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Tetrahedron Letters 45 (2004) 9611–9615
Tetrahedron Letters

Synthesis of 2-oxazolines mediated by *N*,*N*′-diisopropylcarbodiimide

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Received 29 August 2004; revised 15 October 2004; accepted 26 October 2004
Available online 11 November 2004

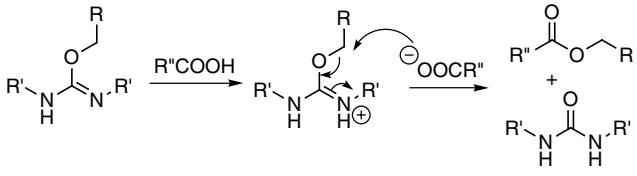
Abstract—*N*-(β-Hydroxy)amides can be cyclised by reaction with diisopropylcarbodiimide (DIC) to give the corresponding 2-oxazolines in high yields. The reaction requires only very mild Lewis-acid catalysis (5 mol% $Cu(OTf)_2$) and can be accomplished with simple heating, or in very short reaction times under microwave irradiation.

Over the years, 2-oxazolines have emerged as a very interesting class of heterocycles with an astonishingly wide range of applications in synthetic organic chemistry.[1] Carboxylic acids as well as β-amino alcohols can be protected as a 2-oxazoline,[1,2] and 2-oxazolines have been used as building blocks in organic synthesis.[3] Homochiral 2-oxazolines have been used as auxiliaries for a number of applications.[4] Many examples of useful homochiral ligands based on 2-oxazolines for a wide range of transformations have been reported.[4c,5] In addition, the 2-oxazoline ring occurs in natural products and in drug-like compounds,[6] and has been employed as a hydrolysable precursor for carboxylic acids in prodrugs.[7]

Many synthetic procedures exist for the formation of 2-oxazolines and new ones continue to be developed.[1,4d,5a,c] Starting from amino alcohols, reaction with carboxylic acids,[7,8a,b] *ortho* esters,[8c] nitriles,[8d,e,f] imino ethers[8g] and acyl benzotriazoles[8h] have been reported. The other major synthetic methods start from β-hydroxy amides, with cyclisation achieved with a number of reagents including Burgess' reagent,[9a,b] DAST,[9c] PPh_3/DIAD[9d] and immobilised *p*-toluenesulfonyl chloride/Et_3N.[6a,9e] Other methods include the reaction between an aldehyde and a β-hydroxy azide.[10]

As part of a research programme investigating the synthetic utility of isoureas,[11] we were intrigued by the possibility of using isoureas as intermediates in 2-oxazoline synthesis. *O*-Alkylisoureas are easily formed by the addition of an alcohol to a dialkylcarbodiimide under copper catalysis.[12] Isoureas, as such, are poor leaving groups, and need to be activated by protonation. A typical example is the protonation of an *O*-alkylisourea by a carboxylic acid, leading to the formation of a carboxylate anion that subsequently displaces the protonated isourea moiety to give a carboxylic ester (Scheme 1).[12] We have reported an alternative activation of isoureas using acetyl halides (Cl, Br), ultimately leading to a one-pot conversion of alcohols into alkyl halides.[11b] Isoureas derived from chiral, secondary alcohols are displaced with inversion of configuration.[11b,13]

There are very few examples of isoureas being used in cyclisation reactions. Alexandre reported that heating isoureas derived from γ-hydroxyketones leads to



Scheme 1. Typical reaction of isoureas by protic activation, followed by nucleophilic substitution.

Keywords: 2-Oxazoline; Isourea; Lewis acid; Microwave irradiation; Carbodiimide.
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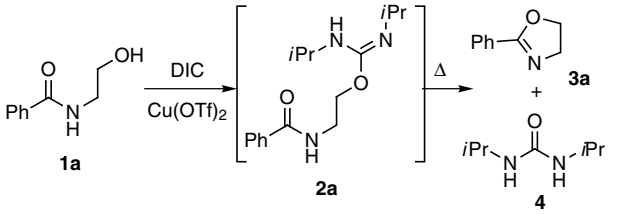
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.143



Scheme 2. Planned cyclisation of amide isoureas **2** to 2-oxazolines **3**.

α,β-cyclopropyl ketones and 2,3-dihydrofurans.[14] Grayson recently reported the synthesis of 2,5-dihydrofurans from (*Z*)-1,4-dihydroxyalk-2-enes by monoaddition of DCC, followed by heating the hydroxyisourea intermediate with 13 mol% of trifluoroacetic acid.[15]

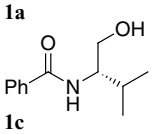
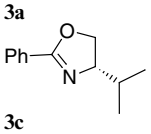
It is known that amides do not react with isoureas. Nevertheless, as amides have a similar acidity to ketones, we envisioned that intra- or intermolecular activation of isoureas **2** would be possible, and that the cyclisation to form 2-oxazolines **3** as depicted in Scheme 2 would be feasible without added acid. In this communication, we report our results regarding this novel isourea transformation.[16] From the outset, it was envisioned that the process would not be investigated starting from isolated isoureas **2**, but that **2** would be made in situ from the corresponding *N*-(β-hydroxyethyl)amides **1**, which are easily synthesised from 2-aminoalcohols.

To this end, *N*-(2-hydroxy-1,1-dimethylethyl)benzamide **1b** was reacted with 1 equiv of diisopropylcarbodiimide (DIC) under Cu(II) catalysis to give the corresponding *O*-alkylisourea **2b**. The reaction could easily be monitored by IR for disappearance of the carbodiimide band at 2110 cm^{-1} and the appearance of the isourea band at 1655 cm^{-1}. When judged complete, and without removing the copper salt, the isourea intermediate was heated at 60 °C for 2 days. The appearance of a white crystalline diisopropylurea precipitate **4** signalled that the reaction had occurred. Purification by filtration followed by column chromatography gave 4,4-dimethyl-2-phenyl-2-oxazoline **3b** in 74% yield.

With this preliminary result in hand, further optimisation was carried out (Table 1). *N*-(β-Hydroxyethyl)amide **1a** in THF was mixed with DIC (1 equiv) and $Cu(OTf)_2$, and refluxed for the times indicated. The reaction was incomplete after 24 h, with 63% isolated yield after chromatography (entry 1). However, complete reaction could be achieved after refluxing for 48 h (92%, entry 2), but when the reaction time was too long, product degradation was observed (entry 3). Subjecting *N*-(β-hydroxyethyl)amide **1c** to the optimal conditions (48 h) yielded the corresponding oxazoline **3c** in 97% yield (entry 4). Despite the high yields, the reaction time required was a drawback to the utility of the process. Hence, the reaction was investigated in 1,4-dioxane as a higher boiling solvent (Table 2).

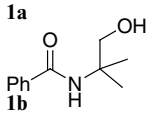
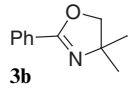
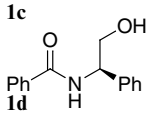
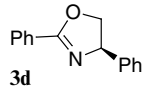
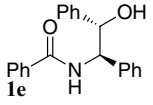
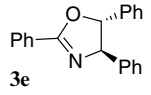
When the reaction was carried out at reflux for 20 h, a yield of 81% was obtained (entry 1). This was improved after increasing the amount of catalyst (entry 2) or reducing the reaction time to just 5 h (entry 3). A number of other *N*-(β-hydroxyethyl)amide substrates were investigated under these conditions, with excellent results when α-substitution was present (entries 4–6). The yield was somewhat decreased when β-substitution was present (entry 7).

Table 1. Formation of 2-oxazolines in THF (reflux) with DIC (1 equiv) and $Cu(OTf)_2$ (5 mol%)

Entry	Starting material	Time (h)	Product	Yield[a] (%)
1	**1a**	24	**3a**	63
2	**1a**	48	**3a**	92
3	**1a**	72	**3a**	68[b]
4	 **1c**	48	 **3c**	97

[a] Isolated yield after chromatography.
[b] 6 mol% $Cu(OTf)_2$.

Table 2. Formation of 2-oxazolines in 1,4-dioxane (reflux) with DIC (1 equiv) and $Cu(OTf)_2$ (5 mol%)[17]

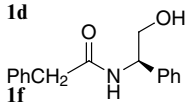
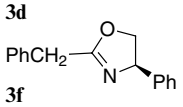
Entry	Starting material	Time (h)	Product	Yield[a] (%)
1	**1a**	20	**3a**	81[b]
2	**1a**	18	**3a**	96[c]
3	**1a**	5	**3a**	97
4	 **1b**	5	 **3b**	97
5	**1c**	5	**3c**	93
6	 **1d**	6	 **3d**	98[b]
7	 **1e**	6	 **3e**	78[d]

[a] Isolated yield after chromatography.
[b] 6 mol% $Cu(OTf)_2$.
[c] 8 mol% $Cu(OTf)_2$.
[d] *Trans:cis* ratio: >95:<5.

We have demonstrated in earlier work that both isourea formation, as well as isourea displacements, can be achieved efficiently, with very short reaction times, under microwave irradiation.[11] Hence, we were keen to investigate whether the whole reaction sequence from **1** to **3** could be carried out in this way in the hope of shortening reaction times further (Table 3).

We were delighted to find that mixing **1a** or **1b** with DIC and $Cu(OTf)_2$, followed by heating for only 5 min at 150 °C in a focused microwave oven, yielded **3a**,**b** in 87% and 93% isolated yields, respectively, after chromatography (entries 1 and 2). Performing the reaction at lower temperatures gave lower yields despite doubling the reaction time (entry 3 vs 2). When **1a** was heated in a microwave oven in the absence of DIC, no reaction was observed. Substitution at the α-position generally

Table 3. Microwave-assisted cyclisation to 2-oxazolines in THF with DIC (1 equiv) and $Cu(OTf)_2$ (5 mol%)[18]

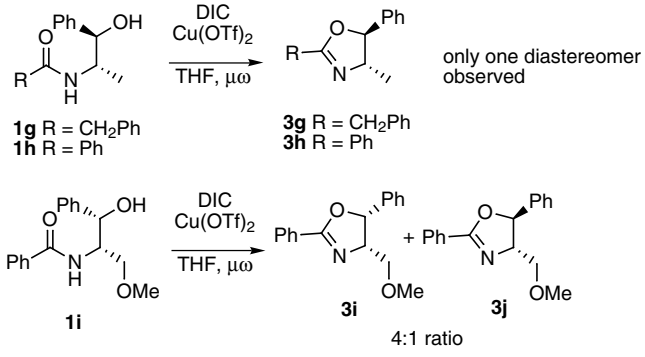
Entry	Starting material	Time (temp) (min, °C)	Product	Yield[a] (%)
1	**1a**	5 (150)	**3a**	87
2	**1b**	5 (150)	**3b**	93
3	**1b**	10 (120)	**3b**	61
4	**1c**	5 (150)	**3c**	92
5	**1d**	5 (150)	**3d**	87
6	 **1f**	5 (100) + 10 (175)	 **3f**	79
7	**1g**	15 (150)	**3g**	83[b]
8	**1h**	5 (150)	**3h**	88[b]
9	**1i**	5 (150)	**3i**	86[c]

[a] Isolated yield after chromatography.
[b] *Trans:cis* ratio: >95:<5.
[c] *Trans:cis* ratio: 1:4. Combined yield of both isomers.

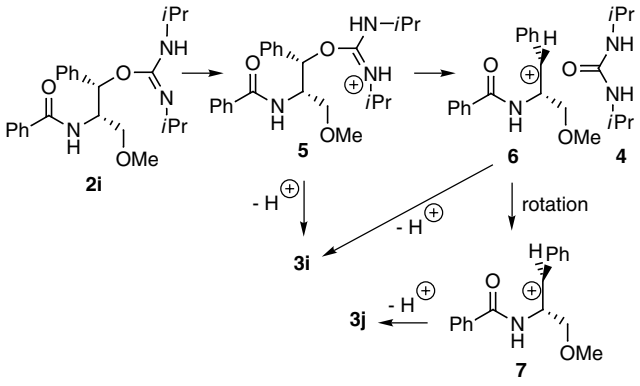
posed no problem (entries 2–5). However, cyclisation of substrates with an aliphatic R_1-substituent ($PhCH_2$–) was slightly more difficult and required higher reaction temperatures and/or longer reaction times (entries 6 and 7). Cyclisation of **1g** and **1h** (derived from (1*R*,2*S*)-norephedrine) yielded a single diastereoisomer, with slightly lower yields because of the β-substitution (entries 7 and 8 and Scheme 3). As a *trans*-substituted oxazoline was obtained (as confirmed by comparison with literature data), the cyclisation must have occurred with inversion of configuration, consistent with the expected S_N2 process.

However, a lower level of diastereoselectivity was observed with amide **1i**, derived from (1*S*,2*S*)-2-amino-3-methoxy-1-phenyl-1-propanol. Only a 4:1 ratio in favour of the expected *cis*-substituted oxazoline over the *trans*-substituted isomer was observed in this case (entry 9 and Scheme 3).

We also sought to verify whether the copper(II) Lewis acid, in addition to catalysing the isourea formation, played a role in the cyclisation step. In the event, amide **1a** was reacted with DIC at room temperature in the presence of the usual quantity of copper(II) triflate. After 4 h, IR and TLC analysis showed that both carbodiimide and **1a** had been consumed, forming the corresponding isourea **2a** (major) plus a minor amount of cyclised product **3a**. At this point the copper catalyst was removed by filtration through an alumina plug, using DCM as eluant. The solution was concentrated under vacuum, placed in a microwave vial and subjected to the usual conditions. TLC analysis indicated complete conversion of the isourea to the oxazoline, and subsequent column chromatography afforded pure **3a** in 84% yield. This suggests that the copper species does not play a significant role in the second step of the reaction.



Scheme 3. Diastereoselective formation of oxazolines derived from (1*R*,2*S*)-norephedrine and (1*S*,2*S*)-2-amino-3-methoxy-1-phenyl-1-propanol.



Scheme 4. Suggested mechanism for the 2-oxazoline formation.

Based on the above, and on the stereochemical findings described in Scheme 3, we suggest a mechanism in which the isourea moiety necessarily has to be activated before cyclisation takes place (Scheme 4).

Given the basicity of isoureas, an intermolecular acid–base reaction would take place leading to the protonated intermediate **5**, upon which cyclisation can occur to give the 2-oxazoline product **3i** with inversion of configuration at the reacting centre. However, because the urea is a good leaving group, the reaction could proceed through an S_N1-type mechanism featuring **6**, especially when the cation is stabilised by a phenyl group. The formation of **3j** can thus be explained by a subsequent rotation about the C–C bond to give **7**, followed by

cyclisation. Given the pK_a value of ureas, we believe it is very unlikely that an *unactivated* isourea can dissociate, even when benzylic. Interestingly however, only one oxazoline diastereomer was observed starting from **1e**, **g** and **h**, which also contain a secondary benzylic alcohol moiety. Hence, the actual cyclisation mechanism is dependent on structural features. With primary alcohols, a true S_N2 process will take place. With secondary benzylic alcohols, an S_N2 mechanism still operates but if α-substitution is present, unfavourable steric interactions may tilt the balance towards an S_N1-type process. In this way, rotation can relieve steric strain that otherwise would build up in the formation of *cis*-substituted 2-oxazolines. Given that **3j** is still the minor diastereoisomer, the inversion process is still the major pathway even with **5** (Scheme 4). Further research to investigate these mechanistic aspects is in progress.

In conclusion, we have discovered that *N*-(β-hydroxyethyl)amides can be cyclised to the corresponding 2-oxazolines by converting them into the corresponding *O*-alkylisoureas in situ, followed by thermally induced cyclisation. It was shown that the cyclisation proceeded in good to excellent yields after 5 h reflux in 1,4-dioxane,[17] and in merely 5 min under microwave irradiation (150 °C).[18] The reaction is easier with aromatic amides, and substitution on the other carbon atoms of the ring is allowed. Inversion of configuration is observed with good to excellent selectivity. Based on the stereochemical observations with chiral substrates, we propose a sequence in which the isourea moiety is protonated prior to the actual cyclisation reaction, which proceeds via an S_N2 mechanism, however, in particular cases having appreciable S_N1 character.

Acknowledgements

The authors thank Personal Chemistry for the donation of a Smith Synthesizer™, and acknowledge the supporting partners of the Southampton Combinatorial Centre of Excellence: AstraZeneca, GlaxoSmithKline and Evotec OAI. The authors thank Dr Joan Street and Dr Neil Wells for assistance with NMR and Ms Julie Herniman and Dr John Langley for assistance with the mass spectrometry. We also wish to acknowledge the use of the EPSRC's Chemical database Service at Daresbury.[19]

References and notes

1. Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297–2360.
2. Saravanan, P.; Corey, E. J. *J. Org. Chem.* **2003**, *68*, 2760–2764.
3. Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1685–1687.
4. (a) Meyers, A. I. *J. Heterocycl. Chem.* **1998**, *35*, 991–1001; (b) Scott, A. *Aust. J. Chem.* **2003**, *56*, 953; (c) Glos, M.; Reiser, O. In *Organic Synthesis Highlights IV*; Schmalz, H.-G., Ed.; Wiley-VCH, 2000; (d) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837–860; (e) Luisi, R.; Capriati, V.; Florio, S.; Piccolo, E. *J. Org. Chem.* **2003**, *68*, 10187–10190.
5. (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45; (b) Gómez, M.; Muller, G.; Rocamora, M. *Coord. Chem. Rev.* **1999**, *193–195*, 769–835; (c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875; Recent examples: (d) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140–1141; (e) Duffey, M. O.; LeTiran, A.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 1458–1459.
6. (a) Pirrung, M. C.; Tumey, L. N.; McClerren, A. L.; Raetz, C. R. H. *J. Am. Chem. Soc.* **2003**, *125*, 1575–1586; (b) Li, Q.; Woods, K. W.; Claiborne, A.; Gwaltney, S. L., II; Barr, K. J.; Liu, G.; Gehrke, L.; Credo, R. B.; Hua Hui, Y.; Lee, J.; Warner, R. B.; Kovar, P.; Nukkala, M. A.; Zielinski, N. A.; Tahir, S. K.; Fitzgerald, M.; Kim, K. H.; Marsh, K.; Frost, D.; Ng, S.-C.; Rosenberg, S.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 465–469; (c) Campani, G.; De Angelis, M.; Armaroli, S.; Fattorusso, C.; Catalanotti, B.; Ramunno, A.; Nacci, V.; Novellino, E.; Grewer, C.; Ionescu, D.; Rauen, T.; Griffiths, R.; Sinclair, C.; Fumagalli, E.; Mennini, T. *J. Med. Chem.* **2001**, *44*, 2507–2510.
7. Bandgar, B. P.; Pandit, S. S. *Tetrahedron Lett.* **2003**, *44*, 2331–2333.
8. (a) Cwik, A.; Hell, Z.; Hegedüs, A.; Finta, Z.; Horváth, Z. *Tetrahedron Lett.* **2002**, *43*, 3985–3987; (b) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353–9372; (c) Kamata, K.; Agata, I. *J. Org. Chem.* **1998**, *63*, 3113–3116; (d) Jnaneshwara, G. K.; Deshpande, V. H.; Lalithambika, M.; Ravindranathan, T.; Bedekar, A. V. *Tetrahedron Lett.* **1998**, *39*, 459–462; (e) Clarke, D. S.; Wood, R. *Synth. Commun.* **1996**, *26*, 1335–1340; (f) Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173–1180; (g) Oussaid, B.; Berlan, J.; Soufiaoui, M.; Garrigues, B. *Synth. Commun.* **1995**, *25*, 659–665; (h) Katritzky, A. R.; Cai, C.; Suzuki, K.; Singh, S. K. *J. Org. Chem.* **2004**, *69*, 811–814.
9. (a) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907–910; (b) Wipf, P.; Venkatraman, S. *Tetrahedron Lett.* **1996**, *37*, 4659–4662; (c) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168; (d) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267–6270; (e) Pirrung, M. C.; Tumey, L. N. *J. Comb. Chem.* **2000**, *2*, 675–680.
10. Badiang, J. G.; Aubé, J. *J. Org. Chem.* **1996**, *61*, 2484–2487.
11. (a) Crosignani, S.; White, P. D.; Linclau, B. *J. Org. Chem.* **2004**, *69*, 5897–5905; (b) Crosignani, S.; Nadal, B.; Li, Z.; Linclau, B. *Chem. Commun.* **2003**, 260–261; (c) Li, Z.; Crosignani, S.; Linclau, B. *Tetrahedron Lett.* **2003**, *44*, 8143–8147.
12. Mathias, L. J. *Synthesis* **1979**, 561–576.
13. Kaulen, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 773–774.
14. Alexandre, A.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1971**, 1837–1840.
15. Duffy, M. G.; Grayson, D. H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1555–1563.
16. During the course of this research, we found that a similar reaction to the one reported here has been suggested as an intermediate step in the reaction of acetic acid with the isourea of α-chymotrypsin (obtained by reaction of α-chymotrypsin with a water-soluble carbodiimide). However, no proof of the proposed reaction pathway was given and the reaction has never been exploited in synthesis Banks, T. E.; Blossey, B. K.; Shafer, J. A. *J. Biol. Chem.* **1969**, *244*, 6323–6333.
17. Typical procedure: To a solution of amide **1b** (999 mg, 5.2 mmol) and $Cu(OTf)_2$ (100 mg, 0.28 mmol) in anhydrous 1,4-dioxane (10 mL) was added DIC (654 mg, 5.2 mmol) and the solution was heated at reflux for 5 h.

The resulting white precipitate was filtered (washed with ethyl acetate), and the solution evaporated under reduced pressure. The oily residue was purified by column chromatography (hexane:ethyl acetate 60:40), to give 880 mg (97%) of **3b**.

18. Typical procedure: amide **1b** (193 mg, 1 mmol), DIC (126 mg, 1 mmol) and $Cu(OTf)_2$ (ca. 20 mg, 0.05 mmol) were placed in a microwave vial and dissolved in anhydrous THF. The resulting solution was heated at 150 °C for 5 min by microwave irradiation. The resulting white precipitate was filtered (washed with ethyl acetate), and the solution evaporated under reduced pressure. The oily residue was purified by column chromatography (hexane:ethyl acetate 60:40), to give 163 mg (93%) of **3b**.
19. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746–749.