

## SYNTHESIS OF ALIPHATIC ISOCYANATES VIA A TWO-PHASE HOFMANN REACTION

Anita O Sy\* and Joseph W Raksis  
W R Grace & Co , Washington Research Center  
7379 Route 32, Columbia, Maryland 21044

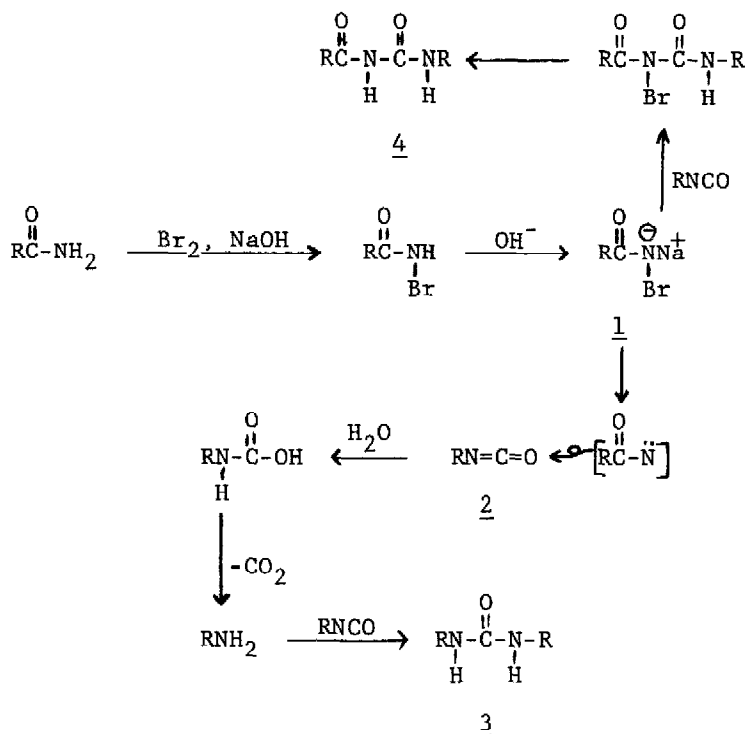
A convenient method of preparing aliphatic isocyanates via a two-phase Hofmann reaction using a phase transfer catalyst is described

Aliphatic isocyanates are most commonly prepared by phosgenation of amines and dehydrohalogenation of the resulting carbamoyl chloride<sup>1</sup> The aliphatic amines are generally obtained from catalytic reduction of nitriles, a complicated process often giving numerous byproducts Amides, on the other hand, can be obtained relatively simply from the nitrile by hydrolysis or from available carboxylic acids Herein is described a method of converting the more accessible amide directly to an isocyanate by using the Hofmann reaction

Under the usual conditions of the Hofmann reaction, the isocyanate formed is readily hydrolyzed to the amine<sup>2</sup> as illustrated in Scheme I We hypothesized that it would be possible to trap the reactive isocyanate intermediate in an organic phase by doing the reaction in a two-phase system, and to use a phase transfer catalyst to facilitate the transfer of the ionic reactants between phases This hypothesis was borne out in our laboratory investigation and the results are reported below

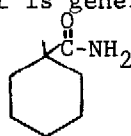
Cyclohexanecarboxamide, when treated with two equivalents of bromine and aqueous sodium hydroxide in methylene chloride and 5 mole percent of tetra-n-butylammonium bisulfate<sup>3</sup> ((nBu)<sub>4</sub>N<sup>+</sup>HSO<sub>4</sub><sup>-</sup>) at room temperature for 5-15 minutes gave the corresponding cyclohexylisocyanate in 70-80 percent yield<sup>4</sup> Longer reaction times at room temperature result in the formation of dicyclohexyl-urea 3 (R=cyclohexyl) However, the reaction time can be extended to one hour with little formation of the urea by keeping the temperature at 5°C In the absence of a phase transfer catalyst, < 3 percent yield of the isocyanate was obtained Other secondary isocyanates obtained are illustrated in Table I (entries 1-5)

## SCHEME I



Primary isocyanates are obtained in relatively poor yields from the corresponding amides under the same reaction conditions. For example, n-heptanecarboxamide gave 16 percent yield of n-hexylisocyanate in the presence of PTC. Without PTC, only a trace of the isocyanate is detected. The major product obtained is the N-acylalkylurea 4 which presumably is formed from the reaction of the N-bromoamide salt 1 and the resulting isocyanate. According to this mechanism, the formation of the acylalkylurea should be minimized by dilution. When the reaction mixture was diluted ten-fold, the yield of the primary isocyanate is increased to 50-60 percent. Other primary isocyanates studied are listed in Table I (entries 6-10).

An example of a tertiary isocyanate was obtained from 1-methylcyclohexanecarboxamide 5. Compound 5 gave the corresponding 1-methylcyclohexylisocyanate in 92-96 percent yield with or without phase transfer catalyst. The fact that the reaction proceeded without the addition of PTC suggests that a species which acts as a phase transfer catalyst is generated in the course of the reaction.

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When chlorine instead of bromine was used in the reaction, considerably poorer yield of isocyanates was obtained. However, when N-chlorocyclohexanecarboxamide<sup>5</sup> in  $\text{CH}_2\text{Cl}_2$  was subjected to aqueous sodium hydroxide and PTC, the corresponding isocyanate was obtained in 80-85 percent yield. It thus appears that the difficulty in the reaction lies in the formation of N-chlorocyclohexanecarboxamide using a two-phase Hofmann reaction condition, but the exact reasons for this difference in the behavior between chlorine and bromine are still under investigation.

Freedman and Lee<sup>6</sup> have studied the hypochlorite reaction of several substrates under PTC conditions and reported that amides undergo several sequential reactions to nitriles and aldehydes or ketone products. We have not detected any of these products in our reaction mixtures, presumably because of differences in the reaction conditions, including the amount and identity of the hypochlorite reagent used.

TABLE I

## ISOCYANATES OBTAINED FROM THE TWO-PHASE HOFMANN REACTION

<u>Entries</u>	<u>Substrates</u>	<u>Reaction Conditions</u>	<u>Yield<sup>7</sup></u>
1	Cycloheptanecarboxamide	W/PTC, 25°C, 15 min	87%
2	Cycloheptanecarboxamide	W/O PTC, 25°C, 15 min	26%
3	2-Norbornanecarboxamide	W/PTC, 25°C, 15 min	76%
4	2-Ethylhexanecarboxamide	W/PTC, 5°C, 1 hr	80%
5	2-Ethylhexanecarboxamide	W/O PTC, 5°C, 1 hr	20%
6	n-Octanecarboxamide	W/PTC, 25°C, 15 min	19%
7	Cyclohexanepropionamide	W/PTC, 25°C, 15 min	16%
8	Cyclohexanepropionamide	W/Dilution <sup>†</sup> , 25°C, 15 min	86%
9	2-Norbornaneacetamide	W/PTC, 25°C, 15 min	26%
10	2-Norbornaneacetamide	W/Dilution <sup>†</sup> , 25°C, 15 min	87%

<sup>†</sup> 2 mmoles of amide, 2 meq  $\text{Br}_2$ , 13 meq of NaOH, 25 ml  $\text{CH}_2\text{Cl}_2$ , 25 ml  $\text{H}_2\text{O}$ , 5 mmole percent PTC

## REFERENCES

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- b) J. H. Saunders and R. J. Slocombe, *Chem. Revs.*, **43**, 203-18 (1948)
- c) R. G. Arnold, J. A. Nelson and J. J. Verbans, *Chem. Revs.*, **57**, 47-76 (1957)
- <sup>2</sup>E. Wallis and J. Lane, *The Hofmann Reaction, Organic Reactions*, John Wiley & Sons, Inc., New York, Vol. 3, 1949, p. 267

- <sup>3</sup>Other phase transfer catalysts that work as well are benzyltriethylammonium chloride and tetra-n-butylphosphonium bromide
- <sup>4</sup>All reactions are done with 2 eq of Br<sub>2</sub>, 13 eq of NaOH, 0.4M organic solution of the substrate and 5 mole percent tetra-n-butylammonium bisulfate
- <sup>5</sup>N-chlorocyclohexanecarboxamide was obtained by bubbling chlorine through a suspension of cyclohexanecarboxamide in 10 percent HCl solution
- <sup>6</sup>G A Lee & H H Freedman, *Tetrahedron Letters*, No 20, 1641-1644 (1976)
- <sup>7</sup>All yields are calculated from the gas chromatogram using calibrated internal standards

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