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A NEW SIMPLE PROCEDURE FOR ALKYLATION OF NITROGEN HETEROCYCLES USING DIALKYL OXALATES AND ALKOXIDES.

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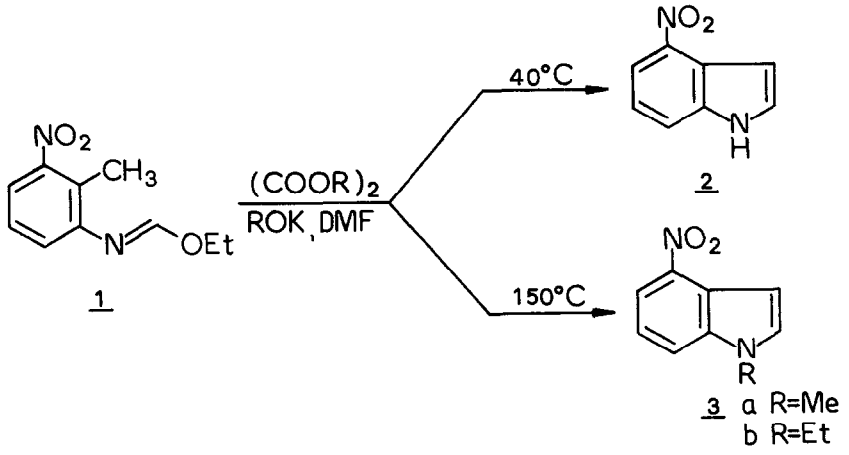
Abstract: A variety of nitrogen heterocycles are N-alkylated in high yields with dialkyl oxalates and potassium alkoxides in refluxing dimethylformamide.

During the development of our synthesis of 4-nitroindoles,[1,2] we observed N-alkylations of the products at elevated temperatures,i.e. methylations or ethylations depending on the oxalate used, (Scheme 1).



SCHEME 1

An effort to cyclize the imidate ester 1 using dimethylformamide-dimethylacetal (DMF-DMA) in refluxing dimethylformamide (DMF), i.e. Batcho/Leimgruber conditions,[3] resulted in formation of 1-methyl-4-nitroindole (3a).
Also the DMF-DMA and the diethyl oxalate/potassium ethoxide complex[4] were shown to cyclize the imidate ester before alkylating on nitrogen. Addition of 4-nitroindole to either DMF-DMA or diethyl oxalate/potassium ethoxide complex in refuxing DMF thus resulted in good yields of 3a and 3b respectively.

Since methylations of nitrogen heterocycles with DMF-DMA are quite well known,[5 6] we conducted a series of comparative alkylations using dialkyl oxalates and alkoxides.

The isolated yields from these reactions (Table 1), indicate that this procedure not only gives less complex product patterns and frequently higher yields than DMF-DMA, it also seems to produce an altered regioselectivity in the alkylations of the ambident heterocycles.

TABLE 1. Alkylation products from dialkyl oxalate reactions in refluxing DMF.

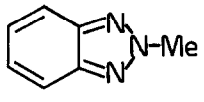
Product	Oxalate	Alkoxide	Yield	m.p. (°C)	Lit. yield (method)
1-Methyl-4-nitroindole	Me	EtOK	91%	112-6	-
1-Ethyl-4-nitroindole	Et	EtOK	94%	50.5	-
7-Ethyl-1,3-dimethyl-4-nitroindole[a]	Me	EtOK	98%	114-8	-
1-Methylindole	Me	t-BuOK	88%	-	85-95%($NaNH_2$/MeI)[7]
1-Methylbenzimidazole	Me	t-BuOK	75%	57-60	38%(DMF-DMA)[5]
1-Methyl-5-nitrobenzimidazole	Me	t-BuOK	43%	209-11	42%(MeI/KOH/18-crown-6)[8]
1-Methyl-6-nitrobenzimidazole	Me	t-BuOK	40%	181-2	28%(MeI/KOH/18-crown-6)[8]
1-Methyl-4-nitroimidazole[b]	Me	t-BuOK	59%	134-5	0.2%(Me_2SO_4)[9]
1-Methyl-1H-benzotriazole (5)	Me	t-BuOK	59%	64-5	10%(DMF-DMA)[5]
2-Methyl-2H-benzotriazole (4)	Me	t-BuOK	35%	-	38%(DMF-DMA)[5]
9-Methyl-9H-purine[b]	Me	t-BuOK	37%	163-5	30%(DMF-DMA)[5]
9-Methyl-9H-adenine[b,c] (6)	Me	t-BuOK	43%	297-9	95%(MeBr/Bu_4NF)[10]

a) N-methylation.

b) Other regio-isomers were not isolated.

c) 9-Methyladenine was isolated in 4% yield as its amidine derivative from reaction with DMF-DMA.[5]

Two representative examples are the syntheses of the methylbenzotriazoles (4 and 5) and 9-methyladenine (6).



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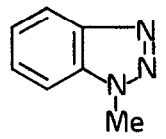

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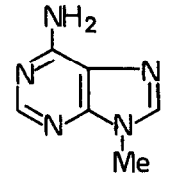

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Benzotriazole (3.57 g,30 mmol), dimethyl oxalate (3.54 g,30 mmol) and t-BuOK (3.36 g,30 mmol) were heated in DMF (50 mL) under reflux (3 h). Addition of aqueous ammonia and extraction with methylene chloride gave the isomeric mixture of products from which 1-methylbenzotriazole (5) was removed by extraction with hydrochloric acid (5 M) giving 2-methylbenzotriazole (4) as a yellow oil (1.38 g; 35%). The acidic extract was made alkaline and extracted with ether giving 5 as white plates (2.36 g; 59%) m.p. 64-5°C.

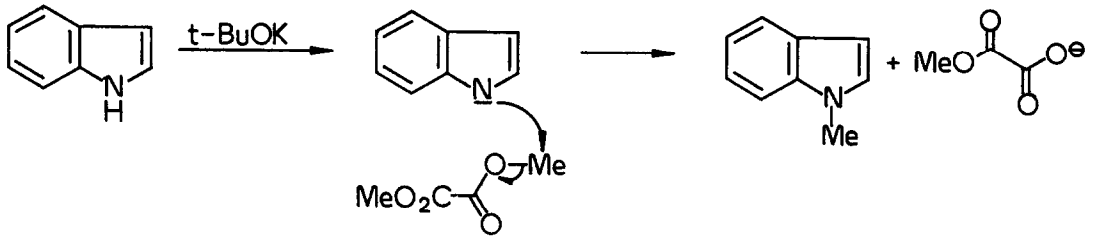
Adenine (2.70 g,20 mmol), dimethyl oxalate (2.36 g,20 mmol) and t-BuOK (2.24 g,20mmol) were heated in DMF (60 mL) under reflux (1 h) after which the solvent was evaporated. The residue was extracted with acetonitrile (ca. 300 mL) and the extract was treated with charcoal and filtered. From this solution, 9-methyl-9H-adenine (6) deposited upon cooling (1.28 g; 43%) m.p. 297-9°C (lit.[11] 300-2°C).

The major advantages of this procedure are the high reaction rates, e.g. 1-methylindole is formed quantitatively (TLC) within 15 min., and the relative ease with which it is conducted. Disturbing side reactions such as quaternization during alkylations of benzimidazoles were not observed. Formation of by-products in the methylations of adenine and purine were avoided by lowering the reaction temperature to 90°C. This led, however, to considerably longer reaction times.

The reversed ratio of regio-isomers was particularly interesting in the case of methylation of 4(5)-nitroimidazole (entry 8 in Table 1). Methylation with dimethyl sulfate gives an isomeric ratio of 350:1 in favour of 1-methyl-5-nitroimidazole[9] while the title procedure resulted in predominantly the 4-nitro isomer (in a ratio 1:4.1[12]).

In the case of the nitrobenzimidazoles, the 6-nitro isomer (which can be regarded as the vinylogue of 1-methyl-5-nitroimidazole) was isolated in a comparatively good yield (isomeric ratio ∿1:1). This may be due to interconversion of the isomers as previously reported by Mathias and Burkett.[8] We did not, however, observe such an interconversion.

The reaction mechanism of the title reaction is not fully understood. The relatively acidic protons present in the substrates used might suggest the simple reaction pathway depicted in Scheme 2.



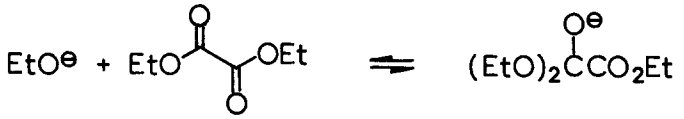
SCHEME 2

On the other hand, we feel that the high reaction rates are not compatible with the expected low electrophilicity of the ester α-carbon. To the best of our knowledge, all nucleophilic substitutions of oxalates proceeds by an initial carbonyl attack.

Furthermore, the comparatively poor yields of alkylated products obtained by substituting the alkoxides for hydrides (e.g. 30% of 1-ethyl-4-nitroindole) also contradicts the mechanism in Scheme 2.

Clearly, the DMF does not participate in the reaction since other aprotic solvents, e.g. diglyme, ethyl ether and dimethyl sulfoxide, can also be used although DMF generally gave the best results.

The dialkyl oxalate/alkoxide complexes, e.g. 7,[4] are most certainly present in the reaction mixtures but their role in the reaction pathway, if any, is not known. A semi-empirical MO-SCF-HAM/3 calculation[13] made on the complex 7,[14] offers no support for such speculations.



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References and Notes

1. J.Bergman,P.Sand and U.Tilstam,Tetrahedron Lett. 24 3665 (1983).
2. J.Bergman and P.Sand, to be published.
3. W.Leimgruber and A.D.Batcho, 3rd Intl.Congr.Het.Chem.Abstr.Pap. p.462,Sendai,Japan,Aug.23-27, (1971).
4. Initially (first three entries in Table 1) we added the oxalates/alkoxides as isolated,solid complexes, cf. F.Adickes, Ber. 65 522 (1932).
5. B.Stanovnik,M.Tisler,A.Hribar,G.B.Barlin and D.J.Brown, Aust.J.Chem. 34 1729 (1981).
6. M.Gacek and K.Undheim,Acta Chem.Scand. B36 15 (1982).
7. K.T.Potts and J.E.Saxton, Org.Synth.Coll.Vol. 5 769 (1973).
8. L.J.Mathias and D.Burkett, Tetrahedron Lett. 4709 (1979).
9. C.E.Hazeldine,F.L.Pyman and J.Winchester, J.Chem.Soc. 125 1431 (1924).
10. K.K.Ogilvie,S.L.Beaucage and M.F.Gillen, Tetrahedron Lett. 1663 (1978).
11. G.B.Elion, J.Org.Chem. 27 2478 (1962).
12. The isomeric ratio was determined by NMR on the crude product.
13. L.Åsbrink,C.Fridh and E.Lindholm, Quant.Chem.Progr.Exch. 12 393 (1981).
14. Copies of these data are available upon request.

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