

New Strategies for the Hofmann Reaction

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Abstract: Some new strategies, such as the use of hydrotropes, surfactants, co-solvent, etc., were applied to the Hofmann reaction of fatty amides to obtain isocyanates, amines and carbamates. Additionally, some industrially important aromatic amines were synthesised.

Key words: Hofmann reaction, amides, synthesis of amines, isocyanates, carbamates, alkylation of carbamates, use of surfactants, hydrotropes, co-solvent.

INTRODUCTION

The synthesis of RNH_2 via isocyanates by the Hofmann reaction is well known.¹ The Hofmann reaction is an oxidative rearrangement and has been carried out using various reagents, e.g. NaOBr ,¹ CH_3OBr ,² $\text{Pb}(\text{OAc})_4$,³ hypervalent organoiodine compounds,⁴ NaBrO_2 ⁵ or $\text{NBS-Hg}(\text{OAc})_2$.⁶

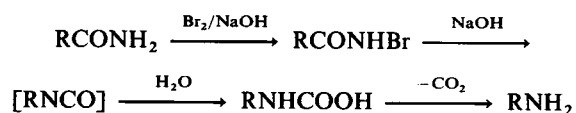
In the present paper, some novel strategies were adopted for the Hofmann reaction, and this reaction was applied to aliphatic fatty amides to give isocyanates, amines and carbamates. It was also applied to aromatic amides to give industrially important aromatic amines.

Two-phase synthesis of aliphatic isocyanates by the Hofmann reaction

Aliphatic isocyanates are commonly prepared by phosgenation of amines,⁷ reaction of alkenes with isocyanic acid,⁸ reaction of amines with dimethyl carbonate followed by thermolysis,⁹ or by thermolysis of ureas.¹⁰ Herein is described a method of converting a more accessible amide directly to an isocyanate in high yields, by using a second liquid phase in which the isocyanates show a high distribution coefficient, which avoids the use of phosgene.

Sy and Raksis¹¹ and Wang *et al.*¹² have carried out the Hofmann reaction in a two-phase system to trap the reactive isocyanate intermediates. The success of the classical Hofmann reaction depends on the capture of the intermediate isocyanate by a hydroxide ion (or water)

and the spontaneous decarboxylation of the carbamic acid thus produced, as shown in Scheme 1.



Scheme 1

We have carried out further investigations into the Hofmann reaction (using solid–liquid or liquid–liquid/phase transfer catalytic (PTC) technique) using the substrates shown in Table 1, some of which have potential industrial importance.

For various amides, the yield of isocyanates was found to be better in the $\text{NaOH (S)}/\text{Br}_2/\text{CH}_2\text{Cl}_2$, i.e. solid–liquid system than the aqueous $\text{NaOH}/\text{Br}_2/\text{CH}_2\text{Cl}_2$, i.e. liquid–liquid system. This was possibly due to the fact that the absence of the aqueous phase in the solid–liquid system is favorable to the stability of isocyanates.

The nature of the carbon atom (primary/secondary/tertiary) attached to the amide group was found to play a very important role in terms of selectivity for isocyanates, and this was in agreement with the principle proposed by Sy and Raksis,¹¹ i.e. tertiary > secondary >> primary. 2-Ethylhexylamide under both liquid–liquid and solid–liquid conditions gave 90% yield of 3-heptylisocyanate (Table 1, entry 1). Moreover by distillation under reduced pressure (63–65°C/15 mm) it was possible to isolate the pure product in about 70% yield. The yields of various isocyanates obtained in solid–liquid or liquid–liquid mode are given in Table 1.

Neither caprylamide (Table 1, entry 7) nor laurylamide

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TABLE 1
Isocyanates Obtained from the Two-Phase Hofmann Reaction

Entry	Amide	Mode	Yield ^{a,b} (%)	b.p./m.p. (°C)
1	2-Ethylhexylamide	L-L	90	63-65/15 mm
		S-L	93	
2	Cyclohexanecarboxamide	L-L	80	65-66/15 mm
		S-L	94	
3	Ibuprofenamide	S-L	94	103-4 mm
4	Trimethylacetamide	L-L	95	84-85/760 mm
5	Dehydroabietic acid amide	L-L	96	Viscous oil
6	Tetrahydroabietic acid amide	L-L	95	m.p. = 59-61
7	Caprylamide	L-L	45 ^c	75-78/10 mm
		S-L	30	
8	Laurylamide	L-L	48 ^c	130-32/10 mm
		S-L	24	

^a All isocyanates show strong absorption at 4.5 μ , i.e. 2270 cm^{-1} .

^b Estimation of isocyanates was carried out by the *n*-butylamine method.¹³

^c Aqueous phase was further diluted ten times, in the presence of PTC.

(Table 1, entry 8) (in which the amide group is attached to primary carbon atom) in the liquid-liquid phase in the absence of PTC, gave any isocyanates. When the aqueous phase was diluted further and PTC was added, a poor yield of isocyanates resulted. However, in the solid-liquid system, in the absence of catalyst, it was possible to obtain isocyanate from the caprylamide in 30% yield. In the case of 2-ethylhexylamide, in the liquid-liquid phase, the catalyst was found to increase the yield of isocyanate to 93% from 53% in the absence of PTC. Moreover, under solid-liquid phase conditions, irrespective of the presence or absence of catalyst, 3-heptylisocyanate was formed in high yield (93%).

The above facts implied that when amides undergo a Hofmann reaction in a biphasic system, they do not necessarily need a catalyst; PTC, in general, can increase the yield of isocyanates. This is possibly because they can increase or decrease the dissociation of OBr^- , RCON^-Br , etc., in the organic phase and are favorable for isocyanate formation in the liquid-liquid system. This may also be responsible for reducing the side reaction caused by the aqueous phase. The non-aqueous phase in solid-liquid conditions is even more favorable for, and increased the stability of, isocyanates. Amides in which the amide group is attached to tertiary carbon atom give isocyanates in high yield under liquid-liquid conditions without a catalyst.

Freedman and Lee¹⁴ have reported the sequential reaction of amides with hypochlorite to nitriles, aldehydes or ketones. We have not detected any of these products in our reaction mixture nor the trimerisation of isocyanates to isocyanurates as reported by Dehmlow *et al.*¹⁵

Synthesis of aliphatic/aromatic amines: use of hydrotropes/surfactants and co-solvent

The yield of fatty amides in the Hofmann reaction decreases as the number of carbon atoms increases ($> \text{C}_6$). Side reactions such as the formation of acyl-alkyl ureas and nitriles are responsible for lowering the yield.¹ The low stability of higher amides in aqueous NaOCl is responsible for the failure of reaction. These stability limitations cannot be overcome by using a higher temperature because of the instability of hypochlorite above 40°C. Herein, we wish to report a new and practical method for conversion of aliphatic and aromatic amides into amines using hydrotropes/surfactants/co-solvent.

The increased solubility of organic materials in aqueous hydrotrope/surfactants solution is a phenomenon that has found application in many scientific and technological areas. During the last few years, surfactants/hydrotropes-aided synthetic organic conversions such as etherification, de-etherification, oxidation, and nucleophilic displacement reaction, have received considerable attention. Hydrotropic substances are chemical compounds which are not surface active themselves, but which are capable of increasing the solubility of sparingly soluble compounds in water. It was thought desirable to investigate the effect of these agents (Fig. 1) which could result in minimising or eliminating side reactions and thereby improve the yield of amines.

Cationic surfactants are less popular than conventional PTCs⁵ owing to the possibility of foaming and work-up problems. Another drawback is the possibility of undergoing Hofmann degradation in the highly alkaline conditions which prevail in the Hofmann reaction. Non-ionics like nonyl phenol ethoxylates (NPE) when used (4.5% (w/w) of amides) with caprylamide gave 15% heptylamide. By increasing the loading of NPE (to 10% (w/w)), the yield of heptylamine increased to 45%, but the residue remaining behind after separating fatty amides was more than the stoichiometric quantity, even after repeated water washings. Thus, the use of nucleophilic surfactants was not advisable. No attempts were made to characterise this urea or carbamate. Anionics

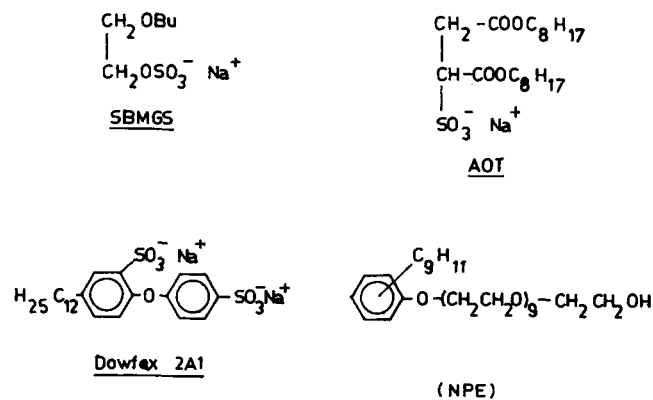


Fig. 1.

TABLE 2
Hofmann Reaction of Aliphatic Amides in the Presence of Dowfax-2Al + AOT and Sulfolane

Entry	Amides	Amines	Dowfax-2Al + AOT	Sulfolane
1	Heptanamide (C ₇)	Hexylamine	75%	85%
2	Caprylamide (C ₈)	Heptylamine	63%	68%
3	2-Ethylhexanamide (C ₈)	1-Ethylpentylamine	65%	69%
4	Caprylamide (C ₁₀)	Nonylamine	20%	25%
5	Undecylamide (C ₁₁)	Decylamine	5%	5%
6	Lauramide (C ₁₂)	Undecylamine	Trace ^a	Trace ^a

^a Major product was *N*-undecyl-*N'*-laurylurea.

TABLE 3
Hofmann Reaction of Aromatic Amides in the Presence/Absence of Dowfax-2Al

Entry	Aromatic amide	Aromatic amine	Yield (%)	
			Presence of Dowfax-2Al	Absence of Dowfax-2Al
1	1-Naphthoic acid amide	1-Naphthylamine	92.7	75
2	4-Chlorobenzamide	4-Chloroaniline	94.7	96
3	3-Chlorobenzamide	3-Chloroaniline	97	95
4	3-Nitrobenzamide	3-Nitroaniline	93.5	95
5	<i>m</i> -Toluamide	<i>m</i> -Toluidine	99	92
6	4-Isopropylbenzamide	4-Cumidine	90	64
7	4- <i>tert.</i> Butylbenzamide	4- <i>tert.</i> Butylaniline	95 ^a	Trace
8	Isonicotinamide	4-Aminopyridine	91	80

^a Along with 2% Dowfax-2Al, 2% (w/w) AOT was added. In the absence of AOT, the yield of 4-*tert.* butylaniline was 79%.

like sodium butyl monoglycol sulfate (SBMGS), dioctyl sodium sulfosuccinate (AOT) and alkylated diphenyl oxide disulfonate (Dowfax-2Al) were tried. When SBMGS was used, it was observed that it was attacked by NaOCl, leading to desulfonation of the hydrotrope giving butyl cellosolve. Thus, the sensitivity of SBMGS towards the oxidising agent prevented its use.

When AOT was used, a marked improvement in yield was observed. It may be attributed to micelle formation or to the excellent wetting property of AOT. With Dowfax-2Al, good yields were obtained. This may be due to the chemical and thermal stability of Dowfax-2Al in the presence of strong alkali, acids, inorganics and oxidising agents such as hypochlorite.¹⁶ The high stability of Dowfax-2Al towards hypochlorite is due to the inertia against chlorination of the di- and tri-substituted benzene ring. The superior solubility characteristics may be due to the presence of two charges per molecule, i.e. high charge density. It was desirable to exploit the combined thermal and chemical stability of Dowfax-2Al with the wetting agent, AOT, in the Hofmann reaction. The combination of AOT (3% (w/w) of amide) and Dowfax-2Al (4.5% (w/w)) was found to have a synergistic effect. The yields of fatty amides are given in Table 2.

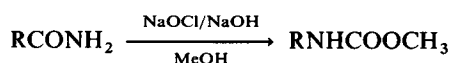
Side reactions in Hofmann reactions can be minimised by the use of an inert solvent.¹⁷ We have chosen sulfolane as a suitable co-solvent because it possesses high polarity, good solubilising property, chemical and thermal stability, low-volatility and non-toxicity. Additionally, sulfolane has been used as the reaction medium for the preparation of isocyanates from phosgene and amine salt.¹⁸ Yields of amines using 33% (v/v) sulfolane are also reported in Table 2.

The effect of Dowfax-2Al, in the preparation of various industrially important aromatic amines by the Hofmann reaction was also investigated. Various derivatives of toluene, xylenes, alkyl-naphthalenes, and picolines serve as base chemicals for air oxidation. Carboxylic acids derived from these chemicals were converted to amides and then to amines. Yields of the various aromatic amines obtained are shown in Table 3.

Preparation and *N*-alkylation of carbamates derived from fatty amides

Higher fatty amides are readily converted to methyl carbamates if the Hofmann reaction is carried out in methanol. This is known as Jeffrey's modification of the Hofmann reaction.¹⁹ Carbamates can be easily isolated

TABLE 4
Preparation of Carbamates



Entry	Amides	Carbamates	Yield (%) (b.p./m.p.)
1	Heptanamide (C ₇)	Methyl <i>N</i> -hexylcarbamate	95 (72–74°C/0.5 mm)
2	Caprylamide (C ₈)	Methyl <i>N</i> -heptylcarbamate	93 (85–88°C/0.5 mm)
3	2-Ethylhexanamide (C ₈)	Methyl <i>N</i> -(1-ethylpentyl)carbamate	92 (oil)
4	Capramide (C ₁₀)	Methyl <i>N</i> -nonylcarbamate	95 (oil)
5	Undecylamide (C ₁₁)	Methyl <i>N</i> -decylcarbamate	94.5 (m.p. = 42–43°C)
6	Lauramide (C ₁₂)	Methyl <i>N</i> -undecylcarbamate	96 (m.p. = 42–43°C)

from the reaction mixture. Hydrolysis of these carbamates produces amines or thermal cracking giving isocyanates.²⁰

Magnien and Baltzly¹⁷ have prepared methyl *N*-undecylcarbamates (in 92% yield) and methyl *N*-penta-decylcarbamates (in 95% yield) by using NaOCl–NaOH–CH₃OH and NaOBr–NaOCH₃–CH₃OH respectively. Radlick and Brown² have prepared CH₃OBr *in situ* using NaOCH₃–Br₂ at –40°C to –15°C, and this CH₃OBr was used to prepare carbamate by Hofmann reaction of various amides in good yield. Recently Jew *et al.*⁶ have prepared aliphatic and aromatic methyl carbamates by using NBS or dibromantoin/Hg(OAc)₂ or AgOAc/methanol in DMF as solvent. However, the use of an equivalent quantity of either Hg(OAc)₂ or AgOAc, an aprotic polar solvent like DMF, in an inert atmosphere makes this process economically and environmentally unattractive.

Jeffrey's modification of the Hofmann reaction^{17,19} has been extended for the preparation of carbamates. A slight excess of freshly prepared NaOCl solution was added to a methanolic solution of fatty amides with good stirring. The mode of mixing of the reactants is important for the preparation of carbamates.²¹ When a methanolic solution of heptanamide was added to preformed NaOCl solution, the yield was found to be lower than with addition of NaOCl solution to amides (80% against 95%). Hence, for the preparation of carbamates, aqueous NaOCl solution was added to the methanolic amide solution immediately. For the preparation of methyl *N*-undecylcarbamates, excess of methanol was required, because undecylamide (C₁₁) and lauramide (C₁₂) are precipitated by water. Table 4 shows the yield of carbamates obtained from amides.

Thus, Jeffrey's modification gave excellent yields of amines as their carbomethoxy derivatives. Unfortunately no general method of hydrolysis has been recognised. Acid hydrolysis of these carbamates was very slow, whereas alkaline hydrolysis posed a difficulty due to the insolubility of urethanes.

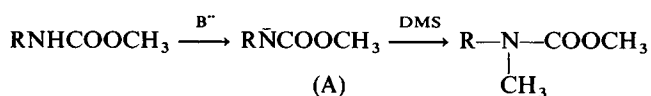
N-Alkylation of carbamates

The alkylation of carbamates R¹NHCOOR² (R¹ = H, alkyl; R² = alkyl) to give *N,N'*-dialkylurethane has not been studied in detail. Muller and Merten²² have reported the alkylation of carbamates with alkenes in the presence of BF₃ to yield *N*-alkylated carbamates. Recently, perfluorinated ion exchange resins,²³ and phase-transfer catalysts²⁴ have been used for alkylation of carbamates. However, the drawbacks of these processes are poor yield, use of aprotic polar solvents and long reaction times.

We would like to report a simple, economical and high yielding method for methylation of fatty amine carbomethoxy derivatives.

In the presence of a base, R¹NHCOOR² can undergo elimination of OR² to give isocyanates or *N*-alkylation. Hence, *N*-alkylation of carbamates is favored when OR² is a poor leaving group, e.g. R² = Me. The reactivity of simple carbamate (R² = alkyl) is more akin to amides than to esters and hence forcing conditions are required for these reactions.²⁵ *N*-Monosubstituted or unsubstituted carbamates are potential nucleophiles themselves. However, they are (by analogy with amides) poor nucleophiles and only act as such when converted to anions or when the nitrogen of the carbamate is adjacent to the reactive centre (neighboring group participation).

The success of this alkylation of methyl-*N*-alkylcarbamates mainly depends on the efficient formation of anion (A) (Scheme 2) from the corresponding carbamates,

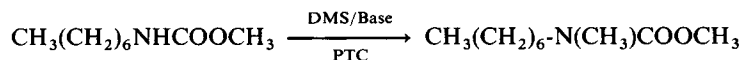


Scheme 2

its extraction into the organic phase and subsequent reaction with alkylating agent, i.e. dimethyl sulfate (DMS).

This was achieved by employing tetra-*n*-butylammonium

TABLE 5
Effect of Various PTCs and Bases Used for Alkylation Reaction



Entry	PTC	Base	Reaction (%)	Yield (%)
1	Triethyl- <i>n</i> -butylammonium bromide	50% NaOH	30–35	—
2	Tetra- <i>n</i> -butylammonium bromide	50% NaOH	30–35	—
3	Tetra- <i>n</i> -butylammonium hydrogen sulfate	50% NaOH	30–35	8
4	Tetra- <i>n</i> -butylammonium hydrogen sulfate	Powdered NaOH	30–35	75
5	Tetra- <i>n</i> -butylammonium hydrogen sulfate	NaOH (S) + K ₂ CO ₃ (S)	30–35	95

hydrogen sulfate (TBA . HSO₄) as PTC, powdered NaOH and K₂CO₃ as the base and toluene as the reaction medium.

The choice of the base was arrived at after employing various bases generally used in the PTC reaction. Aqueous NaOH (50%) furnished only 8% of the product. The yield was drastically increased to 75% when powdered NaOH was used, which was further increased to 95% by the addition of anhydrous K₂CO₃. Anhydrous K₂CO₃ may be acting not only as a base but also as a dehydrating agent preventing the solvation of the carbamate anion (A) and thus facilitating the alkylation. Results of these alkylation studies and the use of various PTCs are shown in Tables 5 and 6.

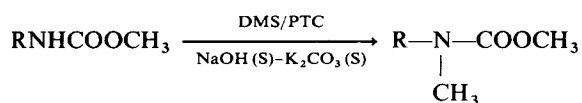
EXPERIMENTAL

Aliphatic and aromatic amides were prepared from the corresponding acid chloride and ammonolysis. All the products were characterised by their physical constants and spectral data.

General procedure of the S–L–PTC reaction for isocyanates

Into a 250 cm³ three necked round bottomed flask was introduced dichloromethane (100 cm³), sodium hydroxide grains (0.54 mol), amide (0.04 mol) and tetrabutylammonium bromide (0.008 mol). After stirring for 5 min, bromine (0.05 mol) was added and the reaction continued with stirring for 30 min in a water bath at 15°C. After the reaction was over, the stirring was discontinued and the supernatant dichloromethane transferred to a separating funnel. The sodium hydroxide in the first flask was washed with dichloromethane and transferred to the separating funnel. The combined dichloromethane was washed with cold (5°C) water, followed by washing with a cold aqueous solution of sodium hyposulfate, followed by cold water. The dichloromethane layer was dried over anhydrous Na₂SO₄, and the solvent recovered by

TABLE 6



Entry	R	Reaction conditions		Yield (%)
		Temp. (°C)	Time (h)	
1	Hexyl	35–40	4	95
2	Heptyl	35–40	4	94
3	1-Ethylphenyl	50–55	4	74
4	Nonyl	35–40	4	93
5	Decyl	35–40	4	90
6	Undecyl	35–40	4	92

distillation. The isocyanates were also purified by distillation under reduced pressure. Purity was established by the butylamine method.

General procedure for the L–L–PTC reaction for isocyanate

The procedure followed was the same as that for S–L–PTC except that the powdered NaOH was substituted by aqueous NaOH (40%, 250 cm³).

General procedures for the Hofmann reaction of aliphatic amides using hydrotropes/surfactants

Freshly prepared hypochlorite solution (160 cm³, containing 0.106 mol NaCl and 0.2 mol free alkali), Dowfax-2Al (45% (w/w) strength) 4.5% by weight of amide and AOT, 3% by weight of amide were stirred together. Fatty amide (0.1 mol) was then added and stirring continued until the reaction mixture attained room temperature. Then it was warmed with stirring to 45°C, when the heat of reaction was sufficient to maintain the temperature. When the exothermic reaction had ceased, the solution

was warmed to 80°C and kept at the temperature for 1 h, after which the reaction mixture was cooled. The reaction mixture was extracted with dichloromethane (2 × 50 cm³). The combined extracts were washed twice with water and then with HCl (1 N, 100 cm³). The acid extracts were neutralised and the oil was extracted into dichloromethane. The dichloromethane solution of the base was dried over Na₂SO₄. Dichloromethane was recovered by distillation leaving behind the oily residue of fatty amine.

Using co-solvent

Amide (0.1 mol) was dissolved in sulfolane (80 cm³). To it, freshly prepared hypochlorite solution (160 cm³, containing 0.106 mol NaOCl and 0.2 mol NaOH) was added. The stirring was continued until the reaction mixture attained room temperature. Then it was warmed with stirring to 45°C, when the heat of reaction was sufficient to maintain the temperature. When the exothermic reaction had ceased, the solution was warmed to 80°C and kept at that temperature for 1 h, after which the reaction mixture was cooled. The reaction mixture was extracted with dichloromethane (2 × 50 cm³). The combined extracts were washed twice, with water and then with hydrochloric acid (1 N, 100 cm³). The acid extracts were neutralised and the oil was extracted into dichloromethane. The dichloromethane solution was dried over anhydrous Na₂SO₄. The solvent was recovered by distillation, leaving behind the oily residue of fatty amines.

General procedure for preparation of carbamates

Fatty amide (0.2 mol) was dissolved in methanol (250 cm³) with stirring. To it, a freshly prepared aqueous solution of NaOCl (0.21 mol, 125 cm³) was added immediately with good stirring. Additional methanol (100 cm³) was added to the reaction mixture in the case of undecylamide and lauramide. The temperature rose to about 52–55°C within 30 min and the solution was then refluxed for 2 h. Methanol (200 cm³) was recovered from the reaction mixture by distillation. On cooling the reaction mixture was diluted with water (200 cm³) and extracted with dichloromethane (3 × 50 cm³). The combined extracts were washed with water and dried over Na₂SO₄. Dichloromethane was recovered by distillation, leaving carbamate as the residue.

General procedure for N-alkylation of carbamates

A mixture of carbamate (0.05 mol), toluene (100 cm³), powdered NaOH (0.2 mol), anhydrous K₂CO₃ (0.05 mol) and tetrabutylammonium hydrogen sulfate (0.0025 mol) was stirred at room temperature for 1 h. During stirring, a gelatinous mass was formed. Dimethyl sulfate (0.06 mol) was added to the stirred mass at 30–35°C over a period

of 30 min. The course of the reaction was followed by TLC. The reaction mixture was stirred for 4 h to obtain a clear solution. Inorganics were filtered off and washed with toluene (2 × 20 cm³). The combined filtrate and washings were washed with HCl (2 N, 3 × 50 cm³), water (2 × 50 cm³) and dried over anhydrous Na₂SO₄. Concentration of the solvent yielded the products.

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