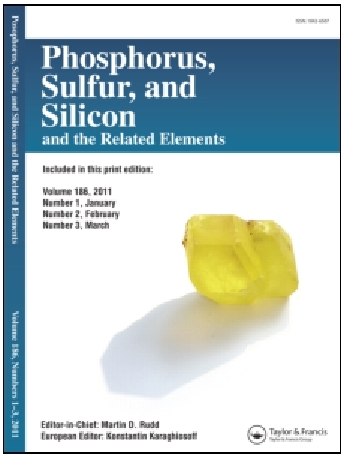


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Silica-Supported 2,4,6-Trichloro-1,3,5-triazine as an Efficient Reagent for Direct Conversion of Carboxylic Acids to Amides Under Solvent-Free Conditions

Ali Khalafi-Nezhad[a]; Abdolkarim Zare[a]; Abolfath Parhami[a]; Mohammad Navid Soltani Rad[b]; Gholam Reza Nejabat[a]
[a] Department of Chemistry, Shiraz University, Shiraz, Iran [b] Department of Chemistry, Shiraz University of Technology, Shiraz, Iran

To cite this Article Khalafi-Nezhad, Ali , Zare, Abdolkarim , Parhami, Abolfath , Rad, Mohammad Navid Soltani and Nejabat, Gholam Reza(2007) 'Silica-Supported 2,4,6-Trichloro-1,3,5-triazine as an Efficient Reagent for Direct Conversion of Carboxylic Acids to Amides Under Solvent-Free Conditions', Phosphorus, Sulfur, and Silicon and the Related Elements, 182: 3, 657 — 666

To link to this Article: DOI: 10.1080/10426500601047214

URL: http://dx.doi.org/10.1080/10426500601047214

Phosphorus, Sulfur, and Silicon, 182:657–666, 2007
Copyright © Taylor & Francis Group, LLC
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500601047214

Silica-Supported 2,4,6-Trichloro-1,3,5-triazine as an Efficient Reagent for Direct Conversion of Carboxylic Acids to Amides Under Solvent-Free Conditions

Ali Khalafi-Nezhad
Abdolkarim Zare
Abolfath Parhami
Department of Chemistry, Shiraz University, Shiraz, Iran

Mohammad Navid Soltani Rad
Department of Chemistry, Shiraz University of Technology, Shiraz, Iran

Gholam Reza Nejabat
Department of Chemistry, Shiraz University, Shiraz, Iran

A very simple and efficient solvent-free method for the direct conversion of carboxylic acids to primary, secondary, tertiary alkyl, and aromatic amides in the presence of the corresponding ammonium salts, silica-supported 2,4,6-trichloro-1,3,5-triazine, and triethylamine is described. The reactions proceed rapidly at room temperature, and the products are obtained in moderate to excellent yields.

Keywords 2,4,6-Trichloro-1,3,5-triazine; amide; ammonium salt; carboxylic acid; solvent-free

INTRODUCTION

Solvent-free organic reactions have been applied as a useful technology in organic synthesis.[1] The solid-state technique often leads to a large reduction in reaction time, increased yields, easier workup, and matches with green chemistry protocols, and it may enhance the regio- and stereoselectivity of reactions.[1]

The amide function is significant in organic and biological chemistry. Amides are important as pharmaceuticals[2a] as well as

---

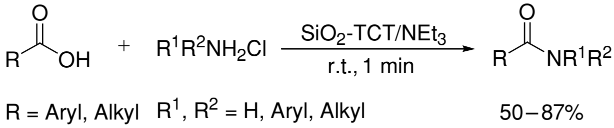
Received November 30, 2005; accepted August 23, 2006.

We thank Shiraz University and the Shiraz University of Technology Research Councils, Shiraz, Iran, for financial support of this work. We are also grateful to Prof. H. Sharghi for helpful discussion and to Mr. H. Sajedian Fard for running the NMR spectra.

Address correspondence to Ali Khalafi-Nezhad, Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran. E-mail: khalafi@chem.susc.ac.ir

agrochemicals.[2b] The conversion of carboxylic acids to amides is one of the important transformations in organic synthesis.[3] In general, the conversion of carboxylic acids to carboxamides requires an activation of the carboxyl group. This can be achieved by conversion of the carboxyl group to a more reactive group such as acyl halide, mixed anhydride, acyl azide, and active ester, or through in situ–activation by coupling reagents including *N*, *N*-dicyclohexyl carbodiimide (DCC),[4] $TiCl_4$,[5] activated phosphate,[6] $Sn[N(TMS)_2]_2$,[7] *N*-halosuccinimide/PPh_3,[8] trichloroacetonitrile/PPh_3,[9] *tert*-butyl-3-(3,4-dihydrobenzotriazine-4-on)yl carbonate (Boc-Odhbt),[10] $ArB(OH)_2$,[11] Lawesson's reagent,[12] $(R_2N)_2Mg$,[13] SO_2ClF,[14] chlorosulfonyl isocyanate,[15] and 2-mercaptopyridone-1-oxide based uronium salts.[16]

There have been several reports on the transformation of carboxylic acids to amides under solvent-free conditions.[17] Recently, we reported a new method for the direct conversion of carboxylic acids to various amides under solvent-free conditions.[18a] To the best of our knowledge, there is no other report for the direct transformation of carboxylic acids to all kinds of amides including primary, secondary, tertiary alkyl, and aromatic amides by this means. Along with our previous work on the direct conversion of carboxylic acids to amides[17d,18a] and also in extension of our previous studies on solvent-free organic reactions,[17d,18] we report here an efficient, rapid, and simple method for the direct conversion of carboxylic acids to primary, secondary, tertiary alkyl, and aromatic amides in the presence of the corresponding ammonium salts, silica-mediated 2,4,6-trichloro-1,3,5-triazine (TCT), and triethylamine under solvent-free conditions at r.t. (Scheme 1).



SCHEME 1

2,4,6-trichloro-1,3,5-triazine was chosen as a condensing agent because this compound and its derivatives have been used as very efficient reagents for the activation of carboxyl groups in the preparation of esters,[19a] peptides,[19a–c] amides,[19a–d] as well as acyl azides.[19e] This reagent has also been used for the synthesis of amides; however, its application was restricted to conversion in solution. Moreover, this amidation reaction needed long reaction times.

Instead of amines, ammonium salts were employed in the reaction because (a) ammonium salts of gaseous or volatile amines such as ammonia, methyl amine, and dimethyl amine can be easily used in the

TABLE I The Effect of Different Ammonium Salts on the Amidation Reaction of Benzoic Acid in the Presence of SiO_2-TCT and Triethylamine at R.T.

Ammonium salt	Time (min)	Yield (%)[a]
NH_4Cl	1	82
NH_4I	1	74
NH_4NO_3	10	67
NH_4OAc	10	71
$(NH_4)_2SO_4$	10	63
$(NH_4)_2CO_3$	10	69

[a] The yield refers to a pure isolated product.

reaction; and (b) amines are hazardous compounds, and application of their salts decreases environmental pollution.

RESULTS AND DISCUSSION

To determine the optimal reaction conditions, we have selected the conversion of benzoic acid to benzamide as a model reaction. Different ammonium salts in the presence of silica-mediated TCT and triethylamine were examined in the reaction. The results are summarized in Table I. As indicated in Table I, ammonium chloride was the most suitable source for in situ–generation of ammonia. In another study, a set of different bases was considered in order to evaluate their capabilities (Table II). As is shown in Table II, the best results were obtained when

TABLE II The Influence of Bases on the Results of the Reaction of Benzoic Acid With Ammonium Chloride in the Presence of SiO_2-TCT at R.T.

Base	Time (min)	Yield (%)[a]
NEt_3	1	82
NBu_3	1	71
NMM	1	74
DMAP	10	65
DBU	10	70
DBN	10	67
DABCO	15	42
K_2CO_3	30	8
Cs_2CO_3	30	11

[a] The yield refers to a pure isolated product.

TABLE III The Effect of Various Supports on the Amidation of Benzoic Acid in the Presence of TCT and Triethylamine

Support	T (°C)	Time (min)	Yield(%)[a]
—	r.t.	60	13
—	70	30	24
SiO_2	r.t.	1	82
Basic Al_2O_3	r.t.	10	37
Neutral Al_2O_3	70	10	49
Clay	70	10	61
Molecular sieve 0.3 nm	70	10	47
Montmorillonite K-10	70	10	33
Graphite	70	10	42

[a] The yield refers to a pure isolated product.

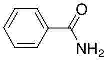
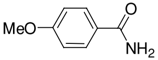
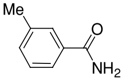
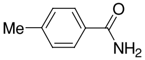
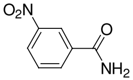
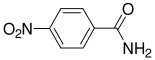
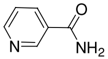
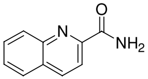
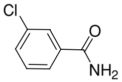
triethylaminewas used; therefore, triethylamine was the base of choice in all reactions. The influence of the supporting material on the result of the reaction was also investigated. The results are in Table III. As becomes clear from Table III, the absence of support in the reaction medium gave low yields of the product even on longer reaction times and higher temperatures. Thus, the support had a remarkable effect on the progress of the reaction. Among the examined supports, silica gel showed the best results.

To investigate the versatility and applicability of this method, the amidation reaction was investigated with various structurally diverse carboxylic acids and ammonium salts. As shown in Table IV, the reactions proceeded efficiently, and the desired amides were obtained in moderate to excellent yields.

We have also studied the effect of electron-donating and electron-withdrawing substituents at the aromatic ring of the carboxylic acid on the result of the reaction. As Table IV demonstrates, electron-donating substituents lowered the yield, while electron-withdrawing substituent (NO_2) increased the reaction yield. Moreover, the presence of a nitrogen atom in the aromatic ring of the acid increased the yield of the amides (Table IV). The presence of halogen atoms (Cl or Br) at the aromatic ring of the acid had no significant effect on the result of the reaction. Interestingly, no Michael addition-side products were observed when cinnamic and crotonic acid were used (Table IV).

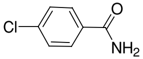
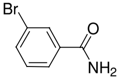
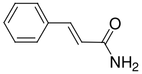
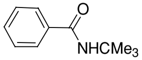
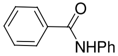
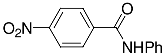
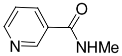
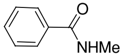
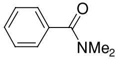
We have extended our reaction to sterically hindered and aromatic ammonium salts. As shown in Table IV, these ammonium salts afforded the corresponding amides in high yields. The procedure works also with aliphatic and dicarboxylic acids.

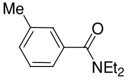
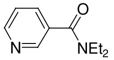
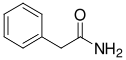
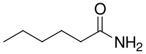
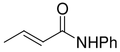
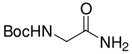
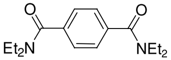
TABLE IV Direct Conversion of Carboxylic Acids to Amides in the Presence of Corresponding Ammonium Salts, SiO_2-TCT, and Triethylamine at R.T.

Acid	Product	$R^1R^2NH_2Cl$	M.P. °C (Lit.)	Yield[a](%)
Benzoic acid		NH_4Cl	127–129 (129.1)[21]	82
4-methoxybenzoic acid		NH_4Cl	114–116 (114–116)[18b]	50
3-methylbenzoic acid		NH_4Cl	93–95 (95)[21]	67
4-methylbenzoic acid		NH_4Cl	158–160 (160)[21]	66
3-nitrobenzoic acid		NH_4Cl	138–140 (141)[21]	87
4-nitrobenzoic acid		NH_4Cl	200–202 (201.5)[21]	85
Nicotinic acid		NH_4Cl	128–130 (129)[21]	87
Quinaldic acid		NH_4Cl	130–132 (133)[21]	84
3-chlorobenzoic acid		NH_4Cl	134–136 (135.5)[21]	82

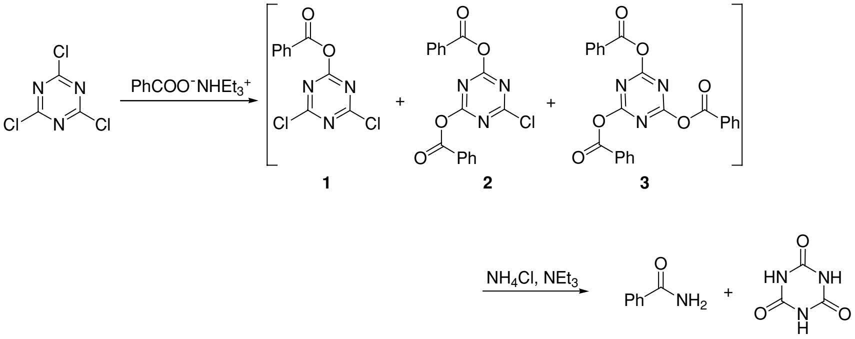
(Continued on next page)

TABLE IV Direct Conversion of Carboxylic Acids to Amides in the Presence of Corresponding Ammonium Salts, SiO_2-TCT, and Triethylamine at R.T. *(Continued)*

Acid	Product	$R^1R^2NH_2Cl$	M.P. °C (Lit.)	Yield[a](%)
4-chlorobenzoic acid		NH_4Cl	176–178 (179)[21]	79
3-bromobenzoic acid		NH_4Cl	154–155 (155.3)[21]	80
Cinnamic acid		NH_4Cl	147–149 (148.5)[21]	79
Benzoic acid		Me_3CNH_3Cl	133–135 (135.1)[14]	75
Benzoic acid		$PhNH_3Cl$	162–164 (163)[21]	83
4-nitrobenzoic acid		$PhNH_3Cl$	214–216 (216)[21]	82
Nicotinic acid		$MeNH_3Cl$	103–105 (104–106)[18b]	83
Benzoic acid		$MeNH_3Cl$	75–77 (75–77)[18b]	77
Benzoic acid		Me_2NH_2Cl	43–45 (43–45)[18b]	75

3-methylbenzoic acid		Et_2NH_2Cl	109–110 (110–112)[18b]	60
Nicotinic acid		Et_2NH_2Cl	25–27 (24–26)[21]	72
Phenylacetic acid		NH_4Cl	154–156 (157)[21]	70
Hexanoic acid		NH_4Cl	99–100 (101)[21]	61
Crotonic acid		$PhNH_3Cl$	113–115 (114)[15]	76
t-butoxycarbonylamino-acetic acid		NH_4Cl	85–87 (84–86)[22]	63
Terephthalic acid		Et_2NH_2Cl	125–126 (127)[21]	67

[a] The yield refers to a pure isolated product.



SCHEME 2

We suggest that the reaction proceeds via the intermediates **1**, **2**, and **3** (Scheme 2). They are formed by the nucleophilic attack of the carboxylate anion to the 2,4,6-trichloro-1,3,5-triazine and further react with the amine, which is generated from the reaction of the corresponding ammonium salt and triethylamine, providing the carboxamide. To explore the formation of intermediates **1–3** during the reaction, a mixture of benzoic acid, TCT, and silica gel were reacted with triethylamine. Intermediates **1**, **2**, and **3** could be observed on a TLC plate; however, they could not be separated and purified using the conventional techniques such as column chromatography or recrystalization. The subsequent addition of ammonium chloride and triethylamine showed the disappearance of the intermediates and the formation of benzamide.

In summary, we have developed a cheap, rapid, and solvent-free method for the direct conversion of carboxylic acids to all sorts of amides at r.t. with moderate to excellent yields.

EXPERIMENTAL

All chemicals were obtained from Merck (Darmstadt, Germany) or Fluka (Buchs, Switzerland). Solvents were purified and dried according to the reported methods and stored over molecular sieves.[20] Progress of the reactions was followed with TLC using silica gel SILG/UV 254 plates. Silica gel 60, 0.063–0.200 mm (70–230 mesh American Standards Testing Methods (ASTM)) was used for column chromatography and support. ^{1}H NMR spectra (250 MHz) were recorded with on a Bruker Avance DPX-250 FT-NMR spectrometer. Melting points were determined on a BÜCHI B-545 apparatus in open capillary tubes and are uncorrected.

Procedure for the Preparation of Silica-Supported TCT

Silica gel (8.00 g) was mixed with a solution of TCT (1.84 g, 10 mmol) in anhydrous CH_2Cl_2 (50 mL). Evaporation of the solvent gave a white powder, which was used as the coupling agent.

General Procedure for the Direct Conversion of Carboxylic Acids to Amides Using TCT as a Condensing Agent

In a mortar, a mixture of carboxylic acid (1 mmol), the respective ammonium salt (2 mmol), and silica-mediated TCT (0.49 g) was crushed vigorously to give a homogeneous mass. The mixture was transferred into a test tube, and then triethylamine (0.40 g, 4 mmol) was added dropwise. After 1 min, the reaction mixture was suspended in ethyl acetate (50 mL), and filtered, and the filtrate was washed with 0.02 N solution of HCl (2 × 50 mL) and water (2 × 50 mL). The organic layer was separated and dried with $MgSO_4$. The solvent was evaporated, and the crude product was purified by column chromatography on silica gel with ethyl acetate/*n*-hexane (1:1).

REFERENCES

[1] (a) K. Tanaka and F. Toda, *Chem. Rev.*, **100,** 1025 (2000) (b) K. Tanaka, *Solvent-Free Organic Synthesis* (Wiley-VCH, Weinheim, 2004).
[2] (a) M. Negwer and H.-G. Scharnow, *Organic-Chemical Drugs and Their Synonyms*, 8th ed., p. 4254 (Wiley-VCH, Weinheim, Berlin, 2001); (b) G. W. A. Milne, *CRC Handbook of Pesticides* (CRC Press, Boca Raton, Florida, 1995).
[3] J. March, in *Advanced Organic Chemistry*, 5th ed., pp. 508–510 (Wiley, New York, 2001); (b) B. M. Trost, in *Comprehensive Organic Synthesis*, Vol. 6, 381–417 (Pergamon Press, Oxford, 1991).
[4] J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77,** 1067 (1955).
[5] J. D. Wilson, C. F. Hobbs, and H. J. Weingarten, *J. Org. Chem.*, **15,** 1542 (1970).
[6] T. Yasuhara, Y. Nagaoka, and K. Tomioka, *J. Chem. Soc., Perkin Trans. 1*, **7,** 2901 (2000).
[7] C. Burnell-Curty and E. J. Roskamp, *Tetrahedron Lett.*, **34,** 5193 (1993).
[8] P. Froyen, *Synth. Commun.*, 959 (1995).
[9] D. O. Jang, D. J. Park, and J. Kim, *Tetrahedron Lett.*, **40,** 5323 (1999).
[10] Y. Basel and A. Hassner, *Tetrahedron Lett.*, **43,** 2529 (2002).
[11] K. Ishihara, S. Ohara, and H. Yamamoto, *J. Org. Chem.*, **61,** 4196 (1996).
[12] M. Thorsen, T. P. Andersen, U. Pedersen, B. Yde, S.-O. Lawesson, and H. F. Hansen, *Tetrahedron*, **41,** 5633 (1985).
[13] R. Sanchez, G. Vest, and L. Depres, *Synth. Commun.*, **19,** 2909 (1989).
[14] G. A. Olah, S. C. Narang, and A. G. Garcia-Luna, *Synthesis*, **8,** 661 (1980).
[15] K. S. Keshavamurthy, Y. D. Vankar, and D. N. Dhar, *Synthesis*, **6,** 506 (1982).
[16] M. A. Bailén, R Chinchilla, D. J. Dodsworth, and C. Najerá, *Tetrahedron Lett.*, **41,** 9809 (2000).

[17] (a) B. W. Baldwin, T. Hirose, and Z. H. Wang, *Chem. Commun.*, 2669 (1996); (b) R. S. Varma and K. P. Naicker, *Tetrahedron Lett.*, **40,** 6177 (1999); (c) L. Perreux, A. Loupy, and F. Volatron, *Tetrahedron*, **58,** 2155 (2002); (d) A. Khalafi-Nezhad, B. Mokhtari, and M. N. Soltani Rad, *Tetrahedron Lett.*, **44**(39), 7325 (2003).

[18] (a) A. Khalafi-Nezhad, A. Parhami, M. N. Soltani Rad, and A. Zarea, *Tetrahedron Lett.*, **46,** 6879 (2005); (b) A. Khalafi-Nezhad, A. Zarea, M. N. Soltani Rad, B. Mokhtari, and A. Parhami, *Synthesis*, 419 (2005); (c) A. Khalafi-Nezhad, M. N. Soltani Rad, and A. Khoshnood, *Synthesis*, 583 (2004); (d) A. Khalafi-Nezhad and B. Mokhtari, *Tetrahedron Lett.*, **45,** 6737 (2004); (e) A. Khalafi-Nezhad, M. N. Soltani Rad, and G. H. Hakimelahi, *Helv. Chim. Acta*, **86,** 2396 (2003); (f) A. Khalafi-Nezhad, F. Alamdari, and N. Zekri, *Tetrahedron*, **56,** 7503 (2000); (g) A. Khalafi-Nezhad and A. Hashemi, *J. Chem. Res., Synop.*, **36,** 720 (1999).

[19] (a) M. K. Venkataraman and D. R. Wagle, *Tetrahedron Lett.*, **20,** 3037 (1979); (b) W. Markowicz and R. Dembinski, *Synthesis*, 80 (2004); (c) H. L. Rayle and L. Fellmeth, Org. *Proc. Res. Develop.,* **3,** 172 (1999); (d) Z. J. Kaminski, P. Paneth, and J. Rudzinski, *J. Org. Chem.*, **63,** 4242 (1998); (e) B. P. Bandgar and S. S. Pandit, *Tetrahedron Lett.*, **43**(18), 3413 (2002).

[20] A. I. Vogel, in *Practical Organic Chemistry*, pp. 161-176 (Longman, Green and Co., London, 1954).

[21] The Combined Chemical Dictionaries on CD-Rom, Version 6.1, Chapman and Hall, 2003.

[22] S. T. Chen, S. H. Wu, and K. T. Wang, *Synthesis*, **1,** 37 (1989).