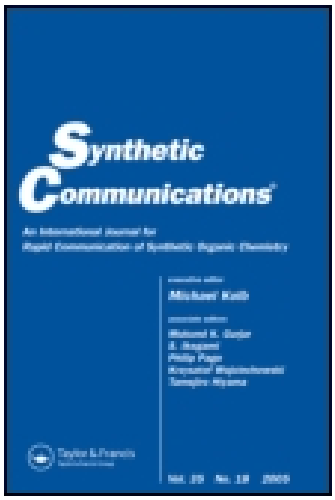


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

An Expeditious Room-Temperature Grinding Method to 5-Aryl-2-furoyl Substituted Thioureas and Thiosemicarbazides

Zhang Zhang [a] , Xicun Wang [a] & Zheng Li [a b]

[a] College of Chemistry and Chemical Engineering , Northwest Normal University , Lanzhou, Gansu, 730070, P.R. China

[b] School of Chemical and Biological Engineering , Lanzhou Jiaotong University , Lanzhou, Gansu, P.R. China

Published online: 21 Aug 2006.

To cite this article: Zhang Zhang , Xicun Wang & Zheng Li (2004) An Expeditious Room-Temperature Grinding Method to 5-Aryl-2-furoyl Substituted Thioureas and Thiosemicarbazides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:8, 1407-1414, DOI: 10.1081/SCC-120030690

To link to this article: http://dx.doi.org/10.1081/SCC-120030690

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 8, pp. 1407–1414, 2004

An Expeditious Room-Temperature Grinding Method to 5-Aryl-2-furoyl Substituted Thioureas and Thiosemicarbazides

Zhang Zhang,[1] Xicun Wang,[1] and Zheng Li[1,2,,*]

[1]College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu, P.R. China
[2]School of Chemical and Biological Engineering, Lanzhou Jiaotong University, Lanzhou, Gansu, P.R. China

ABSTRACT

An expeditious, one-pot, high-yielding and solventless approach to 5-aryl-2-furoyl substituted thioureas and thiosemicarbazides by room-temperature grinding method is described.

Key Words: Thiourea; Thiosemicarbazide; Solventless; Grinding.

*Correspondence: Zheng Li, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, P.R. China; E-mail: lizheng@nwnu.edu.cn.

DOI: 10.1081/SCC-120030690 0039-7911 (Print); 1532-2432 (Online)

INTRODUCTION

The development of solvent-free organic synthesis is of current interest because of the many advantages, such as reduced pollution, low cost, simplicity in process and handling, potential applications in combinatorial chemistry and chemical industry.[1]

Substituted thioureas and thiosemicarbazides have attracted much attention in recent years because of their anti-HIV,[2] bactericidal,[3] and tuberculostatic[4] activities, and their importance in the preparation of corresponding semicarbazides,[5] metal complexes,[6] and heterocyclic compounds.[7–9]

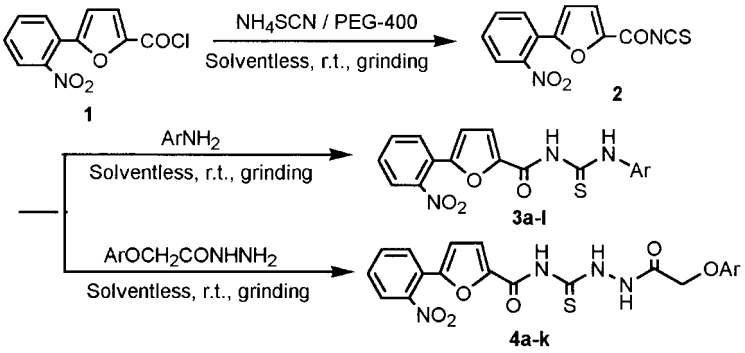
The existing synthetic methods for substituted thioureas and thiosemicarbazides have to conduct the reactions for extended period in the volatile and noxious organic solvents (methylene chloride or acetonitrile).[10–12] Therefore, there is still a need to investigate a new approach to overcome the above drawbacks. In continuation of our ongoing program to synthesize biologically active compounds and develop benign and rapid strategy for organic transformation under solventless conditions and the interest in green chemistry theme with growing emphasis on pollution prevention, we have explored an expeditious, one-pot and solvent-free route to prepare 5-aryl-2-furoyl substituted thioureas and thiosemicarbazides.

5-(2′-Nitrophenyl)-2-furoyl chloride (**1**) was ground with ammonium thiocyanate in the presence of poly(ethylene glycol)-400 (PEG-400) in a mortar at room temperature until the acid chloride **1** disappeared and 5-(2′-nitrophenyl)-2-furoyl isothiocyanate (**2**) was formed according to TLC analysis. In this reaction, PEG-400 acted as a catalyst, which can readily form the complex $(\text{PEG-400-NH}_4)^+\text{SCN}^-$ with ammonium thiocyanate to make the nucleophilic reaction of SCN^- with compound **1** easily take place. It is noteworthy that the reaction without PEG-400 is unavailable for compound **2**.

Compound **2** was in situ ground with equivalent of arylamines or aryloxyacetic acid hydrazides until the significant color changes were observed and the products, *N*-aryl-*N*′-(5-(2′-nitrophenyl)-2-furoyl)-thioureas (**3a–l**) or 1-aryloxyacetyl-4-(5′-(2″-nitrophenyl)-2′-furoyl)-thiosemicarbazides (**4a–k**), were formed. The completion of the reaction was monitored by TLC. Compound **3a–l** and **4a–k**, those are of acceptable purity for most purpose, were given in excellent yield only by washing the resulting solids using water. Furthermore, the by-product, ammonium chloride, can also be easily recovered from the aqueous solution by evaporation. The overall reaction can be completed within 8 min in 82–99% yield (Sch. 1). The results are shown in Table 1 and 2.

In conclusion, the title compounds can be expeditiously synthesized via room-temperature grinding method by one-pot procedure under solvent-free

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



Scheme 1.

Table 1. Solvent-free preparation of **3a–l** and **4a–k** by grinding method.

Compound	Ar	Reaction time (min)	M.p. (°C)	Yield (%)[a]
3a	C_6H_5	4	142–143	92
3b	2-$CH_3C_6H_4$	7	167–168	88
3c	4-$CH_3C_6H_4$	5	158–159	89
3d	2-ClC_6H_4	5	139–140	99
3e	4-ClC_6H_4	4	152–153	98
3f	2-$O_2NC_6H_4$	4	169–170	93
3g	3-$O_2NC_6H_4$	4	179–180	95
3h	2-$CH_3OC_6H_4$	5	198–199	93
3i	4-$CH_3COC_6H_4$	4	208–209	92
3j	2,4,6-$Br_3C_6H_2$	4	192–193	98
3k	1-Naphthyl	3	198–199	99
3l	2-Naphthyl	5	176–177	88
4a	C_6H_5	5	196–197	98
4b	2-$CH_3C_6H_4$	4	198–199	84
4c	4-$CH_3C_6H_4$	4	195–196	99
4d	4-$CH_3OC_6H_4$	5	185–186	82
4e	2-$O_2NC_6H_4$	5	237–238	83
4f	3-$O_2NC_6H_4$	4	246–247	82
4g	4-$O_2NC_6H_4$	5	196–197	95
4h	4-ClC_6H_4	5	202–203	86
4i	2,4-$Cl_2C_6H_3$	6	209–210	99
4j	1-Naphthyl	3	201–202	99
4k	2-Naphthyl	8	222–223	98

[a]Yields refer to the isolated products.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Table 2. IR and ^{1}H NMR data of **3a–l** and **4a–k**.

Compound	IR (cm^{-1}) N–H	C=O	C=S	^{1}H NMR (DMSO-d_6, δ)
3a	3210	1670	1152	6.98–8.36 (m, 11H, Ar-H, and Fu-H), 11.52 (s, 1H, NH), 12.01 (s, 1H, NH)
3b	3201	1673	1156	2.27 (s, 3H, CH_3), 7.09–8.30 (m, 10H, Ar-H, and Fu-H), 11.57 (s, 1H, NH), 12.04 (s, 1H, NH)
3c	3208	1669	1154	2.28 (s, 3H, CH_3), 7.10–8.32 (m, 10H, Ar-H, and Fu-H), 11.56 (s, 1H, NH), 12.03 (s, 1H, NH)
3d	3219	1671	1160	6.91–8.42 (m, 10H, Ar-H, and Fu-H), 11.62 (s, 1H, NH), 12.08 (s, 1H, NH)
3e	3220	1673	1162	7.11–8.47 (m, 10H, Ar-H, and Fu-H), 11.64 (s, 1H, NH), 12.09 (s, 1H, NH)
3f	3218	1670	1155	7.10–8.37 (m, 10H, Ar-H, and Fu-H), 11.77 (s, 1H, NH), 12.58 (s, 1H, NH)
3g	3221	1668	1160	7.08–8.39 (m, 10H, Ar-H, and Fu-H), 11.69 (s, 1H, NH), 12.55 (s, 1H, NH)
3h	3198	1665	1157	3.38 (s, 3H, CH_3), 6.99–8.37 (m, 10H, Ar-H, and Fu-H), 11.67 (s, 1H, NH), 12.43 (s, 1H, NH)
3i	3208	1670	1156	2.54 (s, 3H, CH_3), 7.32–8.31 (m, 10H, Ar-H, and Fu-H), 11.60 (s, 1H, NH), 12.28 (s, 1H, NH)
3j	3355	1689	1149	7.21–8.32 (m, 8H, Ar-H, and Fu-H), 11.78 (s, 1H, NH) 12.60 (s, 1H, NH)
3k	3221	1678	1152	7.12–8.04 (m, 12H, Ar-H, and Fu-H), 11.61 (s, 1H, NH) 12.34 (s, 1H, NH)
3l	3223	1681	1151	7.10–8.12 (m, 12H, Ar-H, and Fu-H), 11.52 (s, 1H, NH) 12.31 (s, 1H, NH)

(*continued*)

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Table 2. Continued.

Compound	IR (cm^{-1}) N–H	C=O	C=S	^{1}H NMR (DMSO-d_6, δ)
4a	3278 3173	1697 1670	1163	4.98 (s, 2H, OCH_2), 7.10–8.23 (m, 11H, Ar-H, and Fu-H), 11.01 (s, 1H, NH), 11.78 (s, 1H, NH), 12.28 (s, 1H, NH)
4b	3290 3154	1701 1672	1166	2.28 (s, 3H, CH_3), 5.03 (s, 2H, OCH_2), 6.98–8.20 (m, 10H, Ar-H, and Fu-H) 10.99 (s, 1H, NH), 11.72 (s, 1H, NH), 12.40 (s, 1H, NH)
4c	3284 3134	1674 1668	1165	2.27 (s, 3H, CH_3), 4.91 (s, 2H, OCH_2), 7.05–8.19 (m, 10H, Ar-H, and Fu-H), 10.97 (s, 1H, NH), 11.76 (s, 1H, NH), 12.38 (s, 1H, NH)
4d	3304 3146	1684 1672	1167	3.51 (s, 3H, CH_3), 4.96 (s, 2H, OCH_2), 7.11–8.27 (m, 10H, Ar-H, and Fu-H), 10.99 (s, 1H, NH), 11.81 (s, 1H, NH), 12.40 (s, 1H, NH)
4e	3268 3174	1676 1663	1166	5.04 (s, 2H, OCH_2), 7.12–8.36 (m, 10H, Ar-H and Fu-H), 11.12 (s, 1H, NH), 11.82 (s, 1H, NH), 12.56 (s, 1H, NH)
4f	3287 3170	1700 1670	1172	5.01 (s, 2H, OCH_2), 7.16–8.28 (m, 10H, Ar-H, and Fu-H), 11.08 (s, 1H, NH), 11.75(s, 1H, NH), 12.60 (s, 1H, NH)
4g	3301 3264	1690 1672	1169	4.99 (s, 2H, OCH_2), 7.29–8.30 (m, 10H, Ar-H, and Fu-H), 11.06 (s, 1H, NH), 11.97 (s, 1H, NH), 12.58 (s, 1H, NH)
4h	3298 3157	1679 1665	1165	5.00 (s, 2H, OCH_2), 7.09–8.30 (m, 10H, Ar-H, and Fu-H), 11.06 (s, 1H, NH), 11.70 (s, 1H, NH), 12.36 (s, 1H, NH)

(*continued*)

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

Table 2. Continued.

Compound	IR (cm^{-1}) N–H	IR (cm^{-1}) C=O	IR (cm^{-1}) C=S	^{1}H NMR (DMSO-d_6, δ)
4i	3280 3163	1674 1665	1170	5.01 (s, 2H, OCH_2), 7.03–8.23 (m, 9H, Ar-H, and Fu-H), 11.07 (s, 1H, NH), 11.82 (s, 1H, NH), 12.48 (s, 1H, NH)
4j	3285 3137	1680 1668	1165	4.94 (s, 2H, OCH_2), 7.01–8.36 (m, 13H, Ar-H, and Fu-H), 11.11 (s, 1H, NH), 11.81 (s, 1H, NH), 12.35 (s, 1H, NH)
4k	3276 3160	1684 1670	1164	5.01 (s, 2H, OCH_2), 7.04–8.34 (m, 13H, Ar-H, and Fu-H), 11.02 (s, 1H, NH), 11.83 (s, 1H, NH), 12.31 (s, 1H, NH)

condition in excellent yield. The features of no use of any hazardous solvents, high rate, and easy handling make this protocol to become a "green" and universal method for the preparation of substituted thioureas and thiosemicarbazides.

EXPERIMENTAL

IR spectra were recorded using KBr pellets on a Nicolet AVATAR 360 FT-IR spectrophotometer and ^{1}H NMR spectra on a Avanci-D2X-200 instrument using $(CD_3)_2SO$ as solvent and Me_4Si as internal standard. Elemental analyses were performed on a Vario El Elemental Analysis instrument. Melting points were observed in an open capillary tube and uncorrected. 5-(2′-Nitrophenyl)-2-furoyl chloride (**1**),[13] aryloxyacetic acid hydrazides[14] were prepared according to literature procedures.

General Procedure for Preparation of 3a–l and 4a–k

The mixture of 5-(2′-nitrophenyl)-2-furoyl chloride (**1**) (0.5 mmol), ammonium thiocyanate (0.5 mmol) and PEG-400 (0.02 mmol) was ground in an agate mortar with a pestle for 2 min, until a yellow solid was

formed, and TLC (ethyl acetate-benzene-ethyl ether 2 : 1 : 1 as eluent) indicated the disappearance of **1**. Then arylamine or aryloxyacetic acid hydrazide (0.5 mmol) was added, and the mixture was further ground for 1–6 min until a color change was observed. The completion of reaction was monitored by TLC using acetone as eluent. Then the resulting solid was washed with distilled water (10 mL) and the product was afforded as solid. The analytic sample was obtained by recrystallization from DMF-EtOH-H_2O (6 : 3 : 1).

ACKNOWLEDGMENT

The authors thank the Scientific and Technological Innovation Engineering of Northwest Normal University (NWNU-KJCXGC-02-08), Natural Science Foundation of Gansu Province (ZS021-A25-006-Z), Environmental Protection Foundation of Gansu Province (GH2002-16) for the financial support of this work.

REFERENCES

1. Tanaka, K.; Toda, F. Chem. Rev. **2000**, *100*, 1025.
2. Venkatachalam, K.; Sudbeck, E.A.; Mao, C.; Uckun, F.M. Bioorg. Med. Chem. Lett. **2001**, *11*, 523.
3. Rollas, S.; Karakus, S.; Durgun, B.B.; Kiraz, M.; Erdeniz, H. Farmaco **1996**, *51*, 811.
4. Milczarska, B.; Foks, H.; Sokolowska, J.; Janowiec, M.; Zwolska, Z.; Anrzejczyk, Z. Acta Pol. Pharm. **1999**, *56*, 121.
5. Li, Z.; Wang, X.C.; Da, Y.X.; Chen, J.C. Synth. Commun. **2001**, *31*, 1433.
6. Palaska, E.; Sahin, G.; Kelicen, P.; Durlu, N.T.; Altinok, G. Farmaco **2002**, *57*, 101.
7. Li, Z.; Wang, X.C.; Da, Y.X. Synth. Commun. **2001**, *31*, 1829.
8. Wang, X.C.; Li, Z.; Zhang, Z.H.; Da, Y.X. Synth. Commun. **2001**, *31*, 1907.
9. Mabrouk, H.E.; El-Asmy, A.A.; Al-Ansi, T.Y.; Mounir, M. Bull. Soc. Chim. Fr. **1991**, 309.
10. Li, Z.; Wang, X.C.; Da, Y.X.; Chen, J.C. Synth. Commun. **2000**, *30*, 2635.
11. Wei, T.B.; Chen, J.C.; Zhang, Y.M.; Wang, L.L. Synth. Commun. **1995**, *25*, 1885.
12. Wei, T.B.; Chen, J.C.; Wang, X.C.; Zhang, Y.M. J. Chem. Res. (s) **1995**, 138.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

13. Krutosikova, A.; Kovac, J.; Sykora, V. Collect. Czech. Chem. Commun. **1976**, *41*, 2577.
14. Hussain, M.I.; Amir, M. J. Indian Chem. Soc. **1986**, *63*, 317.

Received in Japan September 30, 2003

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016