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THE CONDENSATION REACTION BETWEEN ISOCYANATES AND CARBOXYLIC ACIDS. A PRACTICAL SYNTHESIS OF SUBSTITUTED AMIDES AND ANILIDES.

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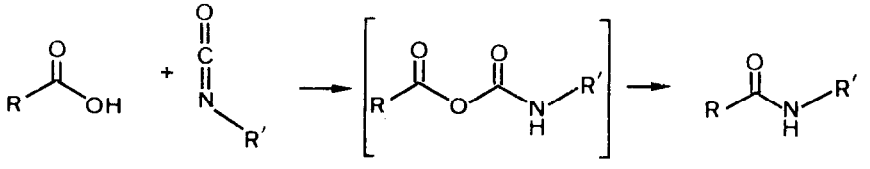
Summary: Addition of a carboxylic acid to an isocyanate initially yields the mixed acid anhydride, decarboxylation of which leads to the N-substituted amide. The conversion of acid into amide was shown to proceed similarly for both aliphatic and aromatic carboxylic acids with a range of substituted isocyanates.

The conversion of the carboxylic acid functional-group into the corresponding carboxylic amide (peptide) is a transformation of paramount importance in bioorganic chemistry and the methods available to achieve this transformation are legion.[1,2] The preparation of amides accomplished by the addition of a carboxylic acid to an isocyanate[3] has received little attention, although the reaction conditions are mild and the yields are frequently good.[4] The reaction does not require any activation of the carboxylic acid functionality (e.g., mixed anhydride or acyl azide), the problem of racemisation of an optically active amide, when HCl is a product of the reaction, is absent and the need for dehydrating agents (e.g., DCC or EEDQ) is also obviated.[5] In this Letter we summarise our observations on the synthetic utility of this approach to N-substituted amides (see Scheme 1).



Scheme 1

Aliphatic isocyanates react readily with carboxylic acids, presumably by addition of the carboxylate salt to the electropositive sp carbon of the isocyanate. The intermediate mixed anhydride is not isolated, indeed it is not stable under the conditions of the reaction. Carbon dioxide is evolved and this, together with the disappearance of the N=C=O stretch in the infrared spectrum (ν 2260 cm^{-1}), allows the progress of the reaction to be monitored.

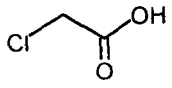
We have found that dry aromatic hydrocarbons are very convenient solvents for the reaction and the pure product can generally be obtained following one recrystallisation of the residue which remains after the solvent has been removed. As with all reactions of isocyanates, the exclusion of atmospheric moisture is essential if hydrolysis is to be avoided.

In a typical procedure, a solution of chloroacetic acid (1) (200 mg, 2.1 mM), 2-chloroethyl isocyanate (2) (446 mg, 4.2 mM) and dry triethylamine (10 mg, 0.05 equiv.) in dry toluene (2 ml) was heated to 60°C in an argon atmosphere for 2 h, when no more CO_2 was evolved. The cooled solution was concentrated *in vacuo* and the residue was recrystallised from hexane which gave the desired (N-2-chloroethyl)-2-chloroacetamide (3) (82%). 3-Phenylpropanoic acid was likewise converted into the amide (4) (73% after chromatography on SiO_2 gel, eluant hexane:EtOAc 3:2). Similarly, phenylacetic acid and benzoic acid gave the N-alkyl amides (5) and (6) in good yields (47% and 53% respectively).

Aromatic isocyanates do not react as efficiently as the aliphatic isocyanates in the preparation of amides. Phenyl isocyanate (7) gave only the urea (8) (carbanilide) (48%) when treated with benzoic acid; the anilide (9) (31%) was prepared, as well as carbanilide (50%), from phenylacetic acid and the isocyanate (7). The biochemically important *p*-nitroanilides are often difficult or impossible to prepare from *p*-nitroaniline.[6] However, *p*-nitrophenylisocyanate (10) can be utilised efficiently in the synthesis of such compounds without any prior activation of the carboxylic acid.[7] The nitroanilide (11) (59%) was obtained from benzoic acid although the reaction was faster than with aliphatic isocyanates (30 mins at 60°C).

N-Chloromethyl amides are a highly reactive class of compounds which have so far received little attention. In a representative procedure[8] for their formation, the carboxylic acid is converted into the unsubstituted amide which is then treated with aqueous formaldehyde and the isolated N-hydroxymethyl amide is exposed to PCl_5 (Scheme 2). Chloromethyl isocyanate (12) is an efficient reagent for achieving all the transformations depicted in Scheme 2 in a "one-pot" and essentially one-step reaction. The N-haloalkyl amides have a reactivity similar to that of acid chlorides;[9] there is a large contribution from the mesoisomerism of the nitrogen lone pair and the methylidene iminium (Mannich-type) salt[10] is an electrophilic species. Not surprisingly, therefore, the N-haloalkyl amides undergo facile hydrolysis. However, the product of the hydrolysis of amide (13) was benzoic acid and not benzamide; this is in contrast to the amide (15), derived from chlorosulphonyl isocyanate (14), the hydrolysis of which is known to yield the primary amide (16).[11]

No mechanism for the decarboxylation step has been presented above; we[12] and others[13,14] have shown that the carbon atom which is lost is the sp carbon of the isocyanate, but the detailed mechanism is not yet known. Nonetheless, isocyanates deserve full consideration as reagents for the synthesis of amides.



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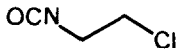

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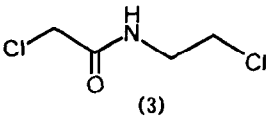

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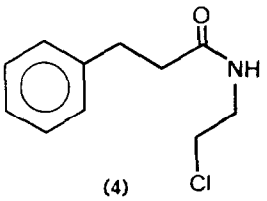

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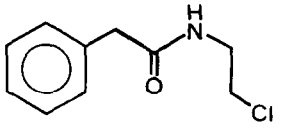

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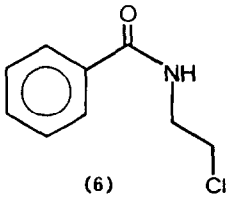

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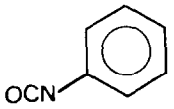

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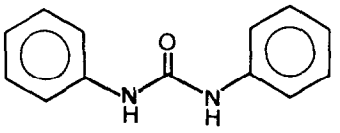

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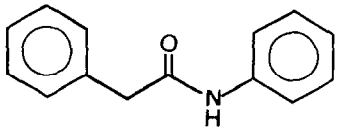

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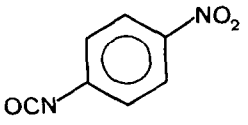

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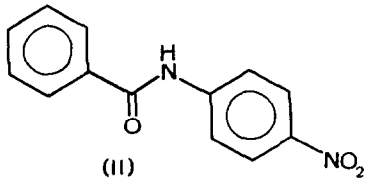

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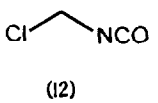
Scheme 2



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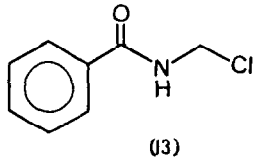

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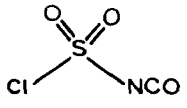

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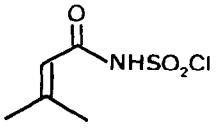

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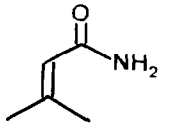

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Acknowledgements

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