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LETTERS

A Mitsunobu-Based Procedure for the Preparation of Alkyl and Hindered Aryl Isocyanates from Primary Amines and Carbon Dioxide under Mild Conditions

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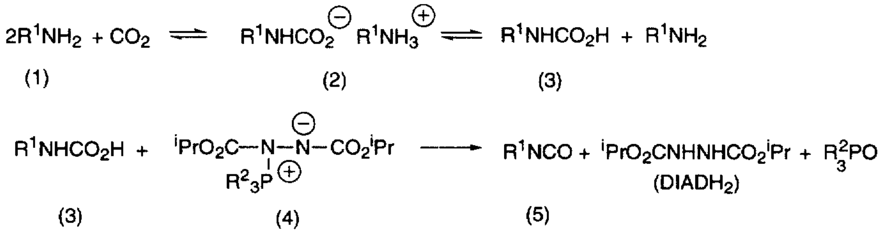
Abstract

A Mitsunobu-based procedure for the preparation of alkyl and hindered aryl isocyanates in excellent yields from primary amines and carbon dioxide under very mild conditions is described.

Keywords: Isocyanates; Mitsunobu reactions; Amines; Carbon dioxide

We wish to report the preparation of alkyl and hindered aryl isocyanates (5) from primary amines (1) and carbon dioxide using Mitsunobu technology. Reactions of solutions of primary aliphatic or hindered aromatic amines (1) in dichloromethane with CO_2 at -5 to -10°C gave carbamate salts (2) which sometimes precipitated from solution. A Mitsunobu zwitterion (4) was prepared by addition of diisopropylazodicarboxylate (DIAD) to a solution of either tri-n-butylphosphine (Bu_3P) or triphenylphosphine (Ph_3P) in dichloromethane at -20°C. Both solutions were cooled to -78°C and the zwitterion cannulated into the carbamate containing solution. More carbon dioxide was passed through the solution after addition, the mixture allowed to warm to ambient temperature and then to stand overnight. The *in situ* yield of isocyanate was estimated by IR spectroscopy based on the cumulated -N=C=O stretch in the isocyanate (2268±10 cm^{-1}). The isocyanates were then isolated either by fractional distillation or flash chromatography. Isolated and *in situ* yields are given in the Tables 1 and 2.



$$\underset{(1)}{2R^1NH_2 + CO_2} \rightleftharpoons \underset{(2)}{R^1NHCO_2^{\ominus}\ R^1NH_3^{\oplus}} \rightleftharpoons \underset{(3)}{R^1NHCO_2H + R^1NH_2}$$

$$\underset{(3)}{R^1NHCO_2H} + \underset{(4)}{{}^iPrO_2C-\underset{R^2_3P^{\oplus}}{N}-\overset{\ominus}{N}-CO_2{}^iPr} \longrightarrow \underset{(5)}{R^1NCO} + \underset{(DIADH_2)}{{}^iPrO_2CNHNHCO_2{}^iPr} + R^2_3PO$$

Scheme 1

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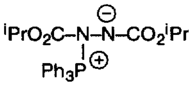
The results in Table 1 involving the Ph_3P-derived zwitterion show that yields of isocyanates prior to distillation were excellent for all amines with secondary (reactions 1, 4 and 7) or tertiary (reactions 3 and 6) alkyl substituents and still good for primary aliphatic amines (reactions 2 and 5). The excellent recovery of isolated isocyanates testifies to the lack of adversely reactive by-products and the mild reaction conditions, as the difficulties in isolating isocyanates are well established, e.g. leading to the formation of isocyanurates and uretidiones.[1] Reactions of aniline (reaction 8), benzylamine (reaction 9) and substituted anilines including the hindered 2,6-diisopropylaniline (reaction 10) gave low yields of isocyanate when the Ph_3P-derived zwitterion was used (Table 1).

Table 1

Yields of isocyanates from reactions of primary amines R^1NH_2 with the Mitsunobu zwitterion,  $^{i}PrO_2C-N-\overset{\ominus}{\underset{Ph_3P^{\oplus}}{N}}-CO_2{}^{i}Pr$ and CO_2[a]

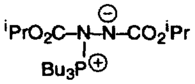
Reaction No.	Amine R^1	Yield (%)	
		Estimated by IR	Isolated
1	^{i}Pr	94	86
2	nBu	76	63
3	^{t}Bu	95	84
4	cyclohexyl	89	80
5	n-octyl	69	65
6	t-octyl	93	87
7	3α-cholestanyl	89	86
8	C_6H_5	<2	-
9	$C_6H_5CH_2$	<5	-
10	2,6-di-$^{i}PrC_6H_3$	20	11

[a] Reactions in dichloromethane from -78°C to ambient temperature.

In contrast reactions using the Bu_3P-derived zwitterion gave excellent yields with aliphatic amines (reactions 11 and 12) and with aromatic amines in which both *ortho*-positions were substituted (reactions 13-17) (see Table 2). A negligible amount of isocyanate was detected when even one of the flanking *ortho*-substituents was removed (reactions 18 and 19).

The reactions are very fast, for an experiment carried out in an n.m.r. tube at -78°C showed complete conversion of the Ph_3P-derived zwitterion to Ph_3PO in a reaction of $^{i}PrNH_2$ and CO_2 with the zwitterion (4; R^2=Ph) in less than 3 minutes. A duplicate reaction was thus allowed to warm to ambient temperature and on workup gave a comparable yield of isocyanate to that recorded in Table 1 for an overnight reaction.

Table 2

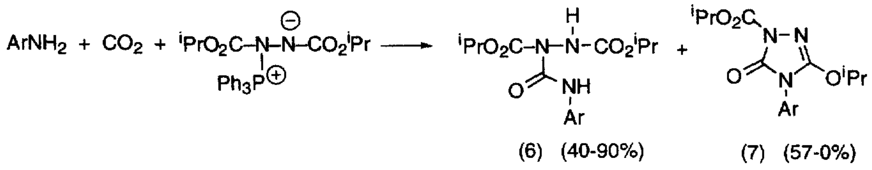
Yields of isocyanates from reactions of primary amines R^{1}NH$_2$ with the Mitsunobu zwitterion,  $^{i}PrO_2C\text{-}N\text{-}\overset{\ominus}{N}\text{-}CO_2{}^{i}Pr$ (N bearing $Bu_3P^{\oplus}$) and CO$_2$[a]

Reaction No.	Amine R^1	Yield (%)	
		Estimated by IR	Isolated
11	^{i}Pr	92	84
12	3α-cholestanyl	100	90
13	2,4,6-tri-MeC$_6$H$_2$	100	92
14	2,6-di-EtC$_6$H$_3$	80	75
15	2,6-di-MeC$_6$H$_3$	100	89
16	2-Me-6-EtC$_6$H$_3$	77	72
17	2,6-di-^{i}PrC$_6$H$_3$	100	89
18	2-^{i}PrC$_6$H$_4$	< 2	-
19	C$_6$H$_5$	< 2	-

[a]Reactions in dichlormethane from -78°C to ambient temperature.

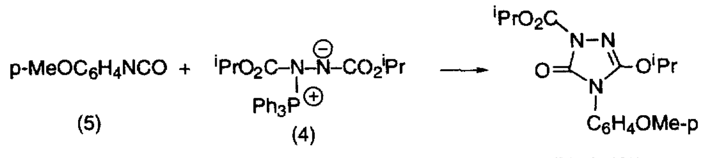
A reaction sequence leading to the formation of isocyanate is shown in Scheme 1 and is similar to that proposed for the formation of carbonate esters from alcohols and CO$_2$ using a Mitsunobu procedure.[2] The high yields of isocyanate show that all of the amine (1) must be available for conversion and that the equilibrium involving the protonated amine salt (2) must readily refurbish free amine as required.

The major products arising from the reactions in Tables 1 and 2 which gave low yields of isocyanates were either carbamoylhydrazines (6) and/or triazolinones (7) (Scheme 2).



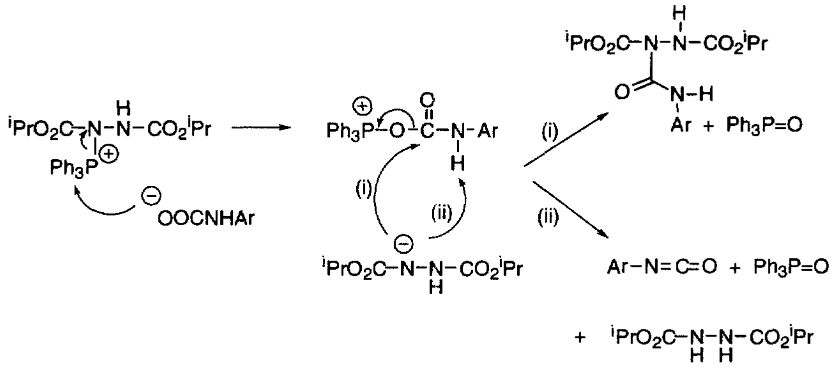
Scheme 2

The latter have been shown to arise from reactions of reactive arylisocyanates with a Mitsunobu zwitterion[3] (4) and this was confirmed by formation of p-methoxyphenyltriazolinone (7; Ar = p-MeOC$_6$H$_4$) from a reaction of p-methoxyphenylisocyanate (5; R^1=p-MeOC$_6$H$_4$) and the zwitterion (4; R^2=Ph) (Scheme 3).



Scheme 3

The carbamoylhydrazines (6) are proposed to arise by attack of the anion on the acyl group of the oxyphosphonium intermediate (i), in contrast to isocyanate formation which involves deprotonation of the NH group (ii) (Scheme 4).



Scheme 4

The use of Mitsunobu technology complements the use of oxophilic reagents, e.g. $POCl_3$ to achieve *in situ* dehydration as described by the Monsanto group.[4] The preparation of isocyanates by reaction of carbon monoxide with preformed phosphorus-containing intermediates has been reported previously.[5,6] Other recently reported syntheses of isocyanates include dimethylaminopyridine-catalysed reactions of hindered aromatic amines with di-t-butylcarbonate[7] and the elimination of methanol from carbamate methyl esters using a mixture of chlorocatecholborane and triethylamine.[8]

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