Pergamon

Tetrahedron Letters, Vol. 35, No. 17, pp. 2729-2732, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0364-4

Direct Conversion of Carboxylic Acids into Carbamoyl Azides

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Abstract: The novel conversion of carboxylic acids and carboxylic acid chlorides directly in a one-pot process into *N*-monosubstituted carbamoyl azides, presumably through the intermediacy of isocyanate derivatives following Curtius rearrangement, is described.

Carbamoyl azides ($R^1R^2NCON_3$) were first studied as participants in the Curtius rearrangement from which it is now known they yield aminoisocyanates (R^1R^2N-NCO) by thermal or photochemical means.[1,2] The resultant aminoisocyanates are reactive and rapidly undergo solvolysis with protic solvents,[3] insertion reactions into neighbouring aryl groups[4-7] or added heterocumulene compounds, such as isocyanates[3,8-12] and carbodiimides,[13] and acetylenes,[14] or dimerization.[7,8] Certain *N*-nitroso derivatives of carbamoyl azides are also regarded as key intermediates in the synthesis of steroidal nitrosoureas that possess antitumor activity.[15-19] Carbamoyl azides are normally prepared using one of only three synthetic methods: (i) nitrosation of semicarbazides; (ii) treatment of carbamoyl halides with inorganic azide salts; and (iii) addition of hydrazoic acid to isocyanates. These procedures suffer limitations associated with availability of precursors (semicarbazides and isocyanates) and hazards in handling reagents (hydrazoic acid). There has also been a report of the formation of carbamoyl azides in fair to moderate yield during the oxidation of aldehydes with pyridinium chlorochromate and other chromium reagents in the presence of sodium azide.[20] The mechanism of the oxidation reaction leading to these substances is unknown but a radical pathway is favoured.

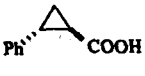
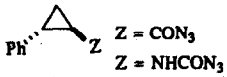
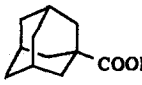
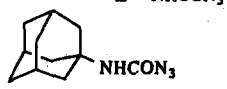
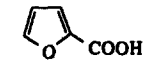
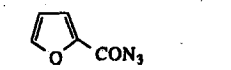
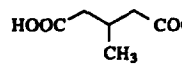
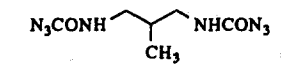
In this paper conditions are disclosed that enable carboxylic acids or carboxylic acid chlorides to be converted directly into carbamoyl azides without the need for isolation of hazardous intermediates (Scheme 1).

$$\text{RCOOH} \xrightarrow[\text{2. } NaN_3 \text{ (5 equiv), } 0^\circ \text{ 3. } 0^\circ \rightarrow \text{r.t.}]{\text{1. } [(CH_3)_2{}^+N{=}CHCl]\ Cl^- \text{ (1.5 equiv) pyridine (1.0 equiv) in } CH_3CN - THF} \text{RNHCON}_3$$

Scheme 1. General Transformation of Carboxylic Acids into Carbamoyl Azides

In the course of other work on 3(2H)-furanoid substances,[21] it was discovered that treatment of an acid chloride, which had been generated *in situ* from the acid using the Vilsmeier salt [$ClCH{=}N^{+}Me_2Cl^{-}$ from Me_2NCHO, $(COCl)_2$] in the presence of pyridine,[22] with 5 mol equiv of NaN_3 in a mixture of THF and MeCN gave remarkably clean conversion to a carbamoyl azide. Further investigation revealed that the same conversion takes place upon mild treatment of a variety of alkanoic acids and arylalkanoic acids, and under more vigorous conditions with more sluggish substrates such as arylcarboxylic acids (Table 1).

Table 1. The Conversion of Selected Carboxylic Acids to Carbamoyl Azides

Entry	Acid	Product	Yield*	m.p.**
a	$CH_3(CH_2)_6$-COOH	$CH_3(CH_2)_6$-$NHCON_3$	78%	22-24°
b	$(CH_3)_2CH{\cdot}CH_2{\cdot}COOH$	$(CH_3)_2CH{\cdot}CH_2{\cdot}NHCON_3$	72%	oil
c	$(CH_3)_2CH(CH_2)_2{\cdot}COOH$	$(CH_3)_2CH(CH_2)_2{\cdot}NHCON_3$	72%	24-26°
d	Ph $(CH_2)_2$-COOH	Ph $(CH_2)_2{\cdot}NHCON_3$	90%	82-84°
e		 Z = CON_3 / Z = $NHCON_3$	95% (70%)#	oil (73-75°)#
f			86%	60-63°
g			84%	58-60°
h			58%	84-85°

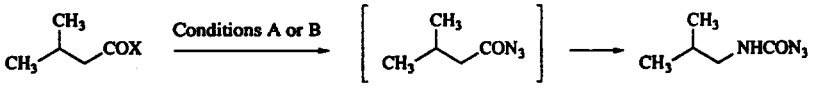
* Crude yield of chromatographically pure material. ** All new compounds gave satisfactory microanalytical data and spectroscopic properties. # Product after warming the reaction mixture at 65-70° overnight before workup.

General procedure: WARNING: *Carbamoyl azides are sensitive to thermal and mechanical shock and should be handled with due care, on small scale, behind a safety shield.* *N,N*-Dimethylchloromethylenammonium chloride (prepared by treatment of DMF (5.0 mmol) with a small excess of $(COCl)_2$ in CH_2Cl_2 followed by removal of solvent) was suspended in a mixture of MeCN (20 mL) and THF (20 mL), the suspension was cooled in a bath at –40°C and a solution of the carboxylic acid (5.0 mmol) and pyridine (5.0 mmol) in THF (20 mL) was added dropwise. The reaction mixture was stirred at –40°C for 2 h before NaN_3 (25.0 mmol) was added in one portion. Stirring was continued at –40°C for 30 min, the bath was removed and the mixture was allowed to stir to room temperature overnight or at 5-10°C for at least 5 h. Extractive workup with Et_2O and chromatography on silica gel gave analytical samples of the products.

The reaction almost certainly proceeds through sequential formation of the acid chloride and acid azide, then rearrangement, and trapping of the resultant isocyanate by the excess azide. In support of this proposal, two of the acid substrates (entries e and g) gave carboxylic acid azide products under normal conditions while one of these, the cyclopropylcarboxylic acid (entry e), gave carbamoyl azide in good yield by warming the reaction mixture to 70° before workup. Also, treatment of 3-methylbutanoyl chloride under the standard reaction conditions, but in the absence of dimethylformamide (DMF), gave the expected carbamoyl azide *albeit* in lower yield than from the acid (see later). The use of 5 mol equiv of NaN_3 appeared to be optimal. Less than this amount gave carbamoyl azide in proportionately lower yields.

Acetonitrile and THF are probably not necessary for the reaction to occur. However, the roles of DMF (which is generated during the reaction of the carboxylic acid and the Vilsmeier reagent) and pyridine were investigated. In the absence of pyridine, the reaction with 3-methylbutanoic acid gave none of the carbamoyl azide and instead a modest yield of the acid azide (Table 2, entry e). Alternative bases such as Et_3N and the acylation catalyst *N,N*-dimethylaminopyridine (DMAP) gave very poor yields of carbamoyl azide while 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave a somewhat higher yield (Table 2, entries b-d). As mentioned above, 3-methylbutanoyl chloride underwent reaction in the absence of DMF but only when pyridine was present. Without pyridine, or when pyridine was replaced by DMAP, the reaction gave mainly the acid azide and none of the carbamoyl azide. Therefore it is believed that pyridine acts principally as a polar aprotic solvent which assists the inorganic azide to dissolve. The presence of pyridine and DMF was beneficial and highest yields were obtained in the presence of both.

Table 2. Variation of Base and DMF Content on the Yield of Carbamoyl Azide



Entry	Substrate X group	Reaction conditions	DMF mmol	Base name	Base mmol	Percent yield of carbamoyl azide
a	OH	A	7.5	pyridine	5.0	72
b	OH	A	7.5	Et_3N	5.0	34
c	OH	A	7.5	DBU	5.0	45
d	OH	A	7.5	DMAP	5.0	29
e	OH	A	7.5	—	–	– (50)*
f	Cl	B	–	pyridine	5.0	54
g	Cl	B	–	DMAP	5.0	– (55)*
h	Cl	B	–	—	–	– (60)*

Condition A: (i) $ClCH{=}N^+Me_2Cl^-$ (7.5 mmol), base (5.0 mmol), –40°C; (ii) NaN_3 (25.0 mmol), –40°C; (iii) –40°C to r.t. overnight. Condition B: (i) base (5.0 mmol), –40°C; (ii) NaN_3 (25.0 mmol), –40°C; (iii) –40°C to r.t. overnight. * Values in parentheses refer to yields of acyl azide.

These results demonstrate the accessibility of carbamoyl azides from readily available carboxylic acids under suitable conditions. Future studies will focus on applications of these new derivatives.

Acknowledgments. We are grateful to the Australian Research Council for financial support of this project and the Australian International Development Assistance Bureau for provision of scholarships for HA and AVB. We wish to thank a referee for alerting us to the results described in reference 20.

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(*Received in UK* 22 *December* 1993; *revised* 14 *February* 1994; *accepted* 18 *February* 1994)