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THE SYNTHESIS, REDUCTION AND CYCLISATION OF N-(3-BUTENYL)-MORPHOLIN- AND -THIOMORPHOLIN-2, 6-DIONES

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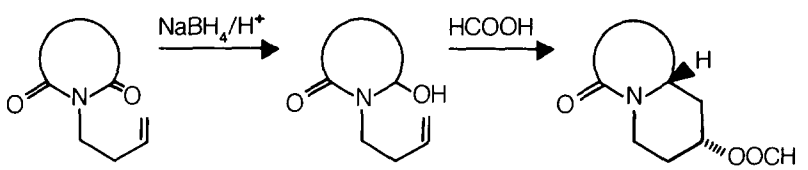
Abstract: A novel one-step synthesis of N-(3-butenyl) imides (1) from dicarboxylic acids, and the sodium borohydride reduction/formic acid cyclisation of the N-(3-butenyl)-morpholin- and thiomorpholin-2, 6-diones are described.

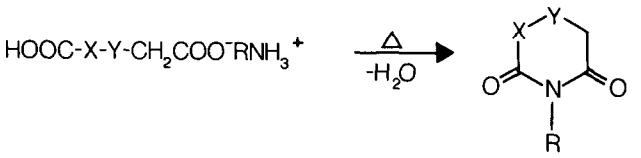
The biomimetic α-acylimminium ion cyclisation of olefins mediated by formic acid to form, in a highly stereospecific manner, equatorial formates with a *trans*-ring junction (3) has been recognised as a valuable method for the synthesis of azapolycycles[1].



(1) (2) (3)

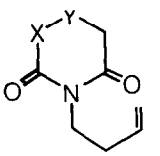
To date the N-substituted imides (1) have been prepared by condensation of an N-unsubstituted imide with the appropriate alcohol in the presence of triphenylphosphine and dimethyl or diethylazodicarboxylate[2]. This method is satisfactory for simple systems where the N-unsubstituted imides are readily available; however, in more complex systems, where prior synthesis of the N-unsubstituted imide from the precursor dicarboxylic acid is necessary, the overall yield is often unsatisfactory.

In this communication we report a high yielding, single step conversion of the precursor dicarboxylic acid to the N- (3-butenyl) imide. This procedure is based upon the pyrolysis of the appropriate monoamine salt[3].



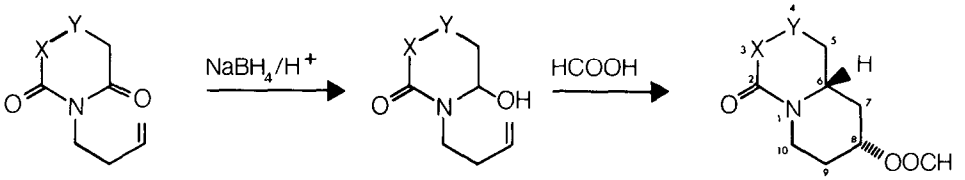
The required amine, 1-amino-3-butene, has been prepared in high yield by the reduction of allyl cyanide with aluminium hydride (generated *in situ* from lithium aluminium hydride and conc. sulphuric acid in THF)[4]. We have found that treatment of the THF solution of the crude amine with an aqueous solution of the dicarboxylic acid (0.9 molar equivalents) and distillation under reduced pressure (100 mmHg, flask temperature 180–230°) gave the crude imides (1a–d) which were purified by extraction into ether and redistillation.

Table 1: Preparation of the Imides (1)



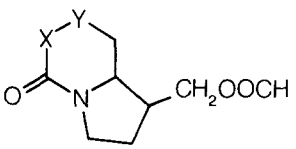
Compound	–X–Y–	Yield (%)	B.P. (°C/mmHg)
1a	$-CH_2-$	73	80–2/0.2
1b	$-CH_2-CH_2-$	75	86–7/0.1
1c [7,8]	$-CH_2-O-$	78	84–8/0.1
1d [7,9]	$-CH_2-S-$	63	106–7/0.4

The novel morpholin-2, 6-dione (1c) and thiomorpholin-2, 6-dione (1d) (0.02M) both underwent the normal reduction with sodium borohydride (0.025M), either with the addition of ethanolic hydrogen chloride[1], or of ethanolic acetic acid (0.025M) at -20° over 5 hours. Normal work-up procedure afforded the crude hydroxy-lactams (2c, 2d) which were cyclised (formic acid, 18h, r.t.) without purification to give, respectively, the 1-aza-8-formyloxy-4-oxabicyclo [4,4,0] decan -2-one[10] (3c) (80%, m.p. 83–5°) and the 1-aza-8-formyloxy-4-thiabicyclo [4,4,0] decan -2-one[11] (3d) (78%, an oil which would not crystallise).



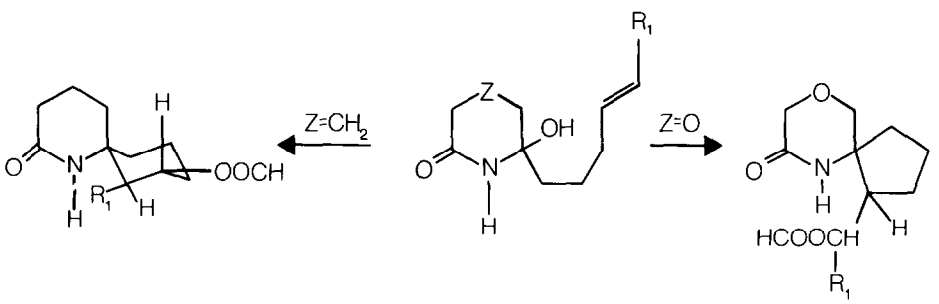
-X-Y-			
$-CH_2-O-$	(1c)	(2c)	(3c)
$-CH_2-S-$	(1d)	(2d)	(3d)

The cyclised products (3c, 3d) are formed by a 6-*Endo*-Trig[5] mode of ring closure as previously observed in the corresponding succinimide (1a) and glutarimide (1b) series[1]. No 5-*Exo*-Trig ring closure products (4c, 4d) were detected.



-X-Y-	
$-CH_2-O-$	(4c)
$-CH_2-S-$	(4d)

These results contrast with the findings of Speckamp *et al.* during their study on the synthesis of perhydrohistrionicotoxin[6]. They reported that formic acid cyclisation of the hydroxy-lactam (5) gave mainly the 6-*Endo*-Trig product (7) whereas the equivalent oxa system (6) gave exclusively the 5-*Exo*-Trig Product (8).



(7)

R_1=n-C_4H_9

(5) Z=CH_2

(6) Z=O

(8)

They suggested that the observed difference in the preferred mode of ring closure to the spiro systems (7 and 8) is due to unspecified minor steric and electronic factors. Our present findings show that these same factors do not appear to influence the mode of ring closure to the related fused systems (3c–3d) and may indicate that the presence of the n-butyl group (R_1) in the spiro system plays an important role in this process.

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[7]. We have also prepared these imides from the N–H imide and 4-bromo-butene by the standard Gabriel synthesis with sodium hydride in DMF.

[8]. ^{1}H–NMR (δ, $CDCl_3$) 4.20 (s. 4H, -CH_2O-).

[9]. ^{1}H–NMR (δ, $CDCl_3$) 3.50 (s. 4H, -CH_2-S-).

[10]. ^{1}H–NMR (δ, $CDCl_3$) 7.91 (s, 1H, OOC*H*); 4.50–5.20 (m, 2H, H_{10}-eq and H_8-ax); 4.05 (s, 2H, H_3-eq and -ax); 3.20–3.45 (m, 3H, H_6, H_5-eq and -ax); 1.20–2.80 (m, 5H).

[11]. ^{1}H–NMR (δ, $CDCl_3$) 7.96 (s, 1H, OOC*H*); 4.50–5.20 (m, 2H, H_{10}-eq and H_6-ax); 1.2–4.0 (m, 10H including 3.27, s, 2H, H_3-eq and -ax).

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