

Accepted Manuscript

Simple one pot synthesis of ketone from carboxylic acid using DCC as an activator

Habtamu Gelaw Mekonnen, Samaresh Jana

PII: S0040-4039(19)30378-8

DOI: <https://doi.org/10.1016/j.tetlet.2019.04.030>

Reference: TETL 50745

To appear in: *Tetrahedron Letters*

Received Date: 23 January 2019

Revised Date: 13 April 2019

Accepted Date: 20 April 2019

Please cite this article as: Mekonnen, H.G., Jana, S., Simple one pot synthesis of ketone from carboxylic acid using DCC as an activator, *Tetrahedron Letters* (2019), doi: <https://doi.org/10.1016/j.tetlet.2019.04.030>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

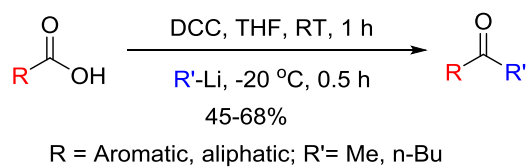


Graphical Abstract

Simple One Pot Synthesis of Ketone from Carboxylic Acid Using DCC as an Activator

Habtamu Gelaw Mekonnen and Samaresh Jana

Leave this area blank for abstract info.





Simple one pot synthesis of ketone from carboxylic acid using DCC as an activator

Habtamu Gelaw Mekonnen^a and Samaresh Jana^{a,*}

^aDepartment of Chemistry, School of Applied Sciences, Kalinga Institute of Industrial Technology (KIIT)-Deemed to be University, Bhubaneswar-751024, Odisha, India

ARTICLE INFO

Article history:

Received
Received in revised form
Accepted
Available online

Keywords:

One pot conversion
Carboxylic acid
Ketone
N,N'-Dicyclohexylcarbodiimide

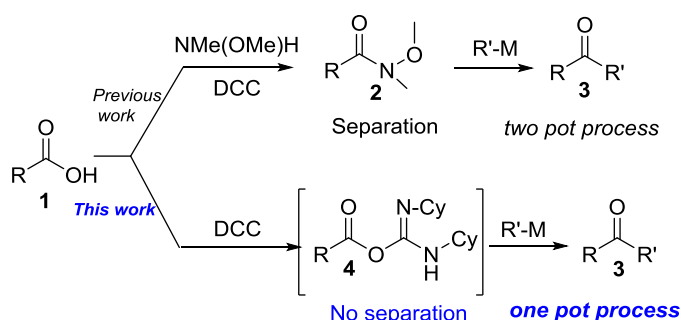
ABSTRACT

Simple one pot procedure for the conversion of carboxylic acid to ketone is described. Various carboxylic acids were converted to the corresponding ketones in excellent manner in presence of N,N'-dicyclohexylcarbodiimide(DCC) and organometallic reagents. Aromatic, heteroaromatic and aliphatic acids were converted to the corresponding ketones smoothly under the optimum conditions using organolithium reagents. In this process, desired products have been isolated from the crude reaction mixtures in moderate yields during the purification process.

Elsevier Ltd. All rights reserved.

Functional group inter-conversion (FGI) is a fundamental transformation in synthetic organic chemistry and very useful during a multistep synthesis of organic compound. Carbonyl group, in particular ketone is considered to be an important and ubiquitous functional group, as numerous natural products and pharmaceuticals consist of this functionality.¹ Moreover, ketones are used as a versatile building block that can be utilized in a various bond formation reactions. Therefore, to access this functionality from a readily available functional group based on a simple chemical transformation should be an exciting task.

Various conventional routes: such as oxidation of an alcohol, conversion of an acid chloride to ketone, amide to ketone, and aldehyde to ketone etc., to access ketone have been developed, including the conversion of carboxylic acid to ketone; which has attracted considerable interest of synthetic chemists since last few decades.² Usually, the transformation of carboxylic acids into ketones is accomplished in a two-step process (Scheme 1) as for example converting carboxylic acid to a Weinreb amide followed by the addition of a suitable organometallic reagent.³ Though, direct procedure is available to access ketone from carboxylic acid using excess organometallic reagents, so far the application of the process in the organic synthesis is limited.⁴

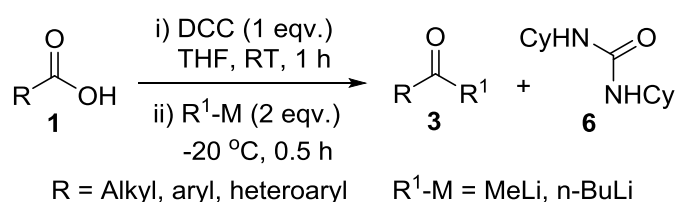


Scheme 1: Ketone synthesis: A comparative study

In fact, most of the developed one pot processes include the usage of expensive metal catalyst to satisfy this purpose.⁵ In this regard, Kangani's team established a one pot method⁶ for this conversion using Weinreb amide concept and deoxo-fluor reagent. Limitations, like selective reduction of acid, harsh reaction conditions, excess reagents other than metal catalyst, longer reaction time and expensive catalyst have promoted synthetic chemist to develop improved protocol for this transformation. To address these difficulties, a simple and general one pot procedure for the synthesis of ketone from the corresponding carboxylic acid using N,N'-dicyclohexylcarbodiimide (DCC) has been developed. DCC is a well-known reagent and enormously used in organic synthesis for the preparation of amide⁷, ester and anhydride⁸ from carboxylic acid. Beside this, alcohols can be oxidized⁹ to carbonyl compounds using DCC as an activator. Although, other coupling

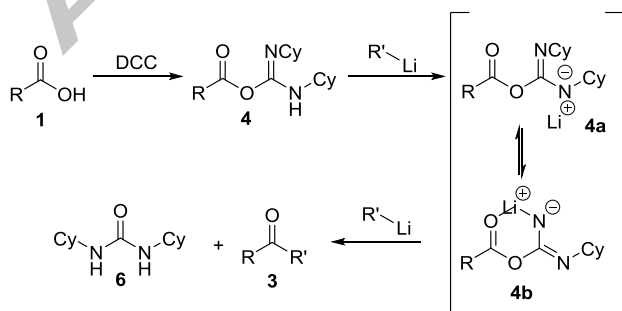
* Corresponding author. Tel.: +91-674-272-5113; fax: +91-674-272-5113; e-mail: samareshfch@kiit.ac.in; samarpdp@yahoo.com

reagents like Benzotriazole derivative, CDMT, CDI have been employed to activate carboxylic acid for ketone synthesis,^{5g,10} still utilization of DCC in preparation of ketone from carboxylic acid is unfamiliar. Hence, we report a simple process to access ketones from the carboxylic acids (Scheme 2) in a one pot approach.



Scheme 2: One pot conversion of carboxylic acid to ketone

Therefore, following the literature procedure¹¹ to synthesize the *O*-acylisourea, initially a reaction was carried out using commercially available benzoic acid (0.5 mmol) and DCC (0.5 mmol) in THF (2.5 mL) at room temperature under N₂ atmosphere. After 1 h, a change in the reaction (monitored by TLC method) was observed. To this mixture, n-BuLi (0.7 mmol, 1.6 M in hexanes) was added slowly at low temperature (-20 °C) and pleasantly a spot of the desired ketone **3a** was noticed in TLC which was further characterized by NMR spectroscopy. Based on this initial result, we paid our attention to optimize the reaction conditions on benzoic acid in presence of n-BuLi. Few reactions were performed to get the best yield of the desired ketone **3a** in THF solvent. After varying the reaction conditions, best yield of **3a** was obtained when 1 equivalent of DCC was added to the equimolar amount of carboxylic acid in THF at room temperature for 1 h, followed by slow addition of n-BuLi (2 equivalents) at -20 °C. Under this optimized conditions,¹² various aliphatic, aromatic and heteroaromatic carboxylic acids were subjected to interact with DCC and n-BuLi to afford the corresponding ketones in good yields. Aromatic carboxylic acids bearing electron withdrawing as well as electron donating groups were found excellent substrates to obtain the desired ketones. To our delight, chloro functionality (Entry 2, table 1) is well tolerated during this process, but nitro group is not compatible under this reaction (Entry 10, table 1) conditions. Gratifyingly, heteroaromatic acids (Entry 5, table 1) showed good results to produce the corresponding ketones. The experiments with aliphatic acids gave the desired ketones in reasonable yields under the standard reaction conditions. To expand this process, MeLi was used as a nucleophile to produce the acetophenones (Entry 8 and 9, table 1) in efficient manner. All the experimental results of the reactions are summarized in table 1.



Scheme 3: Proposed mechanistic pathway

During this study, it was observed that the conversion of the starting acids to the desired ketones is satisfactory almost in all the cases, but some of the ketone products were lost with the urea derivative **6** (Scheme 2) during purification process.

Entry	Substrate	Product	Yield (%)
1			60
2			55
3			52
4			54
5			50
6			45
7			55
8			68
9			61
10			nd
11			nd

Table 1: Substrate scope of ketone synthesis using DCC; Reactions were carried out in 1 mmol scale under N₂ atmosphere. Yields refer to the isolated yield.

A proposed mechanistic pathway of the reaction has been presented in scheme 3. Carboxylic acid **1** reacts with DCC at room temperature to form *O*-acyl isourea derivative **4**. Upon treatment of organolithium reagent, intermediate **4** reacts with one molecule of RLi to produce **4a** which could be in equilibrium with **4b**. Second molecule of RLi attacks on the carbonyl carbon of **4b** to yield the desired product **3** along with the urea derivative **6**.

In conclusions, a simple one pot method for the synthesis of ketone from carboxylic acid has been described. In this process, aliphatic and aromatic acids were treated with DCC to form *O*-acyl isourea derivatives, which upon addition of an organolithium compound provided the desired ketones in exclusive manner. The limitation of this process is the complete removal of the urea derivative from the ketone. This drawback reduced the isolated yields of the desired ketones. Further investigations on this process using different carbon based nucleophiles are in progress in our laboratory and will be reported in due course.

Acknowledgments

Financial support of DST-SERB (Ref. No. SB/FT/CS-049/2013) is acknowledged. HGM appreciates the support of Govt. of Ethiopia for a research fellowship. Both of the authors thank KIIT, Deemed to be University for providing the basic research facility.

References and notes

1. a) Dieter, R. K. *Tetrahedron* **1999**, *55*, 4177; b) Lawrence, N. J. *J. Chem. Soc., Perkin Trans.1* **1998**, 1739; c) McDaniel, R.; Thamchaipenat, A.; Gustafsson, C.; Fu, H.; Betlach, M.; Betlach, M.; Ashley, G. *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 1846; d) Cuquerella, M. C.; Lhiaubet-Vallet, V.; Cadet, J.; Miranda, M. A. *Acc. Chem. Res.* **2012**, *45*, 1558; e) Kamat, P. V. *Chem. Rev.* **1993**, *93*, 267.
2. Few important references are: a) Sibi, M. P. *Org. Prep. Proceed. Int.* **1993**, *25*, 15; b) O'Neil, B. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 399; c) Wilkinson, M. C. *Org. Lett.* **2011**, *13*, 2232; d) Park, A.; Park, K.; Kim, Y.; Lee, S. *Org. Lett.* **2011**, *13*, 944; e) Gooßen, L.; Rodriguez, N.; Gooßen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100.
3. a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815; b) Qu, B.; Collum, D. B. *J. Org. Chem.* **2006**, *71*, 7117.
4. a) Rubottom, G. M.; Kim, C-W. *J. Org. Chem.* **1983**, *48*, 1550; b) Genna, D. T.; Posner, G. *Org. Lett.* **2011**, *13*, 5358; c) Alonso, F.;

- Lorenzo, E.; Yus, M. *J. Org. Chem.* **1996**, *61*, 6058; d) Gilman, H.; van Ess, P. R. *J. Am. Chem. Soc.* **1933**, *55*, 1258; e) Tegner, C. *Acta Chem. Scand.* **1952**, *6*, 782; f) Jorgenson, M. J. *Org. React.* **1970**, *18*, 1; g) Bare, T. M.; House, H. O. *Org. Synth.* **1973**, *5*, 775; h) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1988**, *110*, 7447; i) Levine, R.; Karten, M. J. *J. Org. Chem.* **1976**, *41*, 1176.
5. For metal catalyzed reaction: a) Amani, J.; Molander, G. A. *Org. Lett.* **2017**, *19*, 3612; b) Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1983**, *24*, 3677; c) Gooßen, L. J.; Ghosh, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 3458; d) Gooßen, L. J.; Ghosh, K. *Eur. J. Org. Chem.* **2002**, *2002*, 3254; e) Kakino, R.; Narahashi, H.; Shimizu, I.; Yamamoto, A. *Chem. Lett.* **2001**, *30*, 1242; f) Si, S.; Wang, C.; Zhang, N.; Zou, G. *J. Org. Chem.*, **2016**, *81*, 4364; g) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 1519.
6. Kanagani, C. O.; Kelley, D. E.; Day, B. W. *Tetrahedron Lett.* **2006**, *47*, 6289.
7. a) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557; b) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827.
8. a) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606; b) Selinger, Z.; Lapidot, Y. *J. Lipid Research* **1965**, *7*, 174.
9. a) Moffatt, J. G. *Org. Synth.* **1967**, *47*, 25; b) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1963**, *85*, 3027.
10. a) Baker, D. C.; Putt, S. R. *Synthesis* **1978**, 478; b) Katritzky, A. R.; Abdel-Fattah, A. A.; Gromova, A. V.; Witek, R.; Steel, P. J. *J. Org. Chem.* **2005**, *70*, 9211; c) Staab, H. A.; Jost, E. *Justus Liebigs Ann. Chem.* **1962**, 655, 90.
11. a) Neises, B.; Steglich, W. *Org. Synth.* **1985**, *63*: 183; b) Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* **1978**, *17*, 522;
12. General Experimental procedure: To a stirred solution of carboxylic acid **1** (1 mmol) in THF (3 mL), DCC (1 mmol) was added at room temperature under N₂ atmosphere. After 1 h, the mixture was cooled to -20 °C and n-BuLi (2 mmol) was added to the reaction mixture drop-wise. After 0.5 h the reaction was quenched with saturated NH₄Cl solution (5 mL) at -20 °C. The mixture was warmed to room temperature and extracted with diethyl ether (50 mL × 3). The combined organic layers were washed with water (20 mL × 3), brine (20 mL) and finally dried over MgSO₄. The volatiles were evaporated under reduced pressure to get a crude mass which was then purified by column chromatography on silica gel to obtain pure ketone **3**.

Supplementary Material

Supplementary material is available

Click here to remove instruction text...

Highlights

- ✓ One pot method
- ✓ DCC is used as an activator of carboxylic acid
- ✓ Mild reaction conditions
- ✓ Aromatic, aliphatic acids react smoothly
- ✓ Moderate to good yields of the products

ACCEPTED MANUSCRIPT