Reaction of lactim ethers and lactim sulfides with electrophiles: attack at nitrogen followed by ring-opening under neutral conditions

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Electrophilic push-pull molecules react at the nitrogen of lactim ethers and lactim sulfides; subsequent hydrolysis gives ring-opened products in good yields.

Introduction

The reaction of lactim ethers (or sulfides) with electrophiles can take several routes, in most of which the nitrogen atom of the substrate acts as the nucleophile,

but this is not always the case. There are examples in the literature where C-3 is the site of electrophilic attack. This obviously results from the reaction of the lactim ether as its enamine tautomer. Thus, the five-membered \( \gamma \)-butyrolactim ether \( \text{1a} \) and its six-membered homologue \( \text{1b} \) react with aryl isocyanates at C-3 to form phenylcarbamoyl derivatives

(Scheme 1). The initial nucleophilic attack of one molecule of the lactim ether in its enamine form on another molecule of the lactim ether at the electrophilic carbon has been suggested to account for the products of the reaction of the lactim ether with diketene.

A further variation is provided by the corresponding lactim sulfide \( \text{2} \). Thus, while the 5-membered lactim sulfide \( \text{2a} \) reacts with aryl isocyanates in the enamine form at C-3, the higher ring homologues \( \text{2b} \) and \( \text{2c} \) react at the nitrogen.

Subsequent deprotonation at C-3 leads to enaminoethers. Reaction at the nitrogen with electrophiles can have at least two other sequelae. There are several examples in the literature in which the second step is the attack by the counterion on the alkyl group of the ether leading to N-substituted lactams via alkyl-oxygen cleavage (Scheme 1). This is the case with alkylation, acylation and sulfonylation.

Most interesting in the context of the present discussion are the occasional reports of the reaction of lactim ethers with electrophiles followed by opening of the lactim ring (Scheme 1). Thus

\[ \begin{align*}
\text{NOR} + E^+ & \rightarrow \text{N} \quad \text{NH}_2 \\
\text{E} & \rightarrow \text{NOR} \\
\text{Scheme 1}
\end{align*} \]

\( \omega \)-isocyanato carboxylic acid esters are reported to result from the reaction of lactim ethers with chloroform in aqueous alkali.

Similarly, the lactim ether \( \text{1c} \) reacts with thiophosgene to form an isothiocyanato carboxylic ester.

There is also a recent report that 1,4-naphthoquinone reacts with \( \text{1a} \) in methanol to form 2-(3-methoxy carbonylpropylamino)-1,4-naphthoquinone.

The present report deals with the reaction of lactim ethers and the corresponding sulfides with a series of electrophilic push-pull ethylenes in methanol solution. In all the examples studied, attack took place on the nitrogen atom; this was followed by opening of the ring, leading to the formation of carboxylic esters.

Results and discussion

Reaction of the five-, six- or seven-membered lactim ethers \( \text{1} \) or the corresponding sulfides \( \text{2} \) with a series of electrophilic push-pull ethylenes \( \text{3-6} \) in methanol solution led to the ring-opened products \( \text{7-10} \) in yields in the range 38–79% (Scheme 2).

![Scheme 2](image)

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\( \text{1a} \) with 1,1-bis(1-methoxy-2-nitroethenyl)aminobutanoate \( \text{7a} \) in 43% yield. The inter-
under the same conditions led to higher yields of the products obviously takes place by the water present in the solvent.

Valerolactim ether 1b and ε-caprolactim ether 1c with 1,1-bis(methylthio)-2-nitroethylene 3 in refluxing methanol similarly gave 7b and 7c in 50 and 56% yields, respectively. As expected from the relative nucleophilicity of the nitrogen atom in lactim ethers and lactim sulfides, reaction of the sulfides 2a–c with 3 under the same conditions led to higher yields of the products 7a–c. In all these reactions, hydrolysis of the iminium ion obviously takes place by the water present in the solvent.11

It has been well established earlier that nitro enamines possessing an NH group exist almost exclusively in the intra-molecularly hydrogen-bonded configuration, especially in non-polar solvents. It is also known that the barrier to rotation around the formal double-bond in such systems is low enough to preclude isolation of the less energetically favoured geometrical isomer.12 On this basis, the products 7a–c have been assigned the E configuration (NH and NO \(_2\) cis to each other).

The reaction took a similar course with other electrophilic push-pull ethylene systems as well. Thus ethoxymethylene-acetolactone 4 reacted with γ-butylolactim ether 1a in refluxing methanol to give 8a (48%). The sulfide 2a gave the same product (71%). ε-Valerolactim ether 1b and ε-caprolactim ether 1c condensed with 4 to give 8b (53%) and 8c (68%), respectively, while the corresponding sulfides 2b and 2c led to higher yields of the products. Tables 1 and 2 list the products and yields in these and other related condensations involving ring-opening.

The configuration around the double bond in the aminomethyleneacetoacetoxy ester derivatives 9 is uncertain, although even here, only one species was observed in the NMR spectra in CDCl\(_3\) solution. Also in two of these products 9b and 9c trans-esterification had taken place under the reaction conditions, leading to methyl esters from ethyl ethoxymethylene-acetoacetate 5.

One of our objectives in this area has been to utilise nitroketene O,N-acetals or S,N-acetals (such as 7 and 11) for the synthesis of peptides incorporating non-natural α-alkylated amino acids. The route involves hydrolysis to the nitroacetamides and subsequent regiospecific alkylation of the reactive methylene group, followed by reduction of the NO\(_2\) to NH.13 Towards this end, we treated several cyclodipeptide mono iminoethers 12 with 1,1-bis(methylthio)-2-nitroethylene 3 (Scheme 4), our hope being that the resulting nitroketene

![Scheme 4](insert)

S,N-acetals 13 could be hydrolysed to the corresponding nitroacetamides and then converted in two steps into modified tripeptides.

Unfortunately, the initial condensation was successful only with the cyclo (i-Pro-Gly) monominoether 12 (R = H), leading to 13 (R = H) (32%). The reaction failed with the analogous derivatives of alanine, valine, leucine or phenylalanine, in each case starting materials being recovered.

The ring-opening/N-alkylation reported above has potential in synthesis where the lactim ethers (or lactam) are more easily accessible than the corresponding α-aminoalkyl carboxylic esters. Also, some of the latter may prefer to undergo intramolecular cyclisation to lactams under the reaction conditions.

### Experimental

Melting points were determined with a microscope hot-stage apparatus, and are uncorrected. IR spectra were determined on a Perkin-Elmer-Infracord spectrometer. \(^{1}H\) and \(^{13}C\) NMR spectra were recorded on a Bruker-WH-90 (Spectrospin), Bruker-AC-200, Bruker-M SL-300 or Varian-FT-80A instrument in CDCl\(_3\) solution with tetramethylsilane as internal standard. Coupling constants \(J\) are given in Hz. Mass spectra were determined on a Finnigan-MAT-1020B spectrometer. Microanalyses were performed at the Organic Chemistry Division, NCL.

**Typical procedure**

The lactim ethers were prepared according to the literature method.15 Thio lactams were obtained from their oxygen counterparts using Lawesson's reagent16 and etherified by iodomethane in acetone in the presence of K\(_2\)CO\(_3\). The lactim ether or lactim sulfide (2 mmol) and the electrophile (2 mmol) were mixed in methanol (10 ml). The mixture was refluxed and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude sample was purified by column chromatography over silica gel using acetone-light petroleum.

**Methyl 4-(1-methoxy-2-nitroethenylamino)butanoate 7a.** A yellow oil (43%); \(\nu\)\text{max} cm\(^{-1}\) (neat) 3360, 3260, 2960, 1740 and 1520; \(\delta\) (CDCl\(_3\)) 1.9 (m, 2H, CH\(_2\)), 2.35 (t, 2H, COCH\(_3\)), 8.8.
M ethyl 5-(1-methoxy-2-nitroethenylamino)pentanoate 7b. A yellow gum (50%); \(v_{\text{max}}/\text{cm}^{-1}\) (neat) 3144, 2945, 1729, 1642, 1530 and 1430; \(\delta_{\text{C}}(\text{CDCl}_3)\) 1.55-1.70 (m, 6H), 3.20 (s, 3H, OCH, \(J_{\text{CH}}\) 3.75, 4.20 (s, 2H, CH, \(J_{\text{CH}}\) 5.35, 4.60, 7.35 (s, 3H, OCH, \(J_{\text{CH}}\) 10.50 (br s, 1H, NH); \(\delta_{\text{C}}(\text{CDCl}_3)\) 24.22, 30.42, 39.43, 51.06, 56.57, 57.92, 164.26 and 172.44; m/z 210 (M \(^+\)), 187, 172, 140, 112 (100%) and 98 (Found: C, 43.99; H, 6.24; N, 12.60. C\(_4\)H\(_8\)N\(_2\)O\(_4\) requires C, 44.03; H, 6.42; N, 12.84%).

M ethyl 6-(1-methoxy-2-nitroethenylamino)hexanoate 7c. A colourless oil (57%); \(v_{\text{max}}/\text{cm}^{-1}\) (neat) 3300, 2970, 1650, 1615, 1450 and 1370; \(\delta_{\text{C}}(\text{CDCl}_3)\) 1.55-1.85 (m, 6H), 3.22 (2H, CH, \(J_{\text{CH}}\) 1.95 (s, 3H, CH, \(J_{\text{CH}}\) 3.20 (t, 2H, COCH\(_2\)), 6.20 (s, 1H, OCH), 7.35 (s, 3H, OCH, \(J_{\text{CH}}\) 8.00 (d, 1H, \(-CH,-J_{\text{CH}}\) 14 and 12.45 (br s, 1H, NH); m/z 257, 242, 191, 186, 166, 137 (100%). 124 and 89 (Found: C, 56.18; H, 7.01; N, 5.62. C\(_6\)H\(_8\)N\(_2\)O\(_4\) requires C, 56.03; H, 7.39; N, 5.44%).

M ethyl 6-(2-acetylamino-2-methoxyethoxy)hexanoate 7d. A colourless oil (57%); \(v_{\text{max}}/\text{cm}^{-1}\) (neat) 3300, 2970, 1740, 1650, 1615 and 1450; \(\delta_{\text{C}}(\text{CDCl}_3)\) 1.55-1.75 (m, 6H), 2.85 (2H, CH, \(J_{\text{CH}}\) 1.95 (s, 3H, CH, \(J_{\text{CH}}\) 3.20 (t, 2H, COCH\(_2\)), 6.20 (s, 1H, OCH), 7.35 (s, 3H, OCH, \(J_{\text{CH}}\) 8.00 (d, 1H, \(-CH,-J_{\text{CH}}\) 14 and 12.45 (br s, 1H, NH); m/z 257, 242, 191, 186, 166, 137 (100%). 124 and 89 (Found: C, 56.18; H, 7.01; N, 5.62. C\(_6\)H\(_8\)N\(_2\)O\(_4\) requires C, 56.03; H, 7.39; N, 5.44%).
References

11. This is similar to the ring-opening in methanol reported in ref. 10.

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