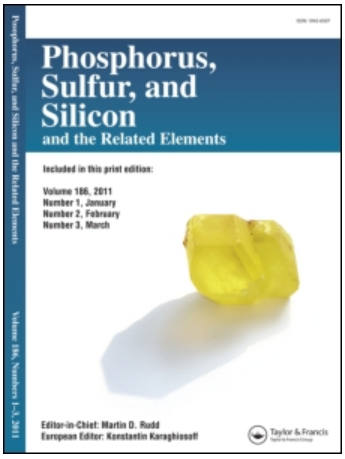


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

TMEDA-CATALYZED SYNTHESIS OF *N*-ARYL-*N'*-ETHOXYCARBONYL THIOUREA AND ARENE (OR POLYMETHYLENE)-BIS-ETHOXYCARBONYLTHIOUREA DERIVATIVES

Qi Lin[a]; You-Ming Zhang[a]; Li-Ming Gao[a]; Tai-Bao Wei[a]; Hai Wang[a]
[a] Department of Chemistry, Northwest Normal University, Lanzhou, Gansu, P.R. China

Online publication date: 16 August 2010

To cite this Article Lin, Qi , Zhang, You-Ming , Gao, Li-Ming , Wei, Tai-Bao and Wang, Hai(2004) 'TMEDA-CATALYZED SYNTHESIS OF *N*-ARYL-*N'*-ETHOXYCARBONYL THIOUREA AND ARENE (OR POLYMETHYLENE)-BIS-ETHOXYCARBONYLTHIOUREA DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 179: 10, 2051 — 2057
To link to this Article: DOI: 10.1080/10426500490474905
URL: http://dx.doi.org/10.1080/10426500490474905

Phosphorus, Sulfur, and Silicon, 179:2051–2057, 2004

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500490474905

Taylor & Francis
Taylor & Francis Group

TMEDA-CATALYZED SYNTHESIS OF *N*-ARYL-*N*′-ETHOXYCARBONYL THIOUREA AND ARENE (OR POLYMETHYLENE)-BIS-ETHOXYCARBONYLTHIOUREA DERIVATIVES

Qi Lin, You-Ming Zhang, Li-Ming Gao, Tai-Bao Wei, and Hai Wang
Department of Chemistry, Northwest Normal University, Lanzhou, Gansu, P.R. China

(Received January 15, 2004; accepted March 17, 2004)

A novel and efficient method for synthesis ethoxycarbonyl isothiocyanate and ethoxycarbonyl thioureas catalyzed by TMEDA is reported. A series of N-*aryl*-N′-*ethoxycarbonyl thioureas and arene (or polymethylene)-bis-ethoxycarbonyl thiourea derivatives have been synthesized in good-to-excellent yields via this method at room temperature.*

Keywords: ethoxycarbonyl isothiocyanate; ethoxycarbonyl thioureas; TMEDA catalysis

INTRODUCTION

N-aryl-*N*′-ethoxycarbonyl thioureas have attracted much attention due to their strong coordination ability.[1] For example, many *N*-substituted-*N*′-ethoxycarbonyl thioureas are commercially utilized as the collector for copper sulfides and precious metals.[2] Moreover, *N*-aryl-*N*′-ethoxycarbonyl thioureas have been found to posses high antibacterial activity.[3] It is also an important intermediate for synthesis of heterocyclic compounds.[4] In view of these facts, and as a part of our work of the synthesis, biological activity, and coordination behavior of thiourea derivatives,[5] herein we report an efficient and novel method for synthesis *N*-aryl-*N*′-ethoxycarbonyl thioureas (**4a–e**)

This work was supported by Natural Science Foundation (No. 20371040) of China, the Foundation (031-A21-004) of Gansu province, and the Foundation (No. 02-18) of Northwest Normal University, which are gratefully acknowledged.

Address correspondence to Tai-Bao Wei, Department of Chemistry, Northwest Normal University, Lanzhou, Gansu, 730070, P.R. China. E-mail: kejichu@nwnu.edu.cn

and arene (or polymethylene)-bis-ethoxycarbonylthiourea derivatives (**5a–f**) catalyzed by N,N,N',N'-tetramethylethylenediamine (TMEDA) under mild conditions.

The common methods for the preparation of these compounds are via the reaction of ethoxycarbonylisothiocyanate (**3**) with corresponding aromatic amines or arene (or polymethylene) diamines. Obviously, the compound **3** is the key intermediate for **4** and **5**. As early as 1908, Dixon and Taylor[7] reported that potassium thiocyanate (**2**) reacted with ethyl chloroformate (**1**) in acetone solutions to gives the compound **3**, but this method gives **3** in very low yield and gives a lot of ethoxycarbonylthiocyanate as by-product.[8] Thus it is not a good method for preparation **3**. In our earlier work, we reported that acyl isothiocyanate could be synthesized in high yield by the reaction of benzoyl chloride with potassium thiocyanate under solid–liquid phase-transfer catalytic conditions;[5b] however, we haven't obtained the compound **3** in high yield using similar method.

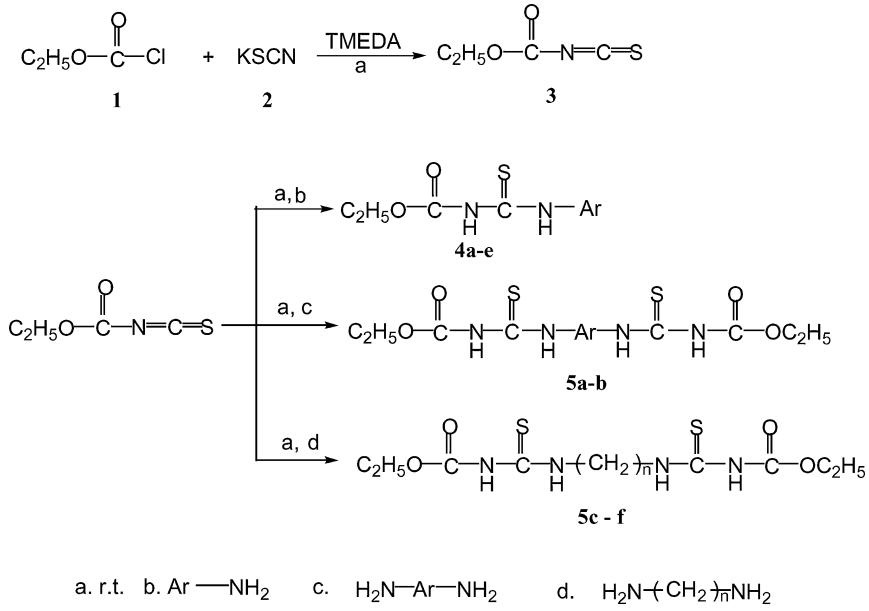
Recently, Tomohumi Sano et al.[9] reported that TMEDA could promote the acylation reaction between benzoyl chloride and alcohols by enhancing the reactivity of benzoyl chloride. In an earlier study, H. Kunz et al.[10] also reported that pyridine could catalyze the reaction between 2-(triphenylphosphonio)ethyl chloroformate and alcohols by enhancing the reactivity of 2-(triphenylphosphonio)ethyl chloroformate. In view of these studies, we think TMEDA and other amines such as pyridine can also catalyze the reaction between **1** and **2** by enhancing the reactivity of **1**. As a result of these ideas, a series of *N*-aryl-*N'*-ethoxycarbonyl thioureas (**4a–e**) and arene (or polymethylene)-bis-ethoxycarbonylthiourea derivatives (**5a–f**) have been synthesized in good-to-excellent yields by the catalysis of TMEDA at room temperature.

RESULTS

TMEDA is an excellent catalyst for the synthesis of this kind of isothiocyanates and thioureas. Compounds **4a–e** and **5a–f** were synthesized in good-to-excellent yields at room temperature catalyzed by TMEDA. The use of TMEDA as the catalyst has many advantages such as excellent chemical yields, high efficiency (10 mmol ethyl chloroformate only need 0.1 mmol TMEDA), mild reaction conditions (All reactions are performed at room temperature), and simple operation. For these reasons, this methodology represents an important improvement for the preparation of this kind of fine chemical.

DISCUSSION

In order to select the best reaction condition and the best catalyst for synthesis **3**, we carried out a series of experiments as follows: at first, we estimated the reactivity of the model reaction (Scheme 1) between **1** (10 mmol) and **2** (12 mmol) under TMEDA (0.1 mmol) catalysis and room temperature conditions in different solvents such as CH_2Cl_2, acetone, and ethyl acetate. Because compound **3** is an oil product, after the reaction completed we didn't separate it, and we added the aniline (10 mmol) slowly to the reaction mixture with constant stirring and stirred at room temperature for 5 h. Then the solvent was evaporated in vacuum and the precipitation was washed with 10 ml 75% EtOH three times and 15 ml water three times. The product **4a** was obtained. The yields of **4a** in different solvents are shown in Table I. From these data we can find the ethyl acetate is the appropriate solvent for this reaction.



SCHEME 1

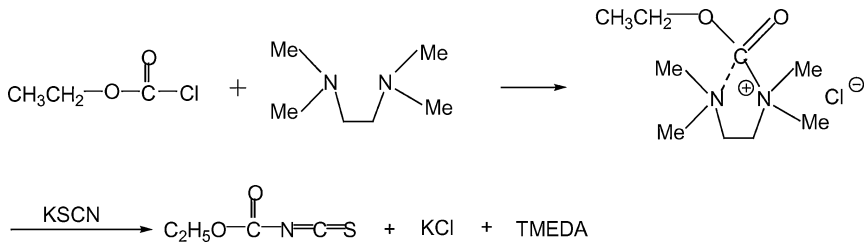
In order to compare the catalytic effect of the TMEDA and other amines, and as the second series of our experiments, we examined a similar reaction via the use of different amines as catalysts. Because it is a solid–liquid phase reaction, we also tested it using polyethyleneglycol

TABLE I Yields of **4a** in Different Solvents Under the Catalysis of TMEDA

Entry	Solvents	Yields of **4a** (%)
1	Acetone (8 ml)	54
2	CH_2Cl_2 (8 ml)	56
3	Ethyl acetate (8 ml)	96
4	Ethyl acetate (20 ml)	68

(PEG)-400 as the phase-transfer catalyst. The results are listed in Table II. From these data we find that the TMEDA is the best catalyst for this reaction, although the pyridine and other amines such as triamyl amine could promote the reaction. We also found the phase-transfer catalysis method couldn't give a satisfied result for this reaction.

Finally, we explored the general validity of the present methodology; different ethoxycarbonylthioreas **4a–e** and **5a–f** were synthesized in excellent yields (Table III). The details of the reaction mechanism are not clear at present, but Sano et al.[9] supposed that a benzoyl chloride–TMEDA complex plays a significant role in enhancing the reactivity of benzoyl chloride. Additionally, Kunz et al.[10] also reported that the 2-(triphenylphosphonio)ethyl chloroformate-pyridine complex is the key intermediate for enhancing the reactivity of 2-(triphenylphosphonio)ethyl chloroformate. Therefore, we think the formation of ethyl chloroformate–TMEDA complex is the key step of the catalytic procedure. On the basis of our experimental results, we tentatively propose the mechanism shown in Scheme 2.



SCHEME 2

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Nicilet NEXUS 670 Fourier transform infrared (FTIR) spectrophotometer, and ^{1}H NMR spectra on a

TABLE II Yields of **4a** under the Catalysis of Different Catalysts

Entry	Catalysts[a]	Yields of **4a** (%)
1	TPA[b]	60
2	TAA[c]	80
3	Pyridine	76
4	TMEDA	96
5	PEG-400[d]	42
6	PEG-400 + TAA	68
7	PEG-400 + Pyridine	45
8	PEG-400 + TMEDA	74

[a]The use of each catalyst is 0.1 mmol.
[b]Tripropyl amine.
[c]Triamyl amine.
[d]PEG-400.

FT-80A instrument using TMS as internal reference. Elemental analysis was determined on PE-2400 CHN instrument.

Typical Procedure for 4a–e and 5a–f

The synthesis of **4a–e** and **5a–f** were carried out by adding powdered 2 (12 mmol) to an ethyl acetate solution of **1** (10 mmol) and TMEDA (0.1 mmol). The reaction mixture was stirred at room temperature for 5 h. Then the aromatic amine (10 mmol) to give **4a–e** or arene (or alkylene) diamine (5 mmol) to give **5a–f** was slowly added to the reaction mixture with constant stirring. The reaction mixture was stirred at room temperature for 5 h again. After evaporating the solvent in

TABLE III Compounds **4a–e** and **5a–f** Prepared

Entry	$Ar/(CH_2)_n$	Products	Yields (%)
1	C_6H_5	**4a**	96
2	$2\text{-}CH_3C_6H_4$	**4b**	88
3	$3\text{-}CH_3C_6H_4$	**4c**	94
4	$2\text{-}ClC_6H_4$	**4d**	80
5	2-Naphthyl	**4e**	89
6		**5a**	76
7		**5b**	80
8	$(CH_2)_2$	**5c**	70
9	$(CH_2)_4$	**5d**	78
10	$(CH_2)_6$	**5e**	89
11	$(CH_2)_{10}$	**5f**	84

vacuum, the products were obtained from washing the precipitation with 10 ml 75% ethanol three times and 15 ml H_2O three times. If necessary, recrystallization **4a–e** from ethanol and **5a–f** from DMF-EtOH-H_2O gave the pure product.

4a. Yield, 96%; m.p. 125–126°C. IR (KBr): $\nu = 3416$ (NH), 3220 (NH), 1712 (C=O), 1596, 1534, 1449 (C=C), 1237 (C=S) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta_H = 11.48$ (s, 1H, NH), 8.29 (s, 1H, NH), 7.50 (m, 5H, ArH), 4.361 (q, 2H, CH_2), 1.368, (t, 3H, CH_3). Anal. Cacld. for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.39; N, 12.49. Found: C, 53.55; H, 5.40; N, 12.54.

4b. Yield, 87%; m.p. 152–153°C. IR (KBr): $\nu = 3415$ (NH), 3217 (NH), 1713 (C=O), 1608, 1579, 1533 (C=C), 1202 (C=S) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta_H = 11.18$ (s, 1H, NH), 8.33 (s, 1H, NH), 7.50 (m, 4H, ArH), 4.35 (q, 2H, CH_2), 2.34 (s, 3H, CH_3), 1.37 (t, 3H, CH_3). Anal. Cacld. for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92; N, 11.76. Found: C, 55.41; H, 5.92; N, 11.78.

4c. Yield, 94%; m.p. 102–103°C. IR (KBr): $\nu = 3422$ (NH), 3212 (NH), 1714 (C=O), 1603, 1538, 1474, (C=C) 1242 (C=S). ^1H NMR ($CDCl_3$): $\delta_H = 11.43$ (s, 1H, NH), 8.30 (s, 1H, NH), 7.29 (m, 4H, ArH), 4.35 (q, 2H, CH_2), 2.40 (s, 3H, CH_3), 1.36, (t, 3H, CH_3). Anal. Cacld. for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92; N, 11.76. Found: C, 55.41; H, 5.92; N, 11.78.

4d. Yield 80%; m.p. 126–128°C. IR (KBr): $\nu = 3415$ (NH), 3166 (NH), 1723 (C=O), 1559, 1539, 1477 (C=C) 1246 (C=S). ^1H NMR ($CDCl_3$): $\delta_H = 11.65$ (s, 1H, NH), 8.29 (s, 1H, NH), 7.37 (m, 4H, ArH), 4.38 (q, 2H, CH_2), 1.38 (t, 3H, CH_3). Anal. Cacld. for $C_{10}H_{11}N_2O_2SCl$: C, 46.42; H, 4.29; N, 10.83. Found: C, 46.27; H, 4.30; N, 10.79.

4e. Yield, 89%; m.p. 159–160°C. IR (KBr): $\nu = 3416$ (NH), 3161 (NH), 1711 (C=O), 1599, 1531, 1472 (C=C), 1247 (C=S). ^1H NMR ($CDCl_3$): $\delta_H = 11.67$ (s, 1H, NH), 8.44 (s, 1H, NH), 7.75 (m, 7H, ArH), 4.37 (q, 2H, CH_2), 1.37 (t, 3H, CH_3). Anal. Cacld. for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.17; H, 5.20; N, 10.30.

5a. Yield, 76%; m.p. 164–165°C. IR (KBr): $\nu = 3388$ (NH), 3192 (NH), 1709 (C=O), 1589, 1535, 1456 (C=C), 1245 (C=S). ^1H NMR ($CDCl_3$): $\delta_H = 11.22$ (s, 2H, NH), 8.48 (s, 2H, NH), 7.34 (m, 4H, ArH), 4.32 (q, 4H, CH_2), 1.33 (t, 6H, CH_3). Anal. Cacld. for $C_{14}H_{18}N_4O_4S_2$: C, 45.39; H, 4.90; N, 15.12. Found: C, 45.41; H, 4.86; N, 15.14.

5b. Yield, 80%; m.p. 180–181°C. IR (KBr): $\nu = 3431$ (NH), 3210 (NH), 1718 (C=O), 1594, 1524, 1445 (C=C), 1244 (C=S). ^1H NMR ($CDCl_3$): $\delta_H = 11.53$ (s, 2H, NH), 8.28 (s, 2H, NH), 7.43 (m, 4H, ArH), 4.34 (q, 4H, CH_2), 1.35 (t, 6H, CH_3). Anal. Cacld. for $C_{14}H_{18}N_4O_4S_2$: C, 45.39; H, 4.90; N, 15.12. Found: C, 45.44; H, 5.06; N, 15.04.

5c. Yield, 70%; m.p. 196–197°C. IR (KBr): $\nu = 3427$ (NH), 3223 (NH), 1721 (C=O), 1241 (C=S). ^1H NMR (DMSO-d_6): $\delta_H = 17.74$ (s, 2H, NH),

9.90 (s, 2H, NH), 4.00 (q, 4H, CH_2), 3.42 (d, 4H, CH_2), 1.21 (t, 6H, CH_3). Anal. Cacld. for $C_{10}H_{18}N_4O_4S_2$: C, 37.25; H, 5.63; N, 17.38. Found: C, 37.36; H, 5.76; N, 17.53.

5d. Yield, 78%; m.p. 154–155°C. IR (KBr): $\nu = 3402$ (NH), 3296 (NH), 1702 (C=O), 1256 (C=S). ^{1}HNMR ($CDCl_3$): δ_H =10.85 (s, 2H, NH), 9.85 (s, 2H, NH), 4.14 (q, 4H, CH_2), 3.56 (t, 4H, CH_2), 1.57 (t, 4H, CH_2), 1.20 (t, 6H, CH_3). Anal. Cacld. for $C_{12}H_{22}N_4O_4S_2$: C, 41.13; H, 6.33; N, 15.99. Found: C, 41.34; H, 6.46; N, 16.03.

5e. Yield, 89%; m.p. 133–134°C. IR (KBr): $\nu = 3328$ (NH), 3265 (NH), 1715 (C=O), 1248 (C=S). ^{1}H NMR ($CDCl_3$): $\delta_H = 9.70$ (s, 2H, NH), 8.11 (s, 2H, NH), 4.28 (q, 4H, CH_2), 3.64 (q, 4H, CH_2), 1.60 (t, 8H, CH_2), 1.31 (t, 6H, CH_3). Anal. Cacld. for $C_{14}H_{26}N_4O_4S_2$: C, 44.42; H, 6.92; N, 14.80. Found: C, 44.35; H, 6.91; N, 14.76.

5f. Yield, 84%, m.p. 112–113°C. IR (KBr): $\nu = 3420$ (NH), 3238 (NH), 1723 (C=O), 1253 (C=S). ^{1}H NMR ($CDCl_3$): $\delta_H = 9.67$ (s, 2H, NH), 8.19 (s, 2H, NH), 4.27 (q, 4H, CH_2), 3.64 (q, 4H, CH_2), 1.38(t, 16H, CH_2), 1.30 (t, 6H, CH_3). Anal. Cacld. for $C_{18}H_{34}N_4O_4S_2$: C, 49.74; H, 7.88; N, 12.89. Found: C, 49.89; H, 7.75; N, 12.98.

REFERENCES

[1] a) X. Shen, T. B. Wen, Q. T. Liu, X. Y. Huang, B. S. Kang, X. L. Wu, Z. S. Huang, and L. Q. Gu, *Polyhedron*, **16,** 2605 (1997); b) W. Z. Shen, D. Fornasieroa, J. Ralstona, *Minerals Eng.*, **11**(2), 145 (1998); c) D. Fornasiero, and J. Ralstona, *Analytica Chimica Acta*, **346,** 237 (1997).

[2] G. Fairthorne, D. Fornasiero, and J. Ralston, *Int. J. Miner. Process.*, **50,** 227 (1997).

[3] a) Z. S. Huang, L. B. Wu, J. G. Xiao, Q. P. Huang, Y. Liu, L. Q. Gu, D. H. Xu, B. J. Li, G. H. Weng, and K. Ma, *Youji Huaxue*, **15**, 221 (1995); b) Z. S. Huang, L. B. Wu, J. G. Xiao, Q. P. Huang, Y. Liu, L. Q. Gu, D. H. Xu, B. J. Li, G. H. Weng, and K. Ma, *Chem. Abstr.*, **122,** 286681 (1995).

[4] M. R. H. Elmoghayar, M. K. A. Ibrahim, and F. M. Darish, *Org. Prep. Proced. Int.*, **16,** 1 (1984).

[5] a) T. B. Wei, J. C. Chen, X. C. Wang, and Y. M. Zhang, *J. Chem. Res. (s)*, 138 (1995); b) Y. M. Zhang, T. B. Wei, and L. M. Gao, *Sythn. Commun.*, **31**(20), 3099 (2001); c) T. B. Wei, Q. Lin, Y. M. Zhang, W. Wei, *Synth. Commun.*, **34**(1), 175 (2004); d) Y. M., Zhang, L. Xian, and T. B. Wei, *Acta Cryst.*, **C59,** m473 (2003).

[6] C. W. Capp, A. H. Cook, J. D. Downer, S. I. Heilbron, *J. Chem. Soc.*, 1340 (1948).

[7] A. E. Dixon and J. Taylor, *J. Chem. Soc.*, **93,** 684 (1908).

[8] T. Akira, K. Hirai, and K. Mastsui, *Bull Chem. Soc. Jpn.*, **36,** 1214 (1963).

[9] T. Sano, K. Ohashi, and T. Oriyama, *Synthesis*, 1141 (1999).

[10] H. Kunz and H.-H. Bechtolsheimer, *Synthesis*, 303 (Ger) (1982).