Pergamon

Tetrahedron Letters 41 (2000) 8673–8676

TETRAHEDRON LETTERS

Macrolactonization of hydroxy acids using a polymer bound carbodiimide

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Received 30 August 2000; revised 12 September 2000; accepted 14 September 2000

Abstract

An efficient macrolactonization procedure using a polymer bound carbodiimide is described. The procedure uses the polymer supported reagent as a replacement for dicyclohexylcarbodiimide and thus considerably simplifies the workup for such reactions. Partitioning between macrolactone and diolide is shown to depend upon the equivalents of reagent used in cases for which lactonization is difficult. © 2000 Published by Elsevier Science Ltd.

In 1985, we reported a macrolactonization procedure using dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), and DMAP·HCl.[1] The results for macrolactonization of a number of simple hydroxy acids were excellent, comparable to or better than those obtainable using considerably more complex procedures available at the time. Moreover, the procedure was attractive in that the activated acyl derivative was generated in situ; thus the procedure is inherently self drying and cannot be compromised by adventitious moisture. We also demonstrated in that work the crucial role of the DMAP·HCl additive in providing high yields and provided evidence that the inclusion of this additive considerably prolonged the lifetime of the activated acyl intermediate and suppressed formation of the *N*-acyl urea byproduct commonly observed in such reactions.

Since our initial report, this procedure has been used successfully in the macrolactonization of much more complex substrates than those originally examined. We have used this procedure for macrolactonization in the synthesis of colletodiol[2] and colletol.[3] It has also been employed by Stork in the synthesis of dihydroerythronolide A,[4] by Evans in the synthesis of calyculin,[5] by Danishefsky in the synthesis of epothilone B,[6] and by Patterson in his synthesis of swinholide.[7] Despite the utility of this method, it suffers from one significant problem, namely that DCC is often used in large (ca. 10 equiv.) excess to achieve optimal yields. This excess DCC is then converted to dicyclohexyl urea upon completion of the reaction by the addition of acetic acid

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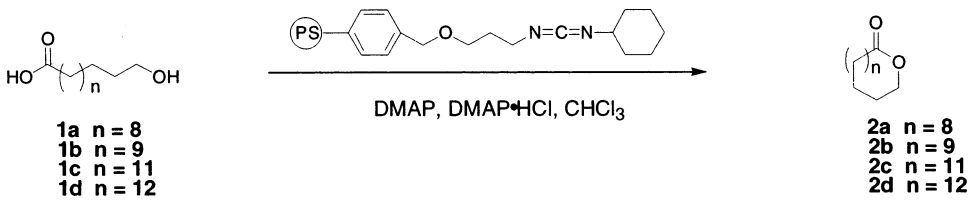
0040-4039/00/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0040-4039(00)01569-0

and methanol, and thus one must isolate the desired lactone from a crude product mixture containing a large amount of the dicyclohexylurea byproduct. Recently we encountered a situation where this proved difficult, and were led to examine the procedure described in this Letter as a possible solution. We record herein the use of a polymer supported carbodiimide reagent in such macrolactonizations, which provides a very convenient solution to this problem.

We began by examining the reaction with the same substrates utilized in our previous study, under the same reaction conditions, but with DCC replaced by the polymer bound carbodiimide 'PS-carbodiimide', which was purchased from Argonaut Technologies.[8] The results of these experiments, shown in Table 1, show that yields using this polymer bound reagent are virtually indistinguishable from those obtained using DCC, except for the case of the 13-membered ring, where the yield of macrolactone is improved relative to diolide using the polymer bound reagent. Care was taken to ensure the reproducibility of these results. Thus the reaction with **1d** was run

Table 1
Lactone yields with polymer-bound carbodiimide



1a n = 8
1b n = 9
1c n = 11
1d n = 12

2a n = 8
2b n = 9
2c n = 11
2d n = 12

Acid	Lactone	Lactone Yield[a] (DCC)	Diolide Yield (DCC)
$HO_2C(CH_2)_{11}OH$ **1a**	**2a**	52% (32%)	33% (32%)
$HO_2C(CH_2)_{12}OH$ **1b**	**2b**	77% (77%)	13% (11%)
$HO_2C(CH_2)_{14}OH$ **1c**	**2c**	97% (95%)	trace (trace)
$HO_2C(CH_2)_{15}OH$ **1d**	**2d**	96% (96%)	0% (0%)

[a] Yields for reactions conducted as previously described using DCC as the reagent are given in parentheses.

multiple times with commercial reagent from three different lots. No significant variation in yield was observed; the range of isolated yields over five experiments was 90–96%, and 95–96% was the norm. Workup of these reactions is greatly simplified, in that simply filtering off the polystyrene beads removes the urea byproduct, which is, of course, now polymer bound, as is any *N*-acyl urea derived from the hydroxy acid substrate. The excess DMAP and DMAP·HCl can be easily removed either by precipitation with ether or by conventional liquid–liquid extraction workup procedures. A representative experimental procedure is provided.[9]

Additional experiments were conducted in an attempt to determine the stoichiometry necessary for high yields. These results are summarized in Table 2. In this vein, the role of DMAP·HCl was also examined; again, it was found to be critical for obtaining the macrolactone. The reaction using hydroxy acid **1d**, which affords nearly quantitative yields of lactone using the normal conditions (entry 1), fails (7% yield) when this additive is omitted (entry 2) as in our previous study. However, in this case, good yields were obtained in experiments where the amounts of reagents were gradually decreased, from 10 to 7.5, and finally 2.5 equiv., where an 82% yield was obtained at the 2.5 equiv. level (entry 4). Yields for substrates which are intrinsically more difficult to lactonize suffer much more significantly as the excess of reagents used decreases. For example, with substrate **1b**, the isolated yield falls from 77% with 10 equiv. (entry 5) to 65%, 57%, and finally 31% as the equivalents are reduced to 7.5, 5, and 2.5, respectively (entries 6–8). However, it is of considerable interest that the yield of diolide *increases* as the equivalents of reagent are decreased. *Thus, the total yield of cyclized material stays reasonably constant (85–100%) from 10 to 2.5 equiv., but the amount of diolide increases at the expense of lactone as the equivalents of reagent decrease.*

Table 2
Lactone and diolide yields as a function of stoichiometry

Entry	Substrate	Ring size	Equivalents PS-DCC[a]	Lactone yield (%)	Diolide yield (%)
1	**1d**	17	10	96	–
2	**1d**	17	10[b]	7	4
3	**1d**	17	7.5	86–95	Trace
4	**1d**	17	2.5	82	9
5	**1b**	14	10	77	13
6	**1b**	14	7.5	65	35
7	**1b**	14	5.0	57	34
8	**1b**	14	2.5	31	55
9	**1a**	13	10	52	33
10	**1a**	13	7.5	35	53

[a] All reagents were used in equimolar amounts in these experiments, thus a reaction using 5 equiv. of PS-DCC also used 5 equiv. each of DMAP and DMAP·HCl.
[b] DMAP·HCl was omitted in this run.

This is understandable on the basis of mechanism for cases in which the intramolecular cyclization of the activated intermediate to give lactone is slow. In such a case, there are two competing reactions available for the hydroxy acid, namely bimolecular reaction with the active intermediate to give a 'pre-diolide' dimeric ester, or reaction with the PS-DCC to form the active intermediate. Clearly, increasing the equivalents of PS-DCC used in such cases will favor the latter pathway at the expense of the former.

Acknowledgements

This work was supported by grants from the National Institutes of Health (grant GM 28961) and Pfizer, Inc.

References

1. Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395.
2. Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896–906.
3. Keck, G. E.; Murry, J. A. *J. Org. Chem.* **1991**, *56*, 6606–6611.
4. Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1986**, *109*, 1565–1567.
5. Evans, D. A.; Gage, J.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434–9453.
6. Danishefsky, S. J.; Su, D. S.; Meng, D. F.; Bertinato, P.; Balog, A.; Sorensen, E. J.; Zheng, Y. H.; Chou, T. C.; He, L. F.; Horwitz, S. B. *Angew. Chem., Int. Ed.* **1997**, *36*, 757–759.
7. Patterson, I.; Yeung, K. S.; Ward, R. A.; Smith, J. D.; Cumming, G.; Lamboley, S. *Tetrahedron* **1995**, *51*, 6497–9486.
8. Argonaut Technologies, San Carlos, CA (888) 598-1350.
9. A representative experimental procedure is summarized here for the preparation of **2c**: DMAP (0.2680 g, 2.19 mmol), DMAP·HCl (0.3575 g, 2.25 mmol)[10] and PS-carbodiimide (1.9547 g, 2.15 mmol) were dissolved in ethanol-free chloroform (25 mL)[10] in a flame dried 50 mL round-bottomed flask equipped with a condenser and stir bar. The mixture was then brought to reflux, and a solution of 15-hydroxypentadecanoic acid (0.0557 g, 0.216 mmol) in dry THF (5 mL) was added via syringe pump over 14 h. A gastight syringe and Teflon tube were used with the Teflon tube inlet placed in the condensate formed at the tip of the reflux condenser. A TLC taken after the addition was completed (50% ethyl acetate in hexanes, R_f 0.78) showed no starting material. The syringe and Teflon tube were rinsed to recover 10.4 mg of hydroxy acid. The reaction mixture was cooled to rt, filtered using a sintered glass funnel, concentrated to approximately 5 mL, diluted with 20 mL of ether, filtered through a pad of Celite, and concentrated. The crude product was purified by flash chromatography (using a 24×1.5 cm column, packed in hexanes, eluted with 20 mL of hexanes followed by 3% THF in hexanes, collecting 6 mL fractions). Concentration of fractions 14–16 yielded 41.1 mg (97%, based on hydroxy acid delivered to the reaction) of lactone. Concentration of fractions 17–22 yielded 1.1 mg of diolide.
10. DMAP·HCl is easily prepared by passing anhydrous HCL into a solution of DMAP in THF and collecting the precipitate. The $CHCl_3$ used was EM Science 'OmniSolve' and contains a hydrocarbon stabilizer; alternatively, ethanol-free $CHCl_3$ can be prepared as described in the following: Perrin, D. D.; Armego, W. L.; Perrin, D. R., Eds. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1966.