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Publisher *Taylor & Francis*

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Journal of Macromolecular Science, Part A

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597274>

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To cite this Article Feld, William A. , Paessun, Rebecca J. and Serve, M. Paul(1981) 'The Phase Transfer Catalyzed Alkylation of 1-Hydroxybenzotriazole. I. Scope', *Journal of Macromolecular Science, Part A*, 15: 5, 891 – 896

To link to this Article: DOI: 10.1080/00222338108056774

URL: <http://dx.doi.org/10.1080/00222338108056774>

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The Phase Transfer Catalyzed Alkylation of 1-Hydroxybenzotriazole. I. Scope

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ABSTRACT

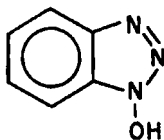
Phase transfer catalyzed alkylation of 1-hydroxybenzotriazole employing a series of alkyl halides was carried out in dichloromethane/water using tetrabutylammonium chloride as the catalyst. Several new 1-alkoxybenzotriazoles were prepared and included the alkyl and benzyl derivatives.

INTRODUCTION

A frequent problem encountered by synthetic chemists is that of bringing two reagents (e.g. salts and organic substrates) together for the purpose of interaction. The problem is frequently overcome by the use of dipolar aprotic solvents like dimethylsulfoxide or dimethylformamide. The major difficulties with such solvents are difficulty in purification and drying and usually nonexistent recovery. Another possibility is the use of hot methanol or ethanol solutions with the problems of limited salt and organic substrate solubility and the effect of heat on certain heat sensitive reagents or substrates.

An alternate approach for bringing reagents together is to employ phase transfer catalysis (PTC) (1,2). In PTC there are generally two immiscible phases. One phase, usually aqueous, contains the salt which will function as the nucleophile or base and the other is organic and contains the substrate on which the salt will act. The addition of a phase transfer catalyst (e.g. a quaternary ammonium salt) allows for anionic transport from the aqueous phase to the organic phase where reaction takes place. Quaternary ammonium salts like tetrabutylammonium bromide, are good examples of phase transfer catalysts and have been shown to be effective in catalyzing a variety of nucleophilic reactions. Interestingly, however, they are considered soft in the HSAB sense (3) and as such will pair with the softest anion available. This can lead to reduced reaction rates and "poisoned" catalysts in certain circumstances.

Most derivatives of 1-hydroxybenzotriazole (1) have substituents on the benzene ring portion of the molecule and many are used as catalysts in peptide syntheses (4). The hydroxyl group has been subjected to esterification (5) and has been alkylated (6) in alcoholic solutions. The pKa of 1-hydroxybenzotriazole is



1

about 7.8, which places it between phenols (pKa=9) and carboxylic acids (pKa=5) in acidity, and makes it a good choice for salt formation in an aqueous solution (7).

The objectives of this research were (1) to employ PTC in the alkylation of 1-hydroxybenzotriazole and (2) to extend the alkylation of 1-hydroxybenzotriazole to include previously inaccessible systems.

RESULTS AND DISCUSSION

A series of phase transfer catalyzed alkylations of 1-hydroxybenzotriazole were carried out employing the alkyl halides listed in Figure 1. Tetrabutylammonium chloride was used as the phase transfer catalyst in all cases and represents a readily available catalyst with an anion similar to the leaving group in most of the alkyl halides employed in this study. The reactions were agitated strongly to provide maximum interfacial contact between the immiscible phases.

The compounds appearing in Table 1 can be compared directly to previously reported 1-alkoxybenzotriazoles as shown. The yields are good but some are low and may represent the "poisoning" effect cited earlier as alkyl iodides were used in some cases. It is also surprising that the cyclopentyl derivative was obtained in such high yield as it represents a secondary alkyl halide.

The examples presented in Table 2 represent new 1-alkoxybenzotriazoles. Of particular interest are the allyl and benzyl derivatives. Each can be unequivocally identified by NMR absorptions characteristic of venvylic and allylic hydrogen shifted downfield (about 1 ppm) by attachment to oxygen in alkoxybenzotriazoles.

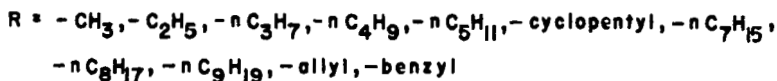
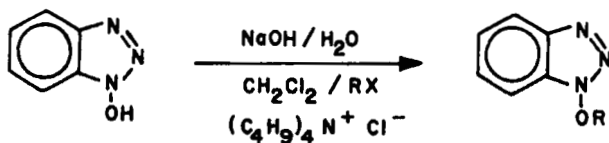
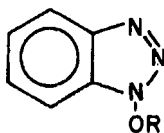


FIG. 1

Table 1



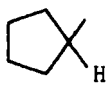
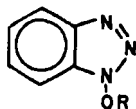
<u>R</u>	<u>Yield (%)</u>	<u>NMR(ppm)</u>	<u>Reference</u>
-CH ₃	59	4.3 (s, 3H)	5,6
-C ₂ H ₅	76	1.45 (t, 3H) 4.6 (q, 2H)	6
-n-C ₃ H ₇	73	1.87 (m, 5H) 4.5 (t, 2H)	6
-n-C ₄ H ₉	74	1.70 (m, 7H) 4.58 (t, 2H)	6
-n-C ₅ H ₁₁	50	1.65 (m, 9H) 4.4 (t, 2H)	6
	96	1.75 (m, 8H) 5.2 (m, 1H)	6

Table 2

New 1-Alkoxybenzotriazoles



<u>R</u>	<u>Boiling Point(°C)</u>	<u>Yield(%)</u>	<u>NMR(ppm)</u>	<u>N%</u>
-n-C ₇ H ₁₅	128-130 (0.25mm)	63	1.6 (m, 13H) 4.5 (t, 2H)	Calcd 18.01 Found 17.69
-n-C ₈ H ₁₇	140-142 (0.05mm)	72	1.3 (m, 15H) 4.5 (t, 2H)	Calcd 16.99 Found 16.54
-n-C ₉ H ₁₉	154-156 (0.05mm)	65	1.4 (m, 17H) 4.55(t, 2H)	Calcd 16.08 Found 15.69
Allyl	a	76	5.0 (d, 2H) 5.65(m, 3H)	Calcd 23.99 Found 23.57
Benzyl	138-140 (0.05mm)	52	5.45(s, 2H)	Calcd 18.66 Found 18.42

a) decomposed on distillation

CONCLUSIONS

Phase transfer catalyzed alkylation of 1-hydroxybenzotriazole proceeds smoothly and in good yield. A variety of functional groups can be introduced which include the thermally sensitive allyl group.

EXPERIMENTAL

Instrumentation and Starting Materials

Infrared spectra were obtained on a Perkin Elmer model 735B spectrometer. Nuclear magnetic resonance spectra were obtained on a Varian model EM-360 spectrometer employing 10-30% w/v solutions in deuteriochloroform with 1% TMS as an internal standard. Alkyl halides and 1-hydroxybenzotriazole were used as received.

General Phase Transfer Catalyzed Alkylation Procedure

A solution of 0.02 mol 1-hydroxybenzotriazole and 0.02 mol NaOH in 75 mL of water was mixed with a solution of 0.06 mol of the alkyl halide and 0.002 mol of tetrabutylammonium chloride in 75 mL of dichloromethane. The mixture was agitated for 36 hr. The organic phase was then separated and evaporated. The residue was dissolved in ether and passed through a short (1.5 X 3 cm) column of neutral alumina. The residue obtained after evaporation of the ether was subjected to NMR and IR spectral analysis.

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