynamically favored N-alkylation product from asymmetrically substituted imidazoles.

Experimental Section

N-alkyl-4-formylimidazole (7 & 8). To a solution of diethylchloroethylidene malonate (6.89 g, 31.3 mmol) in DMF (40 ml) was added aldehyde **1** (2 g, 20.8 mmol) in one portion. The reaction mixture was cooled to 0 °C after **1** was completely dissolved. K_2CO_3 powder (3.2 g, 22.7 mmol) was added in portions to the reaction mixture which was then stirred at room temperature for 20 h. The reaction was quenched with ice water (60 ml) and extracted with EtOAc. The EtOAc extracts were washed with H_2O and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (silica gel, hexane:$CHCl_3$:MeOH 10:10:1) yielded a mixture of the 1,4- and 3,4-alkyl-4-formylimidazole products **7**

and **8** (5.4 g, 93% yield, 97:3 isomer ratio). The analytic data for the mixture: IR (film) 2754, 1726, 1690, 1539 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ 9.72 (1H, s), 7.57 (1H, J = 1.3 Hz, d), 7.55 (1H, J = 1.3 Hz, d), 4.31-4.16 (3H, m), 3.94-3.89 (2H, m), 2.35 (1H, J = 6.5, 6.5 Hz, dd), 1.86 (1H, J = 6.5, 8.3 Hz, dd), 1.21 (3H, J = 7.1 Hz, t), 0.98 (3H, J = 7.1 Hz, t); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.9, 167.4, 164.3, 142.1, 139.1, 124.8, 62.6, 62.5, 39.5, 36.2, 18.7, 14.0, 13.7, HRMS: calcd for $C_{13}H_{16}N_2O_5$ 280.1059, found 280.1059

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References and Notes

1. a) Mishin, M. A.; Poznyakova, L. N.; Piotrovskii, L.B.; Erusalimskii, G. B. *Zh. Obshch. Khim.* **1992**, *62(11)*, 2576-81;

   b) Kuroda, T.; Suzuki, F. *Tetrahedron Lett.* **1991**, *32(47)*, 6915-18;

   c) Piotrovskii, L. B.; Dumpis, M. A. *Khim. Geterotsikl. Soedin.* **1990**, *4*, 475-7;

   d) Papadopoulos, E. P. *J. Org. Chem.* **1977**, *42*, 3925-29.

2. Kelley, J. L.; Miller, C. A.; McLean, E. W. *J. Med. Chem.* **1977**, *20*, 721.

3. Battersby, A. R.; Nicoletti, M.; Staunton, J.; Vleggaar, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 43-51.

4. Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry. A*

Comprehensive Text. 4th ed.; John Wiley & Sons, Inc: New York, **1980**; pp 744-745.

5. Matsuoka, R. T.; Liu, P. US 97-38196; *Chem. Abstr.* **1998**, *129*, 202942.
6. Geen, G. R.; Kincey, P. M.; Choudary, B. M. *Tetrahedron Lett.* **1992**, *33(32)*, 4609-12.

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