Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Convenient Synthesis of N-Hydroxysuccinimide Esters from Carboxylic Acids Using Triphosgene

Misoo Kim [a] & Ki-Jong Han [b]
[a] Department of Basic Science , Hankyong National University , Ansung, Korea
[b] Department of Molecular Science and Technology , Ajou University , Suwon, Korea
Published online: 12 Nov 2009.

To cite this article: Misoo Kim & Ki-Jong Han (2009) Convenient Synthesis of N-Hydroxysuccinimide Esters from Carboxylic Acids Using Triphosgene, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:24, 4467-4472, DOI: 10.1080/00397910902906628

To link to this article: http://dx.doi.org/10.1080/00397910902906628

Synthetic Communications®, 39: 4467–4472, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902906628

Taylor & Francis
Taylor & Francis Group

Convenient Synthesis of *N*-Hydroxysuccinimide Esters from Carboxylic Acids Using Triphosgene

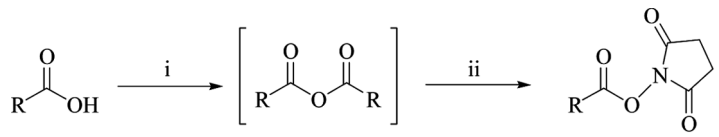
Misoo Kim[1] and Ki-Jong Han[2]
[1]Department of Basic Science, Hankyong National University, Ansung, Korea
[2]Department of Molecular Science and Technology, Ajou University, Suwon, Korea

Abstract: A simple and convenient method for the synthesis of *N*-hydroxysuccinimide ester is developed using triphosgene as an acid activator. Several aromatic and aliphatic *N*-hydroxysuccinimide esters are prepared from their corresponding carboxylic acids at room temperature in good yields in a rapid process using triphosgene. Some of the major advantages are mild conditions, good yields, and easy operation.

Keywords: Carboxylic acids, *N*-hydroxysuccinimide, *N*-hydroxysuccinimide esters, triphosgene

Carboxylic acid esters of *N*-hydroxysuccinimide have been widely used as valuable intermediates in peptide synthesis because they acylate primary amines to give the corresponding amides.[1] For example, several methods have been developed using dicyclohexylcarbodiimide,[2] Ph_3P/diethyl azodicarboxylate,[3] bis(*N*-succinimidyl) carbonate,[4] 2-pyridyl carbonate,[5] *N,N,N′,N′*-tetramethyl(succinimido)uronium tetrafluoroborate,[6] chloro phosphate,[7] 3-(dimethylamino)propylcarbodiimide,[8] *O*-succinimidyl-1,3-dimethyl-1,3-trimethyleneuronium salts,[9] and 1-ethyl-3-(3′-dimethylaminopropyl) carbodiimide.[10] However, these are not free from some

Received January 14, 2009.
Address correspondence to Dr. Misoo Kim, Professor, Department of Basic Science, Hankyong National University, 67 Seogjung-Dong, Ansung 456-749, Republic of Korea. E-mail: mkim@hknu.ac.kr



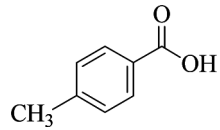
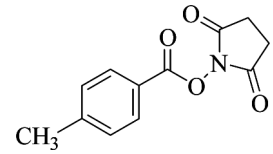
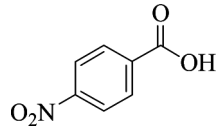
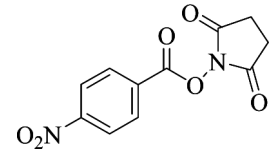
Scheme 1.

drawbacks such as by-product formation, limited availability, inconvenient handling, or poor stability.

Triphosgene is commercially available as a white solid. The synthetic utility of triphosgene has been extensively investigated over the past 20 years.[11] During the past few years, we have been interested in the use of triphosgene in organic synthesis.[12] In continuation of our research to develop new methods using triphosgene as an acid activator, we report herein a simple and convenient method for the preparation of *N*-hydroxysuccinimide esters from their corresponding carboxylic acids using triphosgene, as shown in Scheme 1.

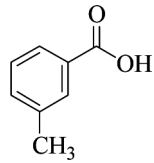
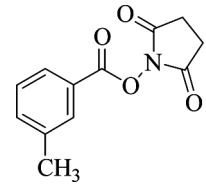
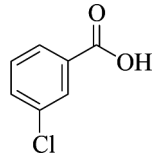
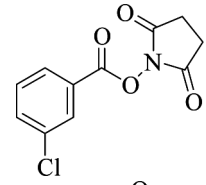
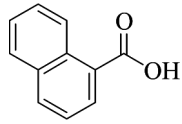
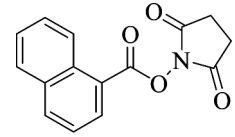
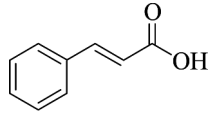
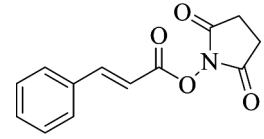
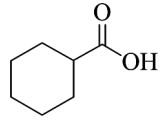
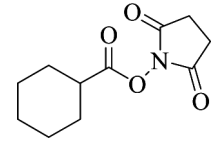
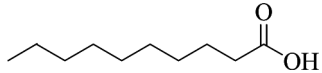
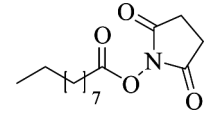
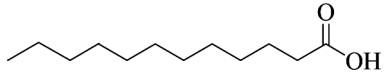
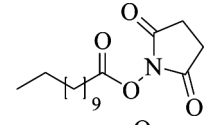
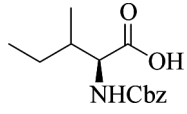
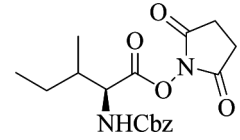
In this procedure, carboxylic acids were first converted into carboxylic acid anhydrides by triphosgene in the presence of triethylamine.[13] *N*-Hydroxysuccinimide esters were formed after addition of *N*-hydroxysuccinimide to the intermediate carboxylic acid anhydrides. In all cases, the reactions proceeded rapidly in methylene chloride at room temperature. As shown in Table 1, a variety of *N*-hydroxysuccinimide esters were prepared from carboxylic acids. Aromatic carboxylic acids containing both electron-donating and electron-withdrawing groups were

Table 1. Synthesis of *N*-hydroxysuccinimide esters

Entry	Acid	Product	Yield[a] (%)
1			95
2			96

(*Continued*)

Table 1. Continued

Entry	Acid	Product	Yield[a] (%)
3			92
4			91
5			93
6			92
7			93
8			93
9			91
10			87

[a]Yields refer to isolated products.

cleanly converted to the corresponding *N*-hydroxysuccinimide esters (entries 1–5). Aliphatic and *N*-Cbz-protected amino acids also afforded the desired products in good yields under these reaction conditions (entries 6–10). The reaction conditions are mild, and the experimental procedure is operationally simple. The products were formed in good yields (87–96%). The structures of all the products were confirmed by ^{1}H and ^{13}C NMR spectroscopy.

In summary, we have developed a simple and convenient method for the conversion of various carboxylic acids to their corresponding *N*-hydroxysuccinimide esters using triphosgene as an acid activator. This method is operationally simple and provides the products in good yields.

EXPERIMENTAL

Triphosgene was purchased from Aldrich Company. Analytical thin-layer chromatography (TLC) was performed on precoated Merck silica-gel 60 F254 TLC plate. Purification was performed by flash-column chromatography using Merck silica gel (230–400 mesh). Melting points were determined in capillary tubes on a Bibby Sterilin apparatus and are corrected. ^{1}H NMR and ^{13}C NMR spectral data were obtained on a Jeol JNM-ECP 400-MHz NMR spectrometer. Identification of the products was ascertained by ^{1}H and ^{13}C NMR spectroscopy and by comparison with published values.[6,8,14]

General Procedure

Triphosgene (1 mmol) and triethylamine (10 mmol) were added at 0°C to a stirred solution of the carboxylic acid (2 mmol) in dichloromethane (10 ml). Then *N*-hydroxysuccinimide (2 mmol) was added to the reaction mixture. The reaction mixture was stirred for 30 min at room temperature. After completion of the reaction, the reaction mixture was filtered by suction filtration. Removal of the filtrate by rotary evaporation followed by short-path silica-gel column chromatography using 20% ethyl acetate in hexane as the mobile phase afforded the pure product.

Selected Spectral Data

N-Hydroxysuccinimide Ester of 3-Toluic Acid (entry **3**)

Mp 116–117°C (lit.[14a] 117–118°C); TLC Rf 0.35 (40% ethyl acetate in hexane); IR (KBr): ν, 3445, 3012, 2938, 1768, 1734, 1603, 1587, 1464,

1435, 1374, 1265, 1184, 1069, 988, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, $J = 8.00$ Hz, 2H), 7.47 (d, $J = 7.60$ Hz, 1H), 7.39 (t, $J = 7.60$ Hz, 1H), 2.87 (s, 4H) 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 162.1, 139.0, 135.8, 131.0, 128.9, 127.8, 125.1, 25.8, 21.3.

N-Hydroxysuccinimide Ester of *N*-Benzyloxycarbonyl-*L*-isoleucine (entry **10**)

Mp 115–116°C (lit.[14c] 115.5–116°C); TLC Rf 0.48 (20% ethyl acetate in chloroform); $[\alpha]_D^{25}$ −15.0° (c = 2.0, dioxane); lit.[14c] $[\alpha]_D^{25}$ −15.5° (c = 2.0, dioxane); IR (KBr): ν, 3292, 2958, 1732, 1657, 1543, 1456, 1337, 1274, 1195, 1098, 985 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, $J = 8.40$ Hz, 1H), 7.41–7.30 (m, 5H), 5.07 (s, 2H), 4.47–4.39 (m, 1H), 2.81 (s, 4H), 1.81–1.69 (m, 2H), 1.67–1.58 (m, 1H), 0.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 169.2, 156.1, 136.7, 128.5, 128.1, 127.9, 66.0, 50.7, 25.6, 24.3, 22.7, 21.1.

ACKNOWLEDGMENT

We gratefully acknowledge financial support from Hankyong National University.

REFERENCES

1. Bodanzsky, M. *Principles of Peptide Synthesis,* 2nd Ed.; Springer-Verlag: New York, 1993.
2. Paquette, L. A. *Encyclopedia of Reagents in Organic Synthesis*; John Wiley & Sons, 1995; p. 2780.
3. Grochowski, E.; Jurczak, J. A new method for the preparation of *N*-acyloxyphthalimides and *N*-acyloxysuccinimides. *Synthesis* **1977**, *4*, 277.
4. Ogura, H.; Kobayashi, T.; Shimizu, K.; Kawabe, K.; Takeda, K. A novel active ester synthesis reagent (*N,N′*-disuccinimidyl carbonate). *Tetrahedron Lett.* **1979**, *20*, 4745.
5. Kim, S.; K. Y. K. A new method for the preparation of active ester using 2-pyridyl carbonate. *J. Chem. Soc., Chem. Commun.* **1985**, 473.
6. Bannwarth, W.; Knorr, R. Formation of carboxamides with *N,N,N′,N′*-tetramethyl(succinimido)uronium tetrafluoroborate in aqueous/organic solvent system. *Tetrahedron Lett.* **1991**, *32*, 1157.
7. Pöchlauer, P.; Hendel, W. One-pot formation of succinimidyl esters by the system chlorophosphate/hydroxysuccinimide/base. *Tetrahedron* **1998**, *54*, 3489.
8. Adamczyk, M.; Fishpaugh, J. R.; Mattingly, P. G. Preparation and use of *N*-hydroxysuccinimidyl active ester resins. *Tetrahedron Lett.* **1999**, *40*, 463.

9. Bailén, M. A.; Chinchilla, R.; Dodsworth, D. J.; Nájera, C. *O*-Succinimidyl-1,3-dimethyl-1,3-trimethyleneuronium salts as efficient reagents in active ester synthesis. *Tetrahedron Lett.* **2002**, *43*, 1661.
10. Fujisaki, F.; Oishi, M.; Sumoto, K. A conventional new procedure for *N*-acylation of unprotected amino acids. *Chem. Pharm. Bull.* **2007**, *55*, 124.
11. (a) Cotarca, L.; Delogu, P.; Nardelli, A.; Šunjić, V. Bis(trichloromethyl) carbonate in organic synthesis. *Synthesis* **1996**, 553, and references therein; (b) Qingmin, W.; Runqiu, H. Two convenient new syntheses of ferrocenoyl chloride by triphosgene. *J. Organomet. Chem.* **2000**, *604*, 287; (c) Cicchillo, R. M.; Norris, P. A convenient synthesis of glycosyl chlorides from sugar hemiacetals using triphosgene as the chlorine source. *Carbohydr. Res.* **2000**, *328*, 431; (d) Gumaste, V. K.; Bhawal, B. M.; Deshmukh, A. R. A. S. A mild and efficient method for the preparation of acyl azides from carboxylic acids using triphosgene. *Tetrahedron Lett.* **2002**, *43*, 1345; (e) Flosser, D. A.; Olofson, R. A. A useful conversion of alcohols to alkyl fluorides. *Tetrahedron Lett.* **2002**, *43*, 4275; (f) Banwell, M. G.; Coster, M. J.; Harvey, M. J.; Moraes, J. Selective cleavage of *N*-benzyl-protected secondary amines. *J. Org. Chem.* **2003**, *68*, 613.
12. Han, K.-J.; Kim, M. Direct synthesis of Weinreb amides from carboxylic acids using triphosgene. *Lett. Org. Chem.* **2007**, *4*, 20.
13. Kocz, R.; Roestamadji, J.; Mobashery, S. A convenient triphosgene-mediated synthesis of symmetric carboxylic acid anhydrides. *J. Org. Chem.* **1994**, *59*, 2913.
14. (a) Lou, R.; VanAlstine, M.; Sun, X.; Wentland, M. P. Preparation of *N*-hydroxysuccinimido esters via palladium-catalyzed carbonylation of aryl triflates and halides. *Tetrahedron Lett.* **2003**, *44*, 2477; (b) Schulze, A.; Giannis, A. IBX-Mediated conversion of primary alcohols and aldehydes to *N*-hydroxysuccinimide esters. *Adv. Synth. Catal.* **2004**, *346*, 252; and (c) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. The use of esters of *N*-hydroxysuccinimide in peptide synthesis. *J. Am. Chem. Soc.* **1964**, *86*, 1839.