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REGIOSELECTIVE N-ALKYLATION OF BENZIMIDAZOLE VIA AN ORGANOTIN ROUTE

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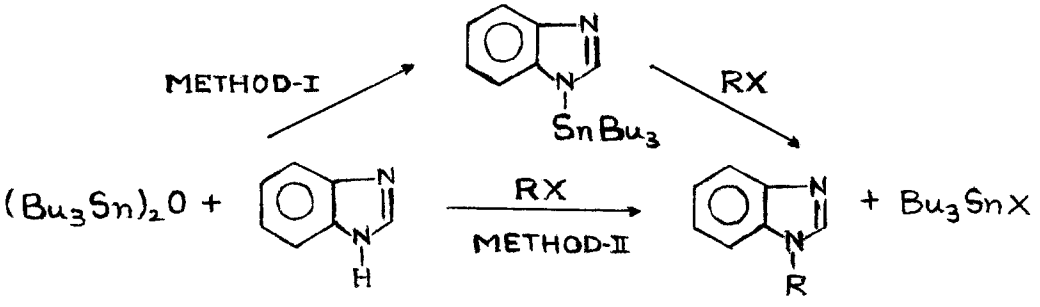
ABSTRACT:- A simple and efficient method for the exclusive N-alkylation of benzimidazole with functional group compatibility has been achieved.

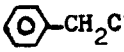
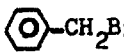
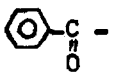
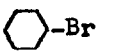
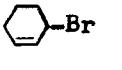
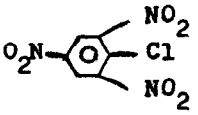
In an attempt to synthesise benzimidazole nuclosides, preliminary investigations have been made on N-alkylation of benzimidazole using a variety of alkyl halides (RX) as model compounds via an organotin route. Although several methods are known in literature[1] for the N-alkylation of heterocycles, they suffer invariably from the following limitations : (i) product distribution[2], (ii) use of strong alkaline media[3] and (iii) heterogeneous reaction conditions[2]. The reactionsare reported to be sluggish even with crown ethers as catalysts[4]. Activation of the nitrogen through organometallation has also been reported for some heterocycles[5-7].

Two procedures have been employed for the title reaction, one in which the organostannyl intermediate is isolated[8] and subsequently treated with RX (method I) and the other in which the intermediate is generated insitu (method II)[9].



A wide range of alkyl halides including primary, secondary, tertiary alkyl, aralkyl, cycloalkyl and aryl halides has been used as alkylating agents and results are summarised in Table-1.

TABLE-1

Sl No.	Halide	Yield (%)[a]	Reaction time(hrs)
1	C_2H_5I	56	12
2	$n\text{-}C_4H_9Br$	45[b]	8
3	$H_2C = CH\text{-}CH_2Br$	65	8
4	$HC \equiv C - CH_2Br$	65	8
5		72	8
6		70	8
7		65	8
8	Me_2CHBr	66[c]	8
9		50[c]	8
10		61	8
11		83	8
12	$Me_3C\text{-}Br$	0[b]	8

a. isolated yields of chromatographically pure compounds.
Solvent: Petroleum ether (60^o-80^oC). b. CH_3CN ; c. DMF.

A perusal of table-1 indicates that even with less reactive secondary halides, N-alkyl derivatives are formed exclusively in good yields. Thus, for the first time, this method provides a convenient procedure for the direct N-alkylation using secondary halides. Reactions are not successful with tertiary halides and unactivated aryl halides[10]. However, it is interesting to note that picrylchloride gives the N-arylated product in excellent yield indicating that even N-arylation could be effected by this method. Further, only in the case of very reactive halides such as benzyl bromide and phenacyl bromide, a competing reaction leading to the corresponding 2-alkylated product is observed[11].

A detailed study of solvent influences on product distribution has been made (Table-2) and it is noticed that between methods I and II, though the yield of N-alkyl product remains almost unaltered, method II gives more of 2-alkyl derivative[12].

TABLE-2

SUBSTRATE : BENZIMIDAZOLE ALKYL HALIDE : BENZYLBROMIDE.

SOLVENT	Yield[a] (%)			
	METHOD I		METHOD II	
	>N-R	>C-R	>N-R	>C-R
Petroleum ether	70	3	65	35
	(72)[b]	(0)	(74)[b]	(8)
n-Hexane	68	20	65	28
Benzene	50	25	65	30
Dimethylformamide	50	35	55	38
Acetonitrile	53	42	55	40
Tetrahydrofuran	65	32	--	--
Acetone	65	32	59	31

a) Isolated yield. b) with benzyl chloride.

In conclusion, our method has the following advantages:- (i) increased regioselectivity, (ii) functional group compatibility, (iii) one-pot reaction under mild and neutral conditions, (iv) homogeneous reaction medium and v) recyclability of tributyltin halide. In view of these merits, the extension of this procedure to the synthesis of benzimidazole nucleosides and other heterocyclic analogues is under investigation.

References and notes:-

1. P.N. Preston, Chemistry of Heterocyclic compounds, 1981, 40(1), 1-285.

2. W.C. Guida and D.J. Mathre and references therein. J. Org. Chem., 46, 3172 (1981)

3. Y. Kikugawa, Synthesis, 1981, 124.

4. C.J. Mathias and D. Burkett, Tetrahedron Lett., 1979, 4709.

5. C.F. Cardy and R.A. Jones, J. Org. Chem., 36, 3993 (1971).

6. R. Gassend, J.C. Maire and J.C. Pommier, J. Organometal Chem., 133 (1977), 169-76.

7. R. Soundararajan, S. Krishnamoorthi, Vilanoor S. Srinivasan and T.R. Balasubramanian, J. Organometal Chem., 255 (1983), 295-97.

8. K. Jones and M.F. Lappert in A.K. Sawyer Ed., Organotin compounds. Vol. II, Marcel Dekker Inc., Amsterdam, Page 520, 1971.

9. Method I:

The tri-n-butylstannyl benzimidazole prepared by refluxing benzimidazole (0.59 g ; 5 mM) and bis (tri-n-butyltin)oxide (TBTO) (1.27 ml ; 2.5 mM) with azeotropic removal of water was treated with benzylchloride (0.58 ml ; 5 mM) in dry petroleum ether (60-80°). After refluxing for 8 hours under anhydrous conditions, the solvent was evaporated and the N-benzylbenzimidazole was separated by column chromatography. (Yield : 0.75 g ; 72%).

Method II:

Benzimidazole (0.59 g ; 5 mM), TBTO (1.27 ml ; 2.5 mM) and benzylchloride (0.58 ml ; 5 mM) were mixed together in dry petroleum ether (60-80°). After refluxing for 8 hours under anhydrous conditions, the solvent was evaporated and ethylacetate (20 ml) was added when 2-benzylbenzimidazole remained insoluble. N-benzylbenzimidazole in ethylacetate was separated by column chromatography.

10. Both tertiary butyl chloride and tertiary butyl bromide failed to react even in highly polar solvent and also in the presence of free radical initiators. Similarly bromobenzene, iodobenzene, 1-bromo-2-phenylethene and 1-bromo-2-phenylethyne did not undergo any reaction under these conditions.

11. In all the other cases, even in polar solvents, exclusive N-alkylation occurs.

12. Also, the presence or absence of oxygen did not influence the yield of the product.

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