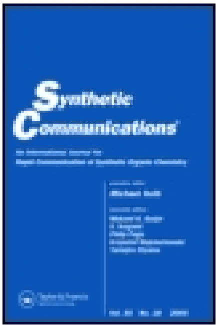

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SYNTHESIS OF ISOCYANATES FROM CARBOXYLIC ACIDS USING DIPHENYLPHOSPHORYL AZIDE AND 1,8-BIS(DIMETHYLAMINO)NAPHTHALENE

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Abstract: A simple phosgene-free method for the synthesis of high-purity isocyanates from carboxylic acids was developed using diphenylphosphoryl azide and 1,8-bis(dimethylamino)naphthalene. Yields for evaluated monoisocyanates ranged from 60.0% to 81.5%.

A traditional approach to the synthesis of isocyanates is the carbonylation of amines with phosgene or phosgene-equivalents such as oxalyl chloride or trichloromethyl chloroformate.[1,2] The classic Curtius route to isocyanates from carboxylic acids via the acyl azide involves three separate synthetic steps, two of which are potentially explosive. A variety of phosgene-free syntheses of isocyanates have also been developed, but many of these methods have limitations.[3]

Yamada *et al.* reported a simple one pot synthesis of urethanes from carboxylic acids using diphenylphosphoryl azide.[4] This procedure involves treating a carboxylic acid with triethylamine to produce the triethylammonium carboxylate salt followed by heating in the presence of diphenylphosphoryl azide to yield the isocyanate via a Curtius-type rearrangement of the acyl azide. The exact mechanistic details of this transfer step have not yet been determined.[5] Both concerted and bimolecular mechanisms have been proposed.[1,2] An alcohol is then introduced, functionalizing the isocyanate *in situ* to yield the urethane.

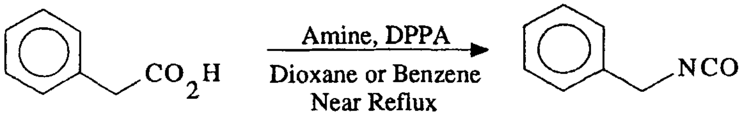
Other groups have applied this procedure, minus the *in situ* functionalization with alcohol, to prepare 1,3-diisocyanatoadamantane[6], n-heptadecylisocyanate[7], and 18-nordehydroabietyl isocyanate[8] from their corresponding carboxylic acids. However, our attempts to synthesize isocyanates from carboxylic acids using Yamada's method were unsuccessful. The reaction of the triethylammonium carboxylate salt with diphenylphosphoryl azide yielded a crude mixture of the isocyanate and a triethylammonium phosphate salt. Attempts to purify this mixture by distillation invariably resulted in low yields (10-20%) and isocyanate contaminated by triethylamine ($\leq$ 30%). This is believed to be due to the equilibrium between the triethylammonium phosphate salt and the free acid and base.[9] During purification by distillation, the volatile triethylamine distills continuously, thereby contaminating the isocyanate as it distills. A further complication is the reaction of the isocyanate with the diphenylphosphoric acid. Heating isocyanates in the presence of even traces of an active-hydrogen compound can result in complete polymerization of the isocyanate.[10] Furthermore, triethylamine is known to catalyze the thermal isomerization of isocyanates to isocyanurates.

In developing this method into a general procedure useful for the synthesis and purification of isocyanates, we surveyed a variety of non-volatile tertiary amine bases which would either completely favor the ammonium phosphate salt and/or form an ammonium phosphate salt which could be removed prior to distillation by precipitation and filtration. These amines were evaluated by treating phenyl acetic acid with tertiary amine base in benzene or dioxane at ambient temperature for 30 minutes. The mixture was then heated four hours just below reflux in the presence of diphenylphosphoryl azide while monitoring nitrogen evolution. After cooling several hours to precipitate the corresponding ammonium phosphate salt, the salt was removed (if it precipitated) by filtration. The filtrate was then distilled to yield the "purified" benzylisocyanate which was characterized by IR, ^{1}H-NMR and ^{13}C-NMR.

Results are shown in Table 1. Only 1,8-bis(dimethylamino)naphthalene resulted in good yield of high purity benzylisocyanate following a simple Kugelrohr distillation. About 75% of the ammonium phosphate salt was removed prior to distillation by precipitation and filtration. Benoit *et al.*[11] have shown that the bidentate nature of 1,8-bis(dimethylamino)naphthalene allows it to form very strong intramolecular hydrogen bonds, which likely favors the formation of the ammonium phosphate salt in the equilibrium.

This new procedure with diphenylphosphoryl azide and 1,8-bis(dimethylamino)naphthalene was tested on several carboxylic acids shown in Table 2. In general, these reactions were performed under nitrogen atmosphere. Special care was taken during all transfers to minimize exposure to atmospheric moisture. The carboxylic acid (40 mmoles) was dissolved in 50 mL dry dioxane or THF (freshly distilled from Na or Na/K benzophenone). 1,8-bis(dimethylamino)-naphthalene (Proton Sponge™; one equivalent per equivalent of carboxylic acid) was then added to the homogeneous acid solution and stirred 15-30 minutes at room temperature. If necessary, the mixture was warmed to 50°C to aid dissolution. Diphenylphosphoryl azide (DPPA; one equivalent per equivalent of Proton Sponge™) was added with a syringe. The mixture was then gradually heated to reflux temperature and held at reflux for 6 hours. The reaction was then allowed to cool to room temperature before storing at -2°C overnight to

Table 1. Survey of Tertiary Amine Bases



AMINE	YIELD
tripropylamine	65%*
tridodecylamine	28%*
1,4-diazabicyclo[2.2.2]octane (Dabco)	22%*
hexamethylenetetramine	not isolable
triphenylamine	no reaction
polyvinylpyridine	no reaction
poly(ethylenimine), benzylated	black tar
Amberlyst™ A-21 Ion Exchange Resin	low conversion
1,8-bis(dimethylamino)naphthalene (Proton Sponge™)	65% (>98% pure)

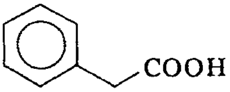
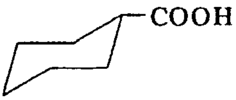
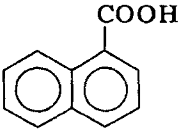
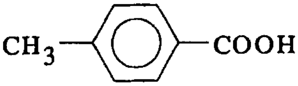
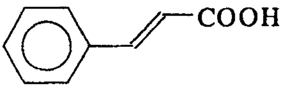
* product contaminated with amine

precipitate out the ammonium phosphate salt. The cold mixture was quickly frit-filtered, washing with anhydrous diethyl ether or a 1:1 v/v diethyl ether/ethyl acetate solution. The filtrate was then reduced in volume to remove solvent and the residual liquid vacuum distilled (short path Vigreaux column distillation apparatus, 0.20 mm Hg) to yield clear, colorless liquid isocyanate product which was characterized by IR, ^{1}H-NMR and ^{13}C-NMR. The spectral data were consistent with the structures shown and indicated very high purity products.

The results in Table 2 show that this method allows preparation of aromatic and aliphatic mono-isocyanates in moderate yield and very high purity. Of the di- and tri-carboxylic acids evaluated, only hexamethylene diisocyanate was successfully synthesized. Glutaric acid, tricarballylic acid, 4-carboxyheptane-

Table 2. Survey of Carboxylic Acids

$$\mathrm{RCOOH} \xrightarrow[\text{Dioxane or THF, Reflux, 4-6 hr}]{\text{DPPA, Proton Sponge}} \mathrm{RNCO}$$

RCOOH	YIELD in dioxane/in THF
	71.3% / 73.5%
	40.7% / 60.5%
	59.5% / 81.5%
	36.1% / 60.0%
	not isolable* / --
$HOOC(CH_2)_6COOH$	65.3% / 76.1%

* isocyanate observable in IR at 2280 cm^{-1}

dioic acid, and 4-nitro-4-(propanoic acid)heptanedioic acid gave 1,2- or 1,3-diisocyanates or triisocyanates in the crude reaction mixture as observed by IR and NMR spectroscopies, but they decomposed upon distillation. In general, 1,2- and 1,3-diisocyanates are very difficult to prepare and purify due to the formation of stable cyclic urea byproducts.[12]

Furthermore, for the unsuccessful reactions, only small quantities of the ammonium phosphate salt were removed due to incomplete precipitation, which was probably due to the increased solubility of the salt in the reaction mixture. We are currently investigating polymeric bases to replace the 1,8-bis(dimethylamino)naphthalene (Proton Sponge™) for this method.

ACKNOWLEDGMENTS

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9. We believe the low yields are due to the following triethylammonium phosphate salt equilibrium:

$$\mathrm{(PhO)_2P(=O){-}OH} + \mathrm{(CH_3CH_2)_3N} \rightleftharpoons \mathrm{(PhO)_2P(=O){-}O^-} \quad \mathrm{{}^+HN(CH_2CH_3)_3}$$

Active-hydrogen Compound

Triethylammonium Phosphate Salt

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