Tetrahedron Letters No. 49, pp 4709 - 4712.

0040-4039/79/1201-4709$02.00/0

N-ALKYLATION OF BENZIMIDAZOLES AND BENZOTRIAZOLE VIA PHASE TRANSFER CATALYSIS

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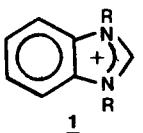
Summary: N-methyl and other N-alkyl benzimidazoles and benzotriazoles were prepared by 18-crown-6 catalysis involving basic aqueous solutions of the heterocycles and organic solutions of alkyl iodides or bromides.

In the course of our work with highly substituted benzimidazoles, we required a mild, clean procedure for introducing methyl and benzyl groups onto the heterocycle nitrogens. Available methods involving refluxing CH_3I in CH_3OH[1] or dimethyl sulfate[2] were unsatisfactory, often leading to large yields of the unwanted N,N'-disubstituted quanternary salts 1. We describe here a new procedure for such alkylations involving phase transfer catalysis with 18-crown-6 (2).



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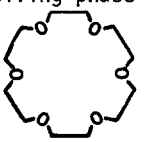

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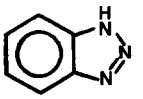

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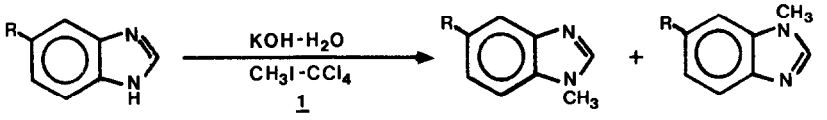
A typical methylation involves dissolving 0.5 g of a benzimidazole 4 or benzotriazole 3 in 5 ml of 3-6N KOH, adding 1.1 eq. CH_3I in CCl_4 followed by 0.05 - 0.1 eq. 2. Stirring rapidly for 4-24 hours leads to essentially complete conversion. The Table lists the reactions examined for 3 and several derivatives of 4.

deriv.	R
a	H
b	CH_3
c	Cl
d	NO_2



4a-d 5 6

The following summarize the advantages, characteristics and observations of this method to date:

1. The reactions are readily followed by NMR for appearance of product(s) in the CCl_4 layer or disappearance of starting heterocyclic salt from the aqueous layer.

2. The procedure is simple, straightforward and very easy to work up: separation and rotary evaporation of the CCl_4 layer for soluble products or simple filtration and washing of the insoluble crystalline products. Essentially pure products were obtained in most cases.

3. The method appears to be general for nitrogen-containing heterocycles which have fairly acidic N-hydrogens.[3]

4. One equivalent of CH_3I was found to be sufficient; excess CH_3I leads to side reactions, such as the ring-opening formation of the bis-$N(CH_3)_2$ compounds for 4a and 4b, a reaction which is under further investigation.

5. Rate of reaction varies with the benzimidazole substituent, with the catalyst concentration and with the alkyl halide. The times for complete reaction of the alkyl halides with

Table. Alkylations of benzimidazoles 4a-4d and benzotriazole 3.[a]

Reactants	Ratio[b]	Time	Products[c]	Isolated yds.
4a + CH_3I	1:1	12h	5a	64%
4a + CH_3I	xs[d]	5h	1, R=CH_3	70%
4b + CH_3I	1:1	10h	5b + 6b (45:55)	80%
4b + CH_3I	xs[d]	5h	5-methyl-1, R=CH_3	e
4c + CH_3I	1:1	18h	5c + 6c (45:55)	76%
4d + CH_3I	1:1	18h	5d + 6d (60:40)	70%
3 + CH_3I	1:1	18h	1- + 2-methyl-3	72%
4a + n-C_4H_9Br	1:1	2w	no reaction	-
4a + n-C_4H_9Br	xs	2w	1-n-butyl-4a	78%
3 + n-C_4H_9Br	1:1	2w	no reaction	-
3 + n-C_4H_9Br	xs	3w	1- + 2-n-butyl-3	84%
4a + p-bromobenzyl bromide	1:1[d]	24h	1, R=p-bromobenzyl	26%
4a + p-bromobenzyl bromide	1:1	4w	Mixture containing > 80% desired product (^1H NMR); chrom. separation gave pure products in low yds.	
3 + p-bromobenzyl bromide	1:1	4w		

a) according to text procedure unless otherwise noted; b) alkyl halide to heterocycle; c) ratios determined by ^1H or ^{13}C NMR; d) with reflux; e) not determined.

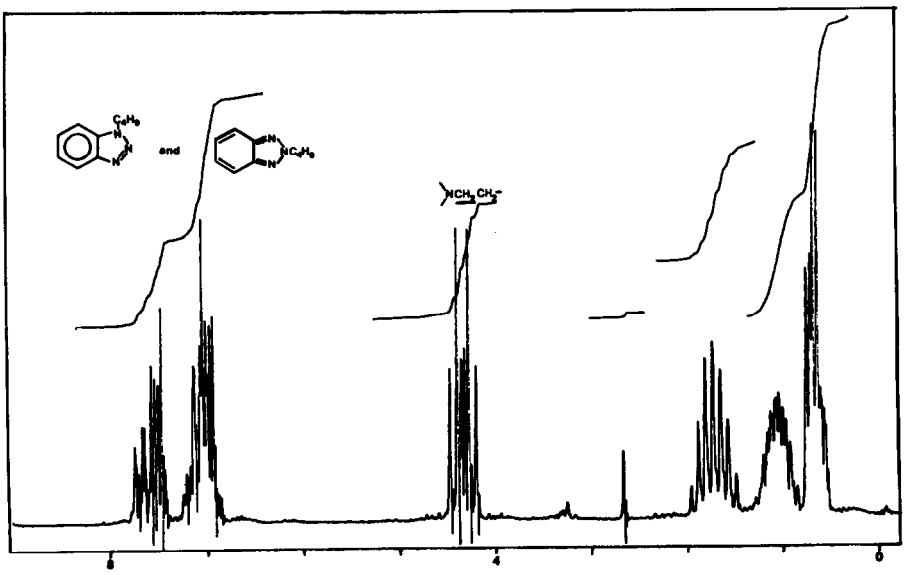


Figure 1. ^1H NMR spectrum (in $CDCl_3$) of the crude reaction mixture containing 1- and 2-n-butylbenzotrizole.

benzimidazole were: CH_3I, 12 hours; p-bromobenzyl bromide, 10 days; and n-butyl bromide, 4 weeks; times for dissappearance of starting halides under conditions in the Table.

6. The ratio of the 1-methyl-5-nitrobenzimidazole (5d) to the 1,6-isomer (6d) was found to vary with reaction time. A possible explanation for this surprising observation is subsequent methylation-demethylation of the initially formed kinetic product to give the thermodynamically more stable isomer. Further work on this point is presently being carried out.

7. The existence and ratios of the two benzimidazole isomers obtained for 4b-d were best determined by ^{13}C NMR analysis. The spectrum in Fig. 2 is of the crude reaction mixture of 4b after the methylation reaction and work-up involving separation, drying and rotary evaporation of the organic layer.

8. The alkylations of benzotrizole led to a mixture of the 1-substituted and 2-substituted isomers in all three cases examined. Similar results were reported in a previously described synthesis of alkylated benzotriazoles employing triethylbenzylammonium chloride as the phase transfer catalyst.[4] Our procedure is milder (25° vs. refluxing benzene); requires much less catalyst (0.05 vs. 0.2-1.0 eq), gives comparable yields, and generally does not require further purification of the products other than isomer separation. Moreover, the use of CCl_4 rather than benzene allows continuous monitering of the reaction with ^1H NMR.

An important application of this method is to the synthesis of various isotopically-enriched benzimidazole derivatives where good yields and conservation of the expensive enriched species is important. For example, both 1-methylbenzimidazole and the two N-methyl isomers of (5)6-nitrobenzimidazole containing 90% enrichment with ^{13}C at the 2-position have been obtained in good yields. We expect to further develop this synthesis for incorporation of ^{13}C in the N-methyl group via $^{13}CH_3I$. In the latter case, it is especially important to be able to employ only one equivalent of the labeled reagent. These isotopically-enriched compounds will be examined for evaluation of long-range ^{13}C-^{13}C and ^{13}C-^1H coupling constants[5] and for determination of the detailed mass spectral fragmentation behavior.[6]

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ACKNOWLEDGEMENT: Grateful acknowledgement is made to Auburn University for a Grant-in-Aid to pursue this work.

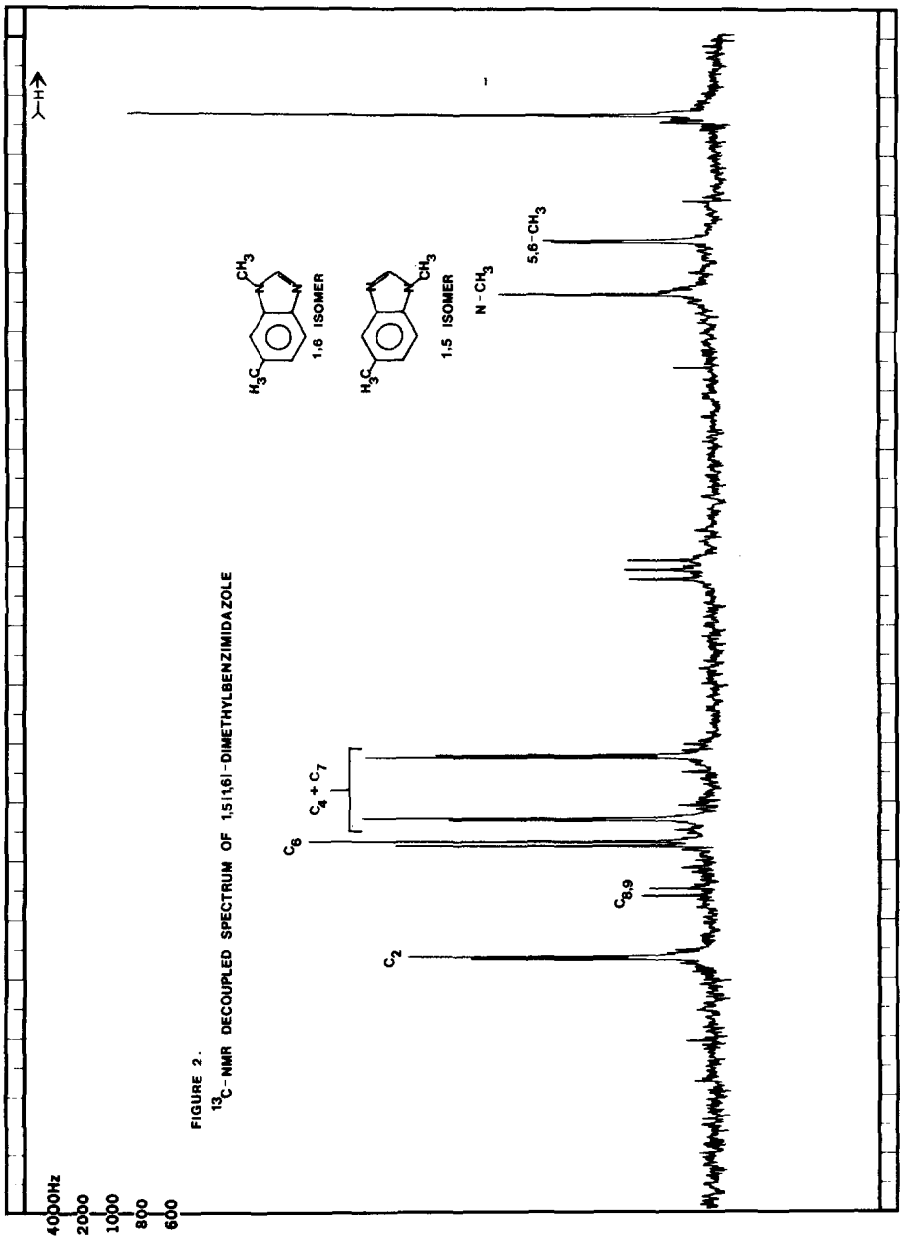

FIGURE 2.
^{13}C-NMR DECOUPLED SPECTRUM OF 1,5(1,6)-DIMETHYLBENZIMIDAZOLE

(Received in U.K. 5 June 1979)