Pergamon

Tetrahedron Letters 41 (2000) 5291–5293

TETRAHEDRON LETTERS

N,*O*-Bis-(ethoxycarbonyl)hydroxylamine: a convenient reagent for the Lossen transformation

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Received 10 April 2000; revised 11 May 2000; accepted 16 May 2000

Abstract

The titled compound effects the Lossen rearrangement on aromatic carboxylic acids, via activation by DCC or formation of the acid chlorides, to furnish the corresponding amines in excellent yields, in an essentially 'one-pot' procedure.

Keywords: amines; carbamates; ethoxycarbonyl; hydroxylamine; Lossen.

Among the synthetically important family of reactions involving migration to electron-deficient nitrogen—the Hofmann, the Curtius and the Lossen reactions—the Lossen reaction has been relatively neglected, largely because of a complicated experimental procedure.[1,2] We report herein a new Lossen reagent which much simplifies the reaction.

The Lossen reaction is preceded by the formation of a hydroxamic acid and its subsequent activation:[1,2] the conversion would be much simplified were these steps to collapse into a single one. This indicates the use of a pre-activated hydroxylamine, e.g. an *O*-acyl derivative, but these are known to isomerise to *N*-acylhydroxylamines,[3] as our own attempts confirmed. Such isomerisation could be avoided by blocking the nitrogen centre, so an *N*,*O*-bis-acylated hydroxylamine was sought. An interesting derivative[4] appeared to be *N*,*O*-bis-ethoxycarbonylhydroxylamine **1** (Scheme 1). It was envisaged that **1** could be acylated with a carboxylic acid or its chloride **2** (R = OH or Cl), to the *N*-acyl-*N*,*O*-bis-ethoxycarbonylhydroxylamine **3**, which appeared well-set to undergo a reaction of the Lossen type on treatment with base. A concerted process in which the departure of the *O*-ester group is assisted by the *N*-ester, via the cyclic intermediate **4** and its subsequent fragmentation as shown, seems likely; the production of the final amine **6** via the isocyanate **5** follows the classical Lossen pathway. (4-Aza analogs of **4** have been prepared[4,5] from **1**.)

The bis-ester **1**—from[4] hydroxylamine and ethyl chloroformate—was readily acylated by various aromatic acid chlorides **2** (X=Cl) to give **3** in excellent yields. The subsequent Lossen conversion of **3** was also effected in high yields, via treatment with triethylamine in refluxing acetonitrile with

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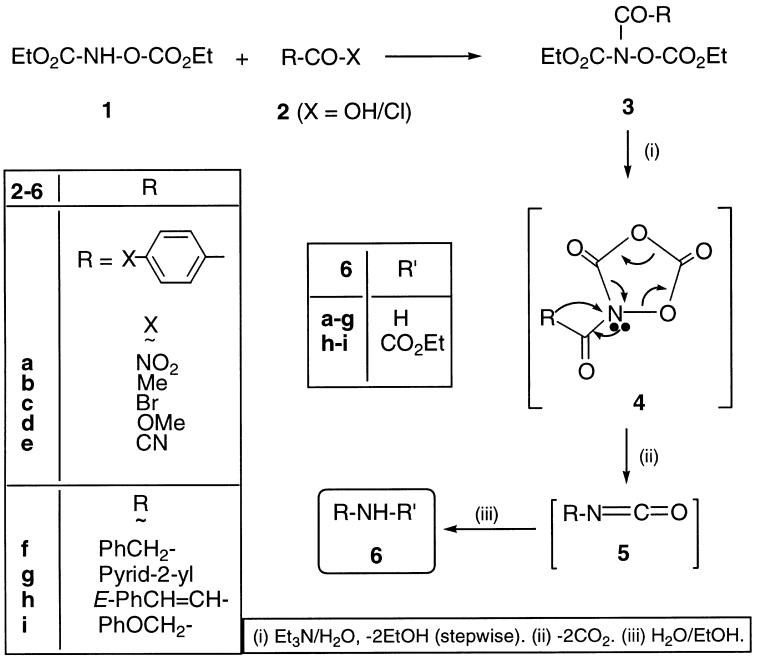
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00808-X



Scheme 1.

Table 1
'One-pot' conversion of carboxylic acids **2** to amines **6** via a Lossen transformation[a]

2	Reaction time (h)	6	% Yield
a	8 (8)	**a**	56 (61)
b	12 (10)	**b**	54 (54)
c	18 (16)	**c**	50 (50)
d	18 (14)	**d**	44 (48)
e	12 (12)	**e**	56 (61)
f	(24)	**f**	(52)
g	(15)	**g**	(40)
h	14 (14)	**h**	36 (43)
i	24 (18)	**i**	31 (42)

[a]With DCC and **1;** values in parenthesis: the acid chloride and **1.** Yields are for purified products. Typical procedure: **1,** the carboxylic acid and DCC (1 mmol each) in MeCN (5 ml) stirred at 25 °C for 5h. The resulting **3** treated with Et_3N (1 mmol) and a drop of water, and the mixture refluxed for 8h, cooled and worked-up. Products purified chromatographically and characterised by IR, ^1H and ^{13}C NMR, and MS; new compounds furnished satisfactory elemental analysis and/or high resolution mass spectra.

a trace of water. Potassium hydroxide led to lower yields, and the substitution of ethanol for water led to the cleavage of the aroyl group. The trace of water apparently facilitates the formation of **4**. The conversion also occurred in 'one pot', i.e. without the isolation of the intermediate **3**, with only a marginal loss of overall yield (Table 1).

The acylated derivatives **3** were also prepared directly from the acids **2** (X=OH) and **1** in the presence of dicyclohexylcarbodiimide (DCC; MeCN/25°C/5 h), in high yields. A 'one-pot' conversion of **2** to the amines **6** by the DCC route was also performed, in yields generally comparable to the acid chloride route (Table 1). Work-up with ethanol afforded the ethyl carbamates **6h** and **6i**.

The above Lossen reaction with **1** failed with aliphatic carboxylic acids, the hydrolysis of the 'introduced' acyl group (RCO) in **3** being observed and the starting acid being recovered. Such deacylation in the aromatic cases—although occurring marginally—is perhaps prevented by conjugation (sterically in the case of phenylacetic acid, **2f→6f**). The above failure in the aliphatic cases is perhaps a strength in terms of selectivity, as aliphatic amines are approached anyway via the Gabriel syntheses.[6] A recent method—reported[2] after the present studies[7] and promoting *N*-*t*-butyloxycarbonyl-*O*-methanesulphonylhydroxylamine as a Lossen reagent—is relatively less facile.

Acknowledgements

CSIR and UGC (N. Delhi) are thanked for generous financial support.

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