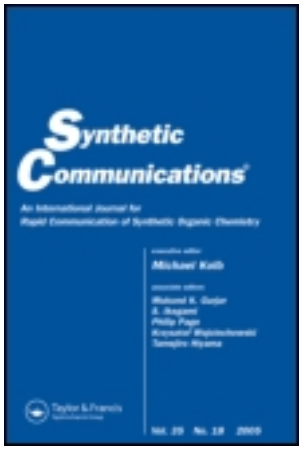


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Novel and Efficient Solid-State Synthesis of 3-Alkyl-6-Aryl-s-triazolo[3,4-b]-1,3,4-thiadiazine Derivatives

Xin-Ping Hui [a] , Ren-Zhong Qiao [a] , Peng-Fei Xu [a] & Zi-Yi Zhang [a]
[a] State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering , Lanzhou University , Lanzhou , China
Published online: 22 Aug 2006.

To cite this article: Xin-Ping Hui , Ren-Zhong Qiao , Peng-Fei Xu & Zi-Yi Zhang (2006) Novel and Efficient Solid-State Synthesis of 3-Alkyl-6-Aryl-s-triazolo[3,4-b]-1,3,4-thiadiazine Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:12, 1655-1660, DOI: 10.1080/00397910600616461

To link to this article: http://dx.doi.org/10.1080/00397910600616461

Synthetic Communications®, 36: 1655–1660, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910600616461

Novel and Efficient Solid-State Synthesis of 3-Alkyl-6-Aryl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazine Derivatives

Xin-Ping Hui, Ren-Zhong Qiao, Peng-Fei Xu, and Zi-Yi Zhang

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou, China

Abstract: A novel and efficient solid-state synthesis of *s*-triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives has been reported. Twelve 3-alkyl-6-aryl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives have been synthesized in excellent yields with short reaction time.

s-Triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives have been reported to show diverse biological activities, including analgesic, anti-inflammatory, antibacterial, and antiviral activities.[1–4] Recently, much interest has been paid to *s*-triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives.[5–8] The condensation of 4-amino-5-mercapto-3-substituted-1,2,4-triazoles with 2-halocarbonyl compounds has been carried out in solution. However, this cyclization afforded different products under various reaction conditions. There are also some problems associated with this synthesis, such as severe conditions, long reaction times, low to moderate yields, difficulty in separating the products, and serious environmental pollution.

Quite a few organic reactions proceed well in solid state. Moreover, solid-state organic synthesis has many advantages, including high efficiency and selectivity,[9] easy separation and purification,[10] and environmental

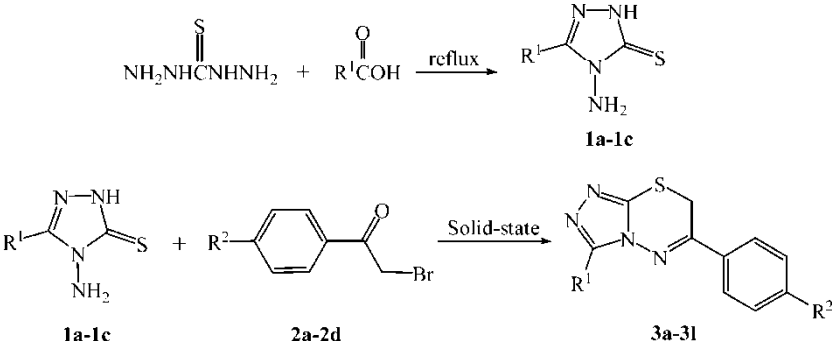
Received in R.O.C. December 8, 2005
Address correspondence to Xin-Ping Hui, State Key Laboratory of Applied Organic Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, China.

acceptability.[11,12] All these merits are in accord with the "green" requirements of energy saving and high efficiency. In recent years, this method hasa been widely used in a variety of organic syntheses, such as substitution,[13] condensation,[14] oxidation–reduction,[15,16] rearrangements,[17] and elimination reactions.[18] However, solid-state synthesis of *s*-triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives has not been reported. This article reports a novel and efficient solid-state condensation reaction of 3-alkyl-4-amino-5-mercapto-1,2,4-triazole with 2-bromo-4′- substituted acetophenone to afford new 3-alkyl-6-aryl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives (Scheme 1).

The target compounds **3a–l** were prepared by heating a mixture of 3-alkyl-4-amino-5-mercapto-1,2,4-triazole (**1a–c**) and 2-bromo-4′-substituted acetophenone (**2a–d**) carefully until melting occurred and were kept 20 min at this temperature. The results are listed in Table 1. From Table 1, we can see that 3-alkyl-4-amino-5-mercapto-1,2,4-triazole and 2-bromo-4′-substituted acetophenone readily participated in this reaction. The yields are high, and the reaction time is short, regardless of the variations in the substituent of the substrate.

The compounds synthesized were characterized by their elemental analyses and spectral data. Their IR spectra showed three characteristic absorption bands at 1583–1609 cm^{-1} (C=N), 1224–1266 cm^{-1} (N-N=C), and 658–691 cm^{-1} (C-S-C), respectively. In the ^1H NMR spectra, SCH_2 protons exhibited signals at around δ 4.0 ppm. Their mass spectra exhibited the expected molecular peaks.

In conclusion, we have developed a novel and efficient solid-state synthesis of 3-alkyl-6-aryl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives in high yields (85–92%) with a short working time (20 min) and easy purification. This procedure also avoids the use of organic solvent.



Scheme 1. $R^1 = n$-Pr, R^2=H (**3a**); $R^1 = n$-Pr, $R^2 = CH_3$ (**3b**); $R^1 = n$-Pr, R^2 = Cl (**3c**); $R^1 = n$-Pr, R^2 = Br (**3d**); $R^1 = n$-Bu, R^2 = H (**3e**); $R^1 = n$-Bu, $R^2 = CH_3$ (**3f**); $R^1 = n$-Bu, R^2 = Cl (**3g**); $R^1 = n$-Bu, R^2 = Br (**3h**); $R^1 = n$-Pentyl, R^2 = H (**3i**); $R^1 = n$-Pentyl, $R^2 = CH_3$ (**3j**); $R^1 = n$-Pentyl, R^2 = Cl (**3k**); $R^1 = n$-Pentyl, R^2 = Br (**3l**).

Table 1. Melting points, yields, and elemental analyses of compounds **3a–l**

Compd.	m.p. (°C)	Yield (%)	Found (Calcd.) (%)		
			C	H	N
3a	153–154	85	60.41 (60.44)	5.32 (5.46)	21.48 (21.69)
3b	175–176	90	61.56 (61.74)	5.73 (5.92)	20.41 (20.57)
3c	186–187	92	53.45 (53.33)	4.40 (4.48)	19.08 (19.14)
3d	191–192	87	46.14 (46.30)	3.94 (3.89)	16.38 (16.61)
3e	114–115	86	61.87 (61.74)	5.98 (5.92)	20.46 (20.57)
3f	140–141	91	62.73 (62.91)	6.14 (6.33)	19.41 (19.56)
3g	147–148	89	54.53 (54.81)	4.80 (4.93)	18.05 (18.26)
3h	163–164	88	47.94 (47.87)	4.55 (4.30)	15.80 (15.95)
3i	115–116	88	62.80 (62.91)	6.58 (6.33)	19.29 (19.56)
3j	107–108	90	64.14 (63.97)	6.52 (6.71)	18.43 (18.65)
3k	171–172	92	56.41 (56.15)	5.11 (5.34)	17.18 (17.46)
3l	177–178	91	49.13 (49.32)	4.87 (4.69)	15.08 (15.34)

EXPERIMENTAL

The melting points were determined on an X-4 microscopic melting-point apparatus and are uncorrected. Elementary analyses were carried out on Elementar Vario EL analyzer. IR spectra were obtained in KBr disc on a 5-DX spectrometer. ^{1}H NMR spectra were recorded in DMSO-d_6 solution on a Mercury-Plus 300 instrument with TMS as an internal standard. MS were performed on a VG-7070E spectrometer (EI at 70 eV).

3-Alkyl-4-amino-5-mercapto-1,2,4-triazoles (**1a–c**) were prepared according to the methods in the literature.[19]

General Procedure for Preparation of 3-Alkyl-6-aryl-s-triazolo[3,4-b]-1,3,4-thiadiazines (3a–l)

A mixture of 3-alkyl-4-amino-5-mercapto-1,2,4-triazoles **1** (0.01 mol) and 2-bromo-4′-substituted acetophenones **2** (0.01 mol) was heated carefully until melting occurred and then was kept at that temperature for 20 min. The reaction mixture was then cooled and mixed with water (50 mL), and the solid product was collected, washed with water, and finally recrystallized from ethanol to give (**3a–l**).

Data

3-Pr-6-phenyl-s-triazolo[3,4-b]-1,3,4-thiadiazines (3a). ^{1}H NMR (DMSO-d_6) δ: 1.06 (t, 3H, $J = 7.2$ Hz, $CH_3CH_2CH_2$), 1.64–2.09 (m, 2H,

$CH_3CH_2CH_2$), 2.94 (t, 2H, $J = 7.2$ Hz, CH_3CH_2 CH_2), 3.97 (s, 2H, SCH_2), 7.62 (s, 5H, ArH); IR (cm^{-1}) (KBr disc): 3051 (w, ArH), 2959, 2900 (w, CH_3, CH_2), 1578 (m, C=N), 1529 (m, C–N); EI-MS (m/z): 258 (M^+, 9), 230 (87), 127 (100), 103 (43), 84 (40), 77 (96).

3-Pr-6-(4-methylphenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazines (3b). ^{1}H NMR (DMSO-d_6) δ: 1.06 (t, 3H, $J = 7.2$ Hz, $CH_3CH_2CH_2$), 1.61–2.08 (m, 2H, $CH_3CH_2CH_2$), 2.46 (s, 3H, CH_3), 2.93 (t, 2H, $J = 7.2$ Hz, $CH_3CH_2CH_2$), 3.96 (s, 2H, SCH_2), 7.46 (d, 2H, $J = 8.8$ Hz, ArH), 7.78 (d, 2H, $J = 8.8$ Hz, ArH); IR (cm^{-1}) (KBr disc): 3036 (w, ArH), 2960, 2931 (w, CH_3, CH_2), 1610 (m, C=N), 1533 (m, C–N); EI-MS (m/z): 272 (M^+, 20), 244 (100), 204 (11), 153 (10), 127 (87), 117 (17), 91 (33).

3-Pr-6-(4-chlorophenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazines (3c). ^{1}H NMR (DMSO-d_6) δ: 1.06 (t, 3H, $J = 7.2$ Hz, $CH_3CH_2CH_2$), 1.66–2.12 (m, 2H, $CH_3CH_2CH_2$), 2.97 (t, 2H, $J = 7.2$ Hz, CH_3CH_2 CH_2), 3.99 (s, 2H, SCH_2), 7.52 (d, 2H, $J = 8.8$ Hz, ArH), 7.87 (d, 2H, $J = 8.8$ Hz, ArH); IR (cm^{-1}) (KBr disc): 3063 (w, ArH), 2958, 2922 (w, CH_3, CH_2), 1588 (m, C=N), 1526 (m, C–N); EI-MS (m/z): 292 (M^+, 5.4), 294 (2), 264 (54), 127 (100), 111 (25), 101 (45), 75 (44).

3-Pr-6-(4-bromophenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazines (3d). ^{1}H NMR (DMSO-d_6) δ: 1.06 (t, 3H, $J = 7.2$ Hz, $CH_3CH_2CH_2$), 1.68–2.10 (m, 2H, $CH_3CH_2CH_2$), 2.95 (t, 2H, $J = 7.2$ Hz, CH_3CH_2 CH_2), 4.00 (s, 2H, SCH_2), 7.48 (d, 2H, $J = 8.8$ Hz, ArH), 7.86 (d, 2H, $J = 8.8$ Hz, ArH); IR (cm^{-1}) (KBr disc): 3059 (w, ArH), 2957, 2922 (w, CH_3, CH_2), 1583 (m, C=N), 1526 (m, C-N); EI-MS (m/z): 336 (M^+, 11), 338 (11), 321 (2), 308 (96), 257 (10), 229 (3), 181 (9), 155 (23), 127 (94), 102 (51), 84 (29), 76 (22), 195 (6).

3-Bu-6-phenyl-s-triazolo[3,4-b]-1,3,4-thiadiazines (3e). ^{1}H NMR (DMSO-d_6) δ: 1.00 (t, 3H, $J = 7.2$ Hz, $CH_3(CH_2)_2CH_2$), 1.12–2.10 (m, 4H, $CH_3(CH_2)_2CH_2$), 2.98 (t, 3H, $J = 7.2$ Hz, $CH_3(CH_2)_2CH_2$), 4.06 (s, 2H, SCH_2), 7.67 (s, 5H, ArH); IR (cm^{-1}) (KBr disc): 3045 (w, ArH), 2965, 2933 (w, CH_3, CH_2), 1599 (m, C=N), 1527 (m, C–N); EI-MS (m/z): 272 (M^+, 7), 243 (21), 230 (100), 169 (8), 140 (13), 127 (28), 103 (6).

3-Bu-6-(4-methylphenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazines (3f). ^{1}H NMR (DMSO-d_6) δ: 1.00 (t, 3H, $J = 7.2$ Hz, $CH_3(CH_2)_2CH_2$), 1.12–2.12 (m, 4H, $CH_3(CH_2)_2CH_2$), 2.37 (s, 3H, $ArCH_3$), 2.97 (t, 3H, $CH_3(CH_2)_2CH_2$), 4.03 (s, 2H, SCH_2), 7.67 (d, 2H, $J = 8.8$ Hz, ArH), 7.82 (d, 2H, $J = 8.8$ Hz, ArH); IR (cm^{-1}) (KBr disc): 3038 (w, ArH), 2955, 2930 (w, CH_3, CH_2), 1594 (m, C=N), 1530 (m, C–N); EI-MS (m/z): 286 (M^+, 14), 257 (21), 244 (100), 229 (4), 204 (9), 169 (8), 140 (30), 127 (81), 117 (14), 91 (33).

3-Bu-6-(4-chlorophenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazines (3g). ^{1}H NMR (DMSO-d_6) δ: 1.00 (t, 3H, $J = 7.2$ Hz, $CH_3(CH_2)_2CH_2$), 1.10–2.12 (m, 4H, $CH_3(CH_2)_2CH_2$), 3.00 (t, 3H, $CH_3(CH_2)_2CH_2$), 4.00 (s, 2H, SCH_2), 7.45

(d, 2H, $J = 8.8$ Hz, ArH), 7.72 (d, 2H, $J = 8.8$ Hz, ArH); IR (cm^{-1}) (KBr disc): 3041 (w, ArH), 2956, 2929 (w, CH_3, CH_2), 1590 (m, C═N), 1525 (m, C–N); EI-MS (m/z): 306 (M^+, 5.4), 308 (2), 264 (57), 127 (100), 111 (25), 101 (52), 75 (50).

3-Bu-6-(4-bromophenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazines (3h). ^1H NMR (DMSO-d_6) δ: 1.00 (t, 3H, $J = 7.2$ Hz, $CH_3(CH_2)_2CH_2$), 1.12–2.14 (m, 4H, $CH_3(CH_2)_2CH_2$), 3.01 (t, 3H, $CH_3(CH_2)_2CH_2$), 4.02 (s, 2H, SCH_2), 7.60 (d, 2H, $J = 8.8$ Hz, ArH), 7.76 (d, 2H, $J = 8.8$ Hz, ArH); IR (cm^{-1}) (KBr disc): 3060 (w, ArH), 2959, 2932 (w, CH_3, CH_2), 1584 (m, C═N), 1522 (m, C–N); EI-MS (m/z): 350 (M^+, 1.4), 352 (2), 308 (15), 183 (11), 155 (13), 140 (30), 127 (91), 102 (65), 80 (100).

3-Penty-6-phenyl-s-triazolo[3,4-b]-1,3,4-thiadiazines (3i). ^1H NMR (DMSO-d_6) δ: 0.92 (t, 3H, $J = 7.2$ Hz, CH_3), 1.19–1.56 (m, 4H, $CH_3(CH_2)_2(CH_2)_2$, 1.70–1.96 (m, 2H, $CH_3(CH_2)_2CH_2$ CH_2, 3.04 (t, $J = 7.2$ Hz, $CH_3(CH_2)_3CH_2$), 4.00 (s, 2H, SCH_2), 7.58 (s, 5H, ArH); IR (cm^{-1}) (KBr disc): 3065 (w, ArH), 2954, 2930 (w, CH_3, CH_2), 1593 (m, C═N), 1533 (m, C–N); EI-MS (m/z): 286 (M^+, 6), 257 (27), 230 (86), 127 (100), 103 (16), 77 (87).

3-Penty-6-(4-methylphenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazines (3j). ^1H NMR (DMSO-d_6) δ: 0.92 (t, 3H, $J = 7.2$ Hz, CH_3), 1.19–1.56 (m, 4H, $CH_3(CH_2)_2(CH_2)_2$, 1.70–1.96 (m, 2H, $CH_3(CH_2)_2CH_2$ CH_2, 2.47 (s, 3H, $ArCH_3$), 2.99 (t, $J = 7.2$ Hz, CH_3 $(CH_2)_3CH_2$), 3.97 (s, 2H, SCH_2), 7.34 (d, 2H, $J = 8.8$ Hz, ArH), 7.81 (d, 2H, $J = 8.8$ Hz, ArH); IR (cm^{-1}) (KBr disc): 3050 (w, ArH), 2961, 2924 (w, CH_3, CH_2), 1588 (m, C═N), 1523 (m, C–N); EI-MS (m/z): 300 (M^+, 21), 272 (28), 257 (70), 244 (100), 204 (11), 186 (8), 140 (58), 127 (67), 117 (16), 91 (41).

3-Penty-6-(4-chlorophenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazines (3k). ^1H NMR (DMSO-d_6) δ: 0.92 (t, 3H, $J = 7.2$ Hz, CH_3), 1.18–1.54 (m, 4H, $CH_3(CH_2)_2(CH_2)_2$, 1.74–1.97 (m, 2H, $CH_3(CH_2)_2CH_2CH_2$, 3.03 (t, $J = 7.2$ Hz, $CH_3(CH_2)_3CH_2$), 4.02 (s, 2H, SCH_2), 7.42 (d, 2H, $J = 8.8$ Hz, ArH), 7.84 (d, 2H, $J = 8.8$ Hz, ArH); IR (cm^{-1}) (KBr disc): 3098 (w, ArH), 2957, 2925 (w, CH_3, CH_2), 1589 (m, C═N), 1532 (m, C–N); EI-MS (m/z): 320 (M^+, 5.3), 322 (2), 264 (61), 154 (24), 140 (100), 127 (74), 111 (24), 101 (50), 84 (75), 75 (58).

3-Penty-6-(4-bromophenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazines (3l). ^1H NMR (DMSO-d_6) δ: 0.92 (t, 3H, $J = 7.2$ Hz, CH_3), 1.18–1.56 (m, 4H, $CH_3(CH_2)_2(CH_2)_2$, 1.72–1.96 (m, 2H, $CH_3(CH_2)_2CH_2CH_2$, 3.02 (t, $J = 7.2$ Hz, $CH_3(CH_2)_3CH_2$), 4.06 (s, 2H, SCH_2), 7.67 (d, 2H, $J = 8.8$ Hz, ArH), 7.82 (d, 2H, $J = 8.8$ Hz, ArH); IR (cm^{-1}) (KBr disc): 3040 (w, ArH), 2959, 2928 (w, CH_3, CH_2), 1590 (m, C═N), 1528 (m, C–N); EI-MS (m/z): 364 (M^+, 7), 366 (8), 335 (8), 321 (44), 308 (63), 285 (6), 250 (7), 195 (8), 181 (20, 168 (18), 155 (20), 140 (89), 127 (100), 102 (64), 76 (22).

ACKNOWLEDGMENT

We are grateful for financial support from the National Natural Science Foundation of China (No. 20021001) and Natural Science Foundation of Gansu Province (3ZS051-A25-005).

REFERENCES

1. Prasad, A. R.; Ramalingam, T.; Rao, A. B.; Diwan, P. V.; Sattur, P. B. *Eur. J. Med. Chem.* **1989**, *24* (2), 199.
2. Turan-Zitouni, G.; Kaplancikli, Z. A.; Erol, K.; Kilic, F. S. *Il Farmaco* **1999**, *54* (4), 218.
3. Holla, B. S.; Kalluraya, B.; Sridhar, K. R.; Drake, E.; Thomas, L. M.; Bhandary, K. K.; Levine, M. J. *Eur. J. Med. Chem.* **1994**, *29* (4), 301.
4. Holla, B. S.; Akberali, P. M. *Il Farmaco* **2001**, *56* (12), 919.
5. Shaaban, M. R.; Fuchigami, T. *Tetrahedron Lett.* **2002**, *43* (2), 273.
6. Mosselhi, M. A. N.; Abdallah, M. A.; Mohamed, Y. F.; Shawali, A. S. *Phosphorous, Sulfur Silicon Relat. Elem.* **2002**, *177* (2), 487.
7. Xiong, Y.; Zhang, L. X.; Zhang, A. J.; Xu, D. J. *Synth. Commun.* **2002**, *32* (22), 3455.
8. Vainilavicius, P.; Smicius, R.; Jakubkiene, V.; Tumkevicius, S. *Monatsh. Chem.* **2001**, *132* (7), 825.
9. Desiraju, G. R. *Organic Solid State Chemistry*; Elsevier Science Publishers B. V.: Amsterdam, 1987; p. 179.
10. Rasmussen, M. O.; Axelsson, O.; Tanner, D. *Synth. Commun.* **1997**, *27*, 4027.
11. Li, X. L.; Wang, Y. M.; Meng, J. B.; Du, C. P. *Chin. J. Org. Chem.* **1998**, *18*, 20; Chem. Abstr. **1998**, 128, 153675k.
12. Zhou, Y. M.; Xin, X. Q. *Chin. J. Inorg. Chem.* **1999**, *15*, 273; Chem. Abstr. **1999**, *131*, 81995b.
13. Goff, D. A.; Zuckermann, R. N. *J. Org. Chem.* **1995**, *60*, 5744.
14. Toda, F.; Tanaka, K.; Hamai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3207.
15. Morey, J.; Frontera, A. *J. Chem. Edu.* **1995**, *72*, 63.
16. Morey, J.; Saa, J. M. *Tetrahedron* **1993**, *49*, 105.
17. Toda, F.; Shigemasa, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 209.
18. Toda, F.; Takumi, H.; Akehi, M. *J. Chem. Soc., Chem. Commmun.* **1990**, 1270.
19. Mohan, J. *Indian J. Chem.* **1983**, *22B*, 270.