Solvent- and Base-Free Dicyclohexylcarbodiimide-Promoted Esterifications

Ludvík Streinz,* Bohumír Koutek, David Šaman

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Prague 6, CZ-166 10, Czech Republic
E-mail: streinz@uochb.cas.cz; koutek@uochb.cas.cz; saman@uochb.cas.cz

Received 13 March 2001

Abstract: *N,N'*-Dicyclohexylcarbodiimide/base-promoted esterification of carboxylic acids containing α-halogen atom(s) gave low yields of products when performed in a solvent. This failure was found to be due to the low stability of appropriate intermediates under the reaction conditions. On the other hand, high yields of esters were obtained, when the same esterification was performed without both the solvent and base. Carboxylic acids without α-halogen atom(s) also undergo the esterification under solvent- and base-free conditions giving products in medium yield.

Key words: esterification, ester, carbodiimide, dicyclohexylcarbodiimide, green chemistry

The *N,N*-dialkyldiimides in general and dicyclohexylcarbodiimide (DCC) in particular, have broadly been used as dehydrating condensing agents.[1-4] There are many examples of their versatile utilization described in the literature including esterification of carboxylic acids,[5-7] fatty acids,[8,9] peptides[10-12] and acids with sensitive functionality in the molecule.[9,13,14] Besides this, *N,N*-dialkyldiimides were also found useful for reduction of carboxylic acids with lithiumborohydride,[15] olefin epoxidation,[16] intramolecular dehydration of β-hydroxyalkyl phosphonic acids,[17] kinetic resolution of racemic carboxylic acids,[18,19] non-classical acetalation of pyranoses[20] and of others. However, in spite of this rather broad applicability range, the most common use of *N,N*-dialkyldiimides remains in their mediation of reactions between alcohols and organic acids.

It has been well documented[1,3,7,21-25] that diimide-promoted esterifications include the formation of O-acyldialkyl urea (O-acyl-DCU)[1,3,21-24] and/or the corresponding anhydride which may originate from the first species by a nucleophilic attack of the second molecule of the acid.[7,25] In addition to these base-catalyzed reactions,[6] the reaction milieu may cause an intramolecular rearrangement of O-acyl-DCU to the corresponding *N*-acyl derivative.[26,27] The independent kinetic experiments by Balcom[28] support the view that the DCC-promoted esterification is a rather complex process affected by interaction between all participating components, including solvents. In other words, the yields of products depend on the stability of reaction intermediates under the reaction conditions used.

As a part of our ongoing work, we recently required access to a series of carboxylic esters containing α-halogen atom(s) in the molecule for the synthesis of biologically interesting targets. Intrigued by the possibility that the DCC-promoted esterification would lead to the desired esters, we investigated this reaction in more details. While the DCC method in its classical form certainly provides a versatile approach for the synthesis of numerous esters, we have found that the conditions are incompatible with the presence of α-halogen functionality. Similar failures have also been previously observed.[6,8] When applied to the α-halogen substituted acids, the method suffers from low ester yields while producing an unacceptably large amount of side-products such as *N*-acyl and *N,N'*-diacyl derivatives. This limitation prompted us to develop a new esterification route to the α-halogen framework employing a solvent- as well as base-free reaction medium.[29] Such a methodology offers an additional advantage since it is in line with the green chemistry (eco-friendly technologies) concept.[30]

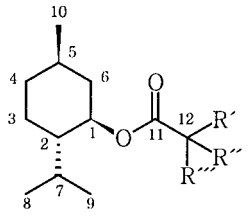
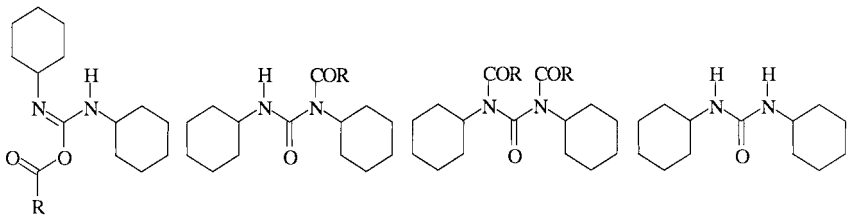


Table Prepared (1*R*,2*S*,5*R*)-(–)-Menthyl Esters (see text for details)

				Method/ Yield [%]					
Ester	R´	R´´	R´´´	A	B	C	D	E	F
1	F	F	F	85	53	15	20	24	19
2	F	F	Cl	70	72	24	34	32	36
3	F	F	H	71	-	31	36	43	44
4[32]	F	Cl	H	70	-	48	60	74	76
5	Cl	H	H	83	45	59	48	77	80
6[32]	Br	H	H	76	65	88	83	92	96
7	CH_3O	CF_3	Phenyl	44	34	61	80	81	82
8	$CH_3(CH_2)_{14}$	H	H	48	-	57	72	78	66

Here we report our results indicating the success of this new strategy when used for the esterification of α-halogen substituted acetic acids with (1*R*, 2*S*, 5*R*)-(-)-menthol as a model alcohol. The menthyl esters prepared in this work are listed in the Table. Mosher and palmitic acids (entry 7, 8) were also included as non-halogen atom containing carboxylic acids.

The Table lists the results of the DCC mediated esterifications performed without the presence of any base and solvent with equimolar amounts of reagents (A) as well as with two-fold excess of an acid (B). In order to compare



9 **10** **11** **12**

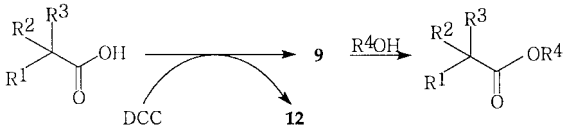
Scheme 1

the new method with those broadly used today, esterifications of particular acids were also done in a solvent under the base catalysis according to Hassner (C, equimolar amounts of all ingredients),[7] Wiener (D, two-fold excess of an alcohol)[8] or Svatoš (E, three-folds excess of DCC and acid, resp.).[24] In addition, all reagents in equimolar quantities were mixed and the base (DMAP) was added as the last (F).

The data obtained revealed that the DCC solvent- and base-free esterifications afford high to medium yields of esters with structurally different carboxylic acids while the yields of reactions performed in the solvent are significantly structure-dependent affording a broad spectrum of yields that range from 20% (entry 1) to more than 90% (entry 6). It appears that these yields approximately correlate with the electronegativity of the acid. Two-fold excess of an acid which is needed when the acid anhydride is assumed to be present as reaction intermediate apparently decreases the yield probably due to acid-catalyzed side-reactions (B).[31]

The relatively high temperature used during the reaction affects the conversion positively even when the temperature-sensitive acids were subjected to the esterification (entry 7). Comparing all the "solvent-based" methods considered, the best results are obtained either with three-fold excess of reagents to the alcohol used (E) or with equimolar quantities of all chemicals when the base is added as the last component which minimizes the neutralization process by excess of an acid (F).

A general comparison of all solvent-based models with our solvent- and base-free method indicates that the solvent- and/or base-mediated consecutive reaction of the rather unstable O-acyl-DCU (**9**) into the undesired *N*-acylderivatives (**10** and **11**) is eliminated. Consequently, only the ester products and DCU (**12**) are present in the reaction mixture. The fact that optimum results are obtained using equimolar amounts of all chemicals led us to believe that the anhydride does not participate in the reaction. This assumption was additionally proved by spectral data (neither NMR or IR spectra of the reaction mixture showed the presence of anhydride-related bands). Thus, compared to the general mechanism of DCC-promoted esterification[1,7,8] the simplified picture shown in the Scheme 2 seems to be the most consistent with experimental evidence given above for solvent- and base-free conditions.



Scheme 2

In conclusion, the method reported here offers a useful alternative to the broadly used DCC promoted esterifications giving satisfactory results with structurally different substrates. It simplifies the reaction because dry solvents as well as base are no more needed. The reaction design suppresses the formation of reaction side-products so high yields can be expected. Reproducibility as well as isolation procedures are high and easy, respectively.

Acknowledgement

The authors wish to thank to the Grant Agency of the Czech Republic (grants Nos. 203/98/0462 and 203/01/0116) for financial support.

References and Notes

(1) Haslam, E. *Tetrahedron* **1980,** *36,* 2409.
(2) Mathias, L.J. *Synthesis* **1979,** 561.
(3) Khorana, H. G. *Chem. Rev.* **1953,** *53,* 145.
(4) Kurzer, F., Douraghi-Zadeh, K. *Chem. Rev.* **1967,** *67,* 107.
(5) Kunstler, T., Schollmeyer, D., Singer, H., Siegerwald, M. *Tetrahedron: Asymmetry* **1993,** *4,* 1645.
(6) Ziegler, F. E., Berger, G. D. *Synth. Commun.* **1979,** *9,* 539.
(7) Hassner, A., Alexanian, V. *Tetrahedron Lett.***1978,** *46,* 4475.
(8) Wiener, H. Gilon, Ch. *J. Mol. Catal.* **1986,** *37,* 45.
(9) Jie, M. S., Mustafa, J., Pasha, M. K. *Chem. Phys. Lipids* **1999,** *100,* 165.
(10) Wasserman, H. H., Lu, T-J. *Tetrahedron Lett.* **1982,** *23,* 3831.
(11) McCarthy, D. G., Hagarthy, A. F., Hathaway, B. *J. Chem. Soc., Perkin Trans. 2* **1977,** 224.
(12) Izdebski, J., Orlowska, A., Anulewicz, R., Witkowska, E., Fiertek, D. *Int. J. Pept. Protein Res.* **1994,** *43,* 184.
(13) Woydowski, K., Liebsher, J. *Tetrahedron* **1999,** *55,* 9205.
(14) Barrow, R.A., Capon, R. J. *Aust. J. Chem.* **1994,** *47,* 1901.
(15) Herbert, J. M., Hewson, A. T., Peace, J. E. *Synth. Commun.* **1998,** *28,* 823.
(16) Murray, R.W., Iyanar, K. *J. Org. Chem.* **1998,** *63,* 1730.
(17) Kawashima, T., Nakamura, M., Nakajo, A., Inamoto, N. *Chem. Lett.* **1994,** *8,* 1483.

(18) Mazon, A., Najera, C., Yus, M., Heumann, A. *Tetrahedron: Asymmetry* **1992,** *3*, 1455.
(19) Chinchilla, R., Najera, C., Yus, M., Heumann, A. *Tetrahedron: Asymmetry.* **1991,** *2*, 101.
(20) Anderson, G. W., Zimmerman J. E.,Callahan, F. M. *J. Am. Chem. Soc.* **1964,** *86*, 1839.
(21) DeTar, D. L. F. Silverstein, R. *J. Am. Chem. Soc.* **1966,** *88*, 1013.
(22) Ibrahim, I. T., Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1459.
(23) Doleschall, G., Lempert, K. *Tetrahedron Lett.* **1963,** *18*, 1195.
(24) Svatoš, A., Valterová, I., Šaman, D., Vrkoč, J. *Collect. Czech Chem. Commun.* **1990,** *55*, 485.
(25) Smith, M., Moffat, J.,G., Khorana, H.G. *J. Am. Chem. Soc.* **1958,** *80*, 6204.
(26) Slebioda, M. *Pol. J. Chem.* **1994,** *68*, 957.
(27) Hegarthy, A. F., McCormack, M. T., Brady, K., Ferguson, G., Roberts, P. J. *J. Chem. Soc., Perkin Trans. 2* **1980,** 867.
(28) Balcom, B. J. Petersen, N. O. *J. Org. Chem.* **1989,** *54*, 1922.
(29) Tanaka, K., Toda, F. *Chem. Rev.* **2000,** *100*, 1025.
(30) Tundo, P., Anastas, P., Black, D.S., Breen, J., Collins, T., Memoli, S., Miyamoto J., Polyakoff, M., Tumas, W. *Pure Appl. Chem.* **2000,** *72*, 1207.
(31) Nakao, K., Hamada, Y., Shiory, T. *Chem. Pharm. Bull.* **1989,** *37*, 930
(32) Representative procedure: A 4 mL Reacti-Vial® equipped with a Teflon-stirrer bar and containing 0.25g (1.2 mmol) DCC was supplied with 0.16g (1.0 mmol) of (–)-menthol. As soon as the mixture solidified, the organic acid was added (1.2 mmol) at once and the vial sealed with a septum cap. The reaction mixture was warmed up to 100 °C and the heating was maintained for three hours under stirring. After being cooled, the crude reaction mixture was diluted with 1.5 mL of diethyl-ether, 3 g of silicagel was added and the solvent evaporated under vacuum. The solid was chromatographed on a silicagel column (10 g) with light-petroleum as eluent.

Representative analyses:
4: Anal. Cald for $C_{12}H_{20}O_2FCl$: C 57.48, H 8.48; Found: C 57.29, H 8.41; ^{1}H NMR (500 MHz, $CDCl_3$/TMS): 6.24 and 6.25 d, 1H (J_{HF} = 50.6) (H-12), 4.82 and 4.83 dt, 1H (J = 4.5, 2 × 11.0) (H-1), 2.03 and 2.02 dddd, 1H (J = 2.0, 3.5, 4.5, 12.0) (H-6e), 1.91 and 1.89 m, 1H (J = 2.8, 6 × 7.0) (H-7), 1.68-1.74 m, 2H (H-4e, H-3e), 1.46-1.50 m, 2H (H-5, H-2a), 1.02-1.13 m, 2H (H-3a, H-6a), 0.93 d, 3H (J = 6.5) (H-10), 0.91 d, 3H (J = 7.0) (H-8), 0.89 ddt, 1H (J = 3.5, 2 × 12.0, 13.0) (H-4a), 0.78 and 0.79 d, 3H (J = 7.0) (H-9); ^{13}C NMR (125.7 MHz, $CDCl_3$): 163.6 (J_{CF} = 4.6) and 163.8 (J_{CF} = 4.9) (C-11), 90.3 (J_{CF} = 10.0) and 92.4 (J_{CF} = 10.7) (C-12), 77.8 (C-1), 46.9 (C-2), 40.2 and 40.3 (C-6), 34.0 (C-4), 31.4 (C-5), 26.1 and 26.3 (C-8), 23.4 and 23.5 (C-3), 21.9 (C-7), 20.6 (C-10), 16.1 and 16.2 (C-9); MS (EI, m/z,%): 249(4), 192(2), 138(67), 123(48), 109(8), 95(100), 81(94), 67(33); IR (CCl_4): 1774, 1755, 1719, 1389, 1372, 1302, 1241, 1230, 1140, 1124, 1086 cm^{-1};
6: Anal. Cald for $C_{12}H_{21}O_2Br$: C 52.00, H 7.64; Found: C 51.86, H 7.38; ^{1}H NMR: 4.73 dt, 1H (J = 4.5, 2 × 11.0) (H-1), 3.82 d, 1H (J = 11.9) (H-12a),3.79 d, 1H (J = 11.9) (H-12b), 2.01 dddd, 1H (J = 2.0, 3.5, 4.5, 12.0) (H-6e), 1.91 m, 1H (J = 2.8, 6 × 7.0) (H-7), 1.70 ddq, 1H (J = 2.0, 3 × 3.5, 13.0) (H-4e), 1.69 dq, 1H (J = 3 × 3.4, 14.0) (H-3e), 1.50 m, 1H (J = 2 × 3.5, 3 × 6.5, 11.0, 12.0) (H-5), 1.43 dddd, 1H (J = 2.8, 3.7, 11.0, 12.4) (H-2a), 1.07 ddt, 1H (J = 3.5, 2 × 12.2, 14.0) (H-3a), 1.02 dt, 1H (J = 2 × 11.0, 12.0) (H-6a), 0.92 d, 3H (J = 6.5) (H-10), 0.90 d, 3H (J = 7.0) (H-8), 0.89 ddt, 1H (J = 3.5, 2 × 12.0, 13.0) (H-4a), 0.77 d, 3H (J = 7.0) (H-9); ^{13}C NMR: 166.9 (C-11), 76.5 (C-1), 47.0 (C-2), 40.5(C-6), 34.1 (C-4), 31.4 (C-5), 26.2 (C-8), 26.2 (C-12), 23.4 (C-3), 21.9 (C-7), 20.7 (C-10), 16.2 (C-9); MS (EI, m/z,%): 138(100), 123(36), 109(9), 95(94), 81(67), 69(14); IR (CCl_4): 1757, 1732, 1423, 1389, 1371, 1287, 1277, 1166, 1108, 1208, 562 cm^{-1}.

Article Identifier:
1437-2096,E;2001,0,06,0809,0811,ftx,en;G04401ST.pdf