A Convenient Procedure for the Preparation of Sulfonamidoureas Using Triphosgene

Javad Safaei-Ghomi, Abdolhamid Bamoniri, and Aboalfazl Abbaszadeh-Nooshabady

Department of Chemistry, Faculty of Science, University of Kashan, 51167 Kashan, Iran

Reprint requests to Dr. Javad Safaei-Ghomi. Fax: (+98) 361 5552932. E-mail: safaei@kashanu.ac.ir

Z. Naturforsch. **2007**, *62b,* 721 – 724; received December 12, 2006

An efficient method for the preparation of sulfonamidourea using triphosgene in organic solvents is reported. Sulfonylhydrazides and acetylsulfanilylhydrazide were transformed into the corresponding intermediates using triphosgene in 1,4-dioxane/water or tetrahydrofuran as solvents.These intermediates were converted *in situ* into symmetrical and unsymmetrical sulfonamidoureas in high yields and shorter periods of time related to previous methods.

Key words: Sulfonamidourea, Triphosgene, Sulfonylhydrazides

Introduction

Sulfonamidoureas, in contrast to sulfonylureas, have received but little consideration [1]. Both the paucity of information regarding the series of sulfonamidoureas and the possibility of useful pharmacological activity of some members of this series motivated this investigation. Some sulfonamidourea derivatives are important compounds as blowing agents in cellular rubber and cellular plastic [2]. Sulfonylureas have found applications as oral antidiabetic drugs [3] and as herbicides [4, 5]. Therefore, it seemed of interest to determine the extent to which sulfonamidoureas might also possess such activities.

The classical methods for the preparation of sulfonamidoureas involve the reaction of sulfonylhydrazides with isocyanates [6], or the reaction of sulfonylchlorides with semicarbazides in an inert solvent [6, 7]. In some of these methods the yields of products are not high and the starting materials such as isocyanates are toxic. These compounds are usually prepared by bubbling phosgene gas through a solution of an amine at elevated temperature [8]. The hazards of handling of phosgene and the drastic conditions detract from these procedures. Over the last few years triphosgene [bis(trichloromethyl)carbonate] has emerged as a versatile synthetic reagent for the synthesis of a large variety of organic compounds [9, 10]. It was successfully used for the sequential synthesis of unsymmetrical ureas by Pavel [11], Weiberth [12], Lopez [13], and also by Suzuki [14] for the preparation of sulfonylamidoureas. This white crystalline compound has replaced its gaseous congener, phosgene, in terms of its reactivity and safe handling.

Table 1. The preparation of symmetrical sulfonamidoureas using triphosgene.

2, **3**	Ar	Time (min)	Yield (%)	M.p. (°C)
a	Ph	10	95	230 – 232
b	4-Me-C_6H_4	10	93	225 – 227
c	4-CH_3CONH-C_6H_4	15	93	218 – 220

Herein we wish to report a simple one-pot method for the preparation of sulfonamidoureas from sulfonylhydrazide and aryl or alkyl amines utilizing commercially available triphosgene in organic and aqueous solvents.

Results and Discussion

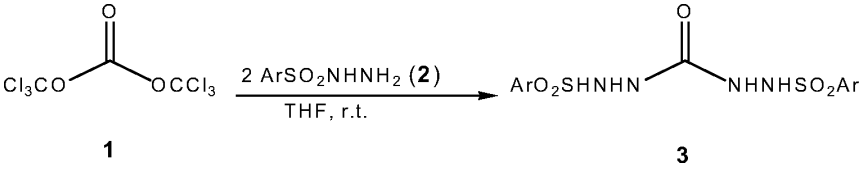
Treatment of two molar equivalents of a sulfonylhydrazide with triphosgene (**1**) in THF at r. t. produced symmetrical sulfonamidoureas as indicated in Table 1 (Scheme 1).

We have now extended the observed different reactivity of triphosgene toward amines and sulfonylhydrazides to a facile one-pot synthesis of unsymmetrically substituted sulfonamidoureas by sequential addition of two different amine components (sulfonylhydrazide and amine) to a solution of triphosgene in THF. In a typical procedure, intermediate **4** was first formed from slow addition of a sulfonylhydrazide to a cooled solution of triphosgene at −5 °C. The amine component **5** was then added as the hydrochloride **5** · HCl to this solution in one portion to provide an unsymmetri-

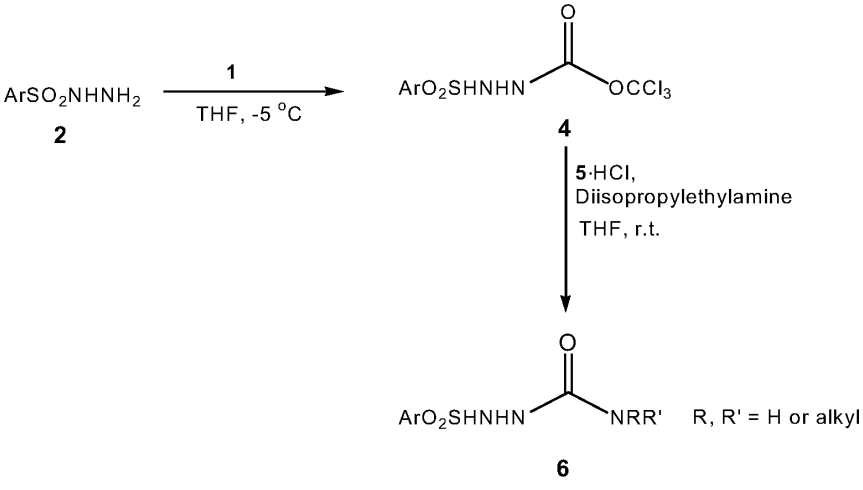
0932–0776 / 07 / 0500–0721 $ 06.00

Table 2. The preparation of unsymmetrical sulfonamidoureas using triphosgene.

6	Ar	**5**	Yield (%)	M.p. (°C)
a	4-$CH_3CONHPh$	NH_3	90	227 – 228 (227 [4])
b	4-$CH_3CONHPh$	$HN(CH_2CH_2)_2O$	80	196 – 198
c	Ph	NH_3	93	220 – 222 (222 [15])
d	Ph	$H_2NCH_2CH_2NH_2$	60	216 – 218
e	Ph	$PhCH_2NH_2$	92	182 – 184
f	Ph	$HN(CH_2CH_3)_2$	95	160 – 162
g	4-MePh	NH_3	89	235 – 237 (234 – 236 [15])
h	4-MePh	$PhCH_2NH_2$	87	192 – 195



Scheme 1.



Scheme 2. (For the amine components **5**, used as hydrochlorides, see Table 2).

cal sulfonamidourea **6** (Scheme 2). $^{i}Pr_2EtN$ was used as an auxiliary base.

In order to prevent the production of undesirable products (symmetrical sulfonamidoureas), a less reactive sulfonylhydrazide was used in the first step of the above procedure. The generality of this reaction was established by preparing various unsymmetrical sulfonamidoureas from the corresponding sulfonylhydrazides and amines (Table 2). Importantly, excellent transformations were obtained when **1** reacted with a water-soluble acetamidosulfonylhydrazide (Table 2, entries **a** and **b**).

In conclusion, we have provided a convenient, one-pot procedure for the preparation of symmetrical and unsymmetrical sulfonamidoureas utilizing easily accessible triphosgene. This compound reacts rapidly with various sulfonylhydrazides and amines in anhydrous or hydrous organic solvents to provide the desired products. The reactions are operationally simple, offer high yields and short reaction times.

Experimental Section

Melting points were determined on a Kofler block and are uncorrected. FT-IR spectra were recorded on a Nicolet Magna 550 spectrometer (KBr). ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker DRX-500 AVANCE (^{1}H: 500 MHz; ^{13}C: 125 MHz) spectrometer using [D_6]DMSO as a solvent and TMS as internal standard. Mass spectra were obtained on a QP 1100 EX spectrometer. Elemental analyses were determined on a Carlo ERBA model EA 1108. Starting materials were either commercially available or prepared according to literature procedures [16].

*General procedure for the preparation of symmetrical sulfonamidoureas (**3a – c**)*

To a stirred solution of triphosgene (0.148 g, 0.5 mmol) in THF (2 mL) was added a solution of sulfonylhydrazide

(1.1 mmol) in THF (5 mL) at r. t. in one portion. The reaction mixture was stirred at this temperature until the sulfonylhydrazide was consumed (as evidenced by TLC). The reaction mixture was then evaporated to dryness and the residue was washed with 5 % aq. HCl and water and dried under reduced pressure to give a white powder. The crude product was recrystallized from ethanol. No additional chromatography was needed. For the preparation of **3c** the sulfonylhydrazide was dissolved in boiling 1,4-dioxane/water (2 : 1.6).

3a: White solid; m. p. 230 – 232 °C. – IR (film): ν = 1160, 1347 (SO_2), 1675 (C=O), 3293, 3375 (NH) cm^{-1}. – ^{1}H NMR: δ = 7.5 – 7.7 (m, 10H, Ar*H*,), 8.3 (s, 2H, -N*H*-CO), 9.4 (s, 2H, SO_2-N*H*-). – ^{13}C NMR: δ = 127.5, 128.8, 132.9, 138.5, 156.3 (C=O). – MS (EI): *m/z* (%) = 372 (4) $[M]^+$, 229 (12), 199 (2), 172 (86), 141 (54), 77 (100). – Analysis for $C_{13}H_{14}N_4O_5S_2$: calcd. C 42.16, H 3.81, N 15.13; found C 42.10, H 3.85, N 15.20.

3b: White solid; m. p. 225 – 227 °C. – IR (film): ν = 1157, 1351 (SO_2), 1668 (C=O), 3237, 3360 (NH) cm^{-1}. – ^{1}H NMR: δ = 2.3 (s, 3H, ArC*H*$_3$), 7.3 (d, *J* = 7.5 Hz, 4H, Ar*H*), 7.6 (d, *J* = 7.5 Hz, 4H, Ar*H*), 8.2 (s, 2H, -N*H*-CO), 9.3 (s, 2H, SO_2-N*H*-). – ^{13}C NMR: δ = 21.1, 127.7, 129.3, 135.6, 143.2, 156.3 (C=O). – MS (EI): *m/z* (%) = 398 (2) $[M]^+$, 243 (10), 213 (14), 156 (86), 139 (78), 91 (100). – Analysis for $C_{15}H_{18}N_4O_5S_2$: calcd. C 45.22, H 4.55, N 14.06; found C 45.31, H 4.50, N 14.11.

3c: White solid; m. p. 218 – 220 °C. – IR (film): ν = 1157, 1337 (SO_2), 1670 (C=O), 3370, 3503 (-NH-NH-) cm^{-1}. – ^{1}H NMR: δ = 2.0 (s, 6H, -NHCOC*H*$_3$), 7.7 (d, *J* = 8.4 Hz, 4H, Ar*H*), 7.8 (d, *J* = 8.4 Hz, 4H, Ar*H*), 8.3 (s, 2H, -N*H*-CO), 9.3 (s, 2H, SO_2-N*H*-), 10.3 (s, 2H, -N*H*-COCH$_3$). – ^{13}C NMR: δ = 24.5, 119.3, 129.8, 132.5, 144.1, 157.3 (C=O), 170 (C=O). – MS (EI): *m/z* (%) = 484 (2) $[M]^+$, 229 (8), 187 (15), 154 (100), 93 (100), 43 (40), 65 (95). – Analysis for $C_{17}H_{20}N_6O_7S_2$: calcd. C 42.14, H 4.16, N 17.35; found C 42.27, H 4.36, N 17.47.

*General procedure for the preparation of unsymmetrical sulfonamidoureas (**6a** – **h**)*

A solution of sulfonylhydrazide (0.7 mmol) in THF (6 mL) was slowly added to the stirred solution of triphosgene (0.148 g, 0.5 mmol in 2 mL of THF) over a period of 40 min at −5 °C. (For **6a** and **6b**, the sulfonylhydrazide was dissolved in 1,4-dioxane/water (2 : 1.6)). After a further 5 min of stirring, a solution of the respective amine **5** as hydrochloride (1 mmol) and diisopropylethylamine (2 mmol) in THF (3 mL) was added in one portion. The reaction mixture was then stirred for 10 min at r. t. and evaporated to dryness. The residue was washed with 5 % aq. HCl and water and then dried under reduced pressure to yield the colorless product. The crude products were recrystallized from ethanol.

6a: White solid; m. p. 227 – 228 °C (227 °C [4]). – IR (film): ν = 1163, 1332 (SO_2), 1654 (C=O), 3385, 3482 (NH, NH_2) cm^{-1}. – ^{1}H NMR: δ = 2.1 (s, 3H, -NHCOC*H*$_3$), 5.9 (s, 2H, -CON*H*$_2$), 7.7 (m, 4H, Ar*H*), 7.9 (s, 1H, -N*H*CONH$_2$), 9.3 (s, 1H, SO_2N*H*-), 10.3 (s, 2H, -N*H*COCH$_3$).

6b: White solid; m. p. 196 – 198 °C. – IR (film): ν = 1163, 1316 (SO_2), 1700 (C=O), 3230, 3324 (NH, NH_2) cm^{-1}. – ^{1}H NMR: δ = 2 (s, 3H, -NHCOC*H*$_3$), 3.1 (t, *J* = 4.6 Hz, 4H, -NC*H*$_2$CH$_2$-O), 3.4 (t, *J* = 4.6 Hz, 4H, -NCH$_2$C*H*$_2$-O), 7.6 (d, *J* = 9 Hz, 2H, Ar*H*), 7.7 (d, *J* = 9 Hz, 2H, Ar*H*), 8.8 (s, 1H, -N*H*CON), 8.9 (s, 1H, SO_2N*H*-), 10.3 (s, 1H, -N*H*COCH$_3$). – ^{13}C NMR: δ = 25.2, 46.9, 67.1, 113.5, 125.3, 134.4, 137.8, 156.5 (C=O), 169.1 (C=O). – MS (EI): *m/z* (%) = 342 (3) $[M]^+$, 229 (14), 187 (28), 154 (100), 93 (100), 87 (10), 43 (57), 65 (80). – Analysis for $C_{13}H_{18}N_4O_5S$: calcd. C 45.61, H 5.30, N 16.36; found C 45.55, H 5.46, N 16.55.

6c: White solid; m. p. 220 – 222 °C (220 °C [15]). – IR (film): ν = 1168, 1326 (SO_2) 1659 (C=O), 3375, 3457 (NH, NH_2) cm^{-1}. – ^{1}H NMR: δ = 5.9 (s, 2 H, -CON*H*$_2$), 7.5 – 7.8 (m, 5H, Ar*H*), 7.9 (s, 1H, -N*H*CO), 9.4 (s, 1H, SO_2N*H*-).

6d: White solid; m. p. 216 – 218 °C. – IR (film): ν = 1169, 1352 (SO_2), 1644 (C=O), 3129, 3446 (NH, NH_2) cm^{-1}. – ^{1}H NMR: δ = 2.8 (s, 4H, C*H*$_2$C*H*$_2$), 6.4 (s, 2H, -N*H*CH$_2$), 7.5 – 7.8 (m, 10 H, Ar*H*,), 8.0 (s, 2H, -N*H*CO), 9.6 (s, 2H, SO_2N*H*-). – ^{13}C NMR: δ = 42.2, 115, 128.6, 129.7, 139.1, 158.4 (C=O). – MS (EI): *m/z* (%) = 258 (20) [M–PhSO$_2$NHNHCO]$^+$, 218 (3), 141 (66), 125 (76), 109 (33), 91 (3), 77 (100), 65 (14). – Analysis for $C_{16}H_{20}N_6O_6S_2$: calcd. C 42.10, H 4.42, N 18.41; found C 42.17, H 4.35, N 18.45.

6e: White solid; m. p. 182 – 184 °C. – IR (film): ν = 1170, 1342 (SO_2), 1644 (C=O), 3250, 3395 (NH) cm^{-1}. – ^{1}H NMR: δ = 4.1 (bs, 2H, ArC*H*$_2$), 6.9 (bs, 1H, Ar-CH$_2$N*H*), 7.1 – 7.3 (m, 5H, Ar*H*,), 7.5 – 7.8 (m, 5H, Ar*H*,), 8.1 (s, 1H, -N*H*CO), 9.5 (s, 1H, SO_2N*H*-). – ^{13}C NMR: δ = 43.5, 126.9, 127.1, 128.8, 128.9, 129.9, 133.8, 139.6, 141.6, 158.1 (C=O). – MS (EI): *m/z* (%) = 305 (2) $[M]^+$, 172 (100), 164 (60), 143 (100), 106 (50), 91 (100). – Analysis for $C_{14}H_{15}N_3O_3S$: calcd. C 55.07, H 4.95, N 13.76; found C 55.25, H 5.11, N 13.45.

6f: White solid; m. p. 160 – 162 °C. – IR (film): ν = 1163, 1326 (SO_2), 1644 (C=O), 3119, 3370 (NH) cm^{-1}. – ^{1}H NMR: δ = 0.9 (t, *J* = 7 Hz, 6H, CH$_2$C*H*$_3$), 3.0 (q, *J* = 7 Hz, 4H, C*H*$_2$CH$_3$), 7.5 – 7.7 (m, 5H, Ar*H*,), 8.6 (s, 2H, -N*H*CO), 8.9 (s, 2H, SO_2N*H*-). – ^{13}C NMR: δ = 14.2, 41.2, 128.6, 129.3, 133.4, 139.4, 156.5 (C=O). – MS (EI): *m/z* (%) = 271 (38) $[M]^+$, 241 (70), 141 (52), 130 (64), 101 (100), 86 (62), 77 (100). – Analysis for $C_{11}H_{17}N_3O_3S$: calcd. C 48.69, H 6.31, N 15.49; found C 48.59, H 6.24, N 15.63.

6g: White solid; m. p. 235 – 237 °C (234 – 236 °C [15]). – IR (film): ν = 1175, 1337 (SO_2), 1654 (C=O), 3375, 3457 (NH, NH_2) cm^{-1}. – ^{1}H NMR (60 MHz): δ = 2.1 (s, 3H, ArC*H*$_3$), 5.4 (s, 2H, CON*H*$_2$,), 6.7 – 7.2 (m, 4H, Ar*H*), 7.3 (s, 2H, -N*H*CO), 8.7 (s, 2H, SO_2N*H*-).

6h: White solid; m. p. 192 – 195 °C. – IR (film): ν = 1168, 1342 (SO_2), 1649 (C=O), 3293, 3411 (NH, NH_2) cm^{-1}. – ^{1}H NMR: δ = 2.3 (s, 3H, ArC*H*$_3$), 4.1 (bs, 2H, ArC*H*$_2$-), 6.9 (bs, 1H, Ar-CH_2N*H*), 7.1 – 7.2 (m, 5H, Ar*H*,), 7.3 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.7 (d, J = 7.6 Hz, 2H, Ar*H*), 8.0 (s, 1H, -N*H*CO), 9.4 (s, 1H, SO_2N*H*-). – ^{13}C NMR: δ = 21.9, 43.4, 127.3, 127.6, 128.6, 128.8, 130.2, 136.2, 141.2, 144.1, 158.4 (C=O). – MS (EI): *m/z* (%) = 319 (6) $[M]^+$, 186 (100), 164 (66), 156 (100), 106 (40), 91 (100), 65 (94). – Analysis for $C_{15}H_{17}N_3O_3S$: calcd. C 56.41, H 5.36, N 13.16; found C 56.35, H 5.40, N 13.21.

[1] F. Kurzer, *Chem. Rev*. **1952**, *50*, 1 – 46.

[2] H. R. Lasman in *Encyclopedia of Polymer Science and Technology*, Vol. 12 (Ed.: N. M. Bikales), John Wiley, New York, **1965**.

[3] S. Ashcroft, F. Ashcroft, *Biochim. Biophys. Acta* **1992**, *1175*, 45 – 59.

[4] E. M. Beyer, M. J. Duffy, J. V. Hay, D. D. Schlueter, *Sulfonylureas in Herbicides: Chemistry, Degradation and Mode of Action*, Vol. 3 (Eds.: P. C. Kearney, D. D. Kaufman), Marcel Dekker, New York, **1988**, p. 117.

[5] S. Bell, A. Bonadio, K. G. Watston, *Aust. J. Chem*. **1995**, *48*, 227 – 232.

[6] J. S. Roth, E. F. Degering, *J. Am. Chem. Soc*. **1945**, *67*, 126 – 128.

[7] E. Niemiec, *J. Am. Chem. Soc*. **1948**, *70*, 1067 – 1068.

[8] J. S. Nowick, N. A. Powell, T. M. Nguyen, G. Noronha, *J. Org. Chem*. **1992**, *57*, 7364 – 7366.

[9] L. Cotarca, P. Delogu, A. Nardelli, V. Sunjic, *Synthesis* **1996**, 553 – 576.

[10] V. K. Gumaste, A. R. A. S. Deshmukh, *Tetrahedron Lett*. **2004**, *45*, 6571 – 6573.

[11] M. Pavel, S. R. Ramnarayan, *J. Org. Chem*. **1994**, *59*, 1937 – 1938.

[12] F. J. Weiberth, *Tetrahedron Lett*. **1999**, *40*, 2895 – 2898.

[13] Ó. Lopez, S. Maza, I. Maya, J. Fuentes, J. G. Fernándes-Bolaños, *Tetrahedron* **2005**, *61*, 9058 – 9069.

[14] T. Suzuki, H. Ohmizu, Y. Hashimura, H. Kubota, K. Tanaka, E. P 790240 A1, **1997**.

[15] R. W. Amidon, U. S. Pat. 3344182, **1967**.

[16] L. Friedman, R. L. Litle, W. R. Reichle, *Org. Synth*. **1960**, *40*, 93.