The Free Internet Journal for Organic Chemistry

Paper

Archive for Organic Chemistry

Arkivoc **2017**, part v, 293-300

Efficient three-component synthesis of *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines under solvent-free condition

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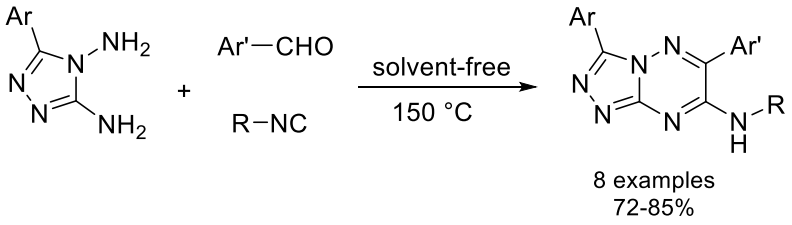
Received 05-18-2017 **Accepted** 09-22-2017 **Published on line** 11-19-2017

Abstract

A simple, efficient and environment-friendly approach is described for the synthesis of *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines based on three-component reaction between 5-aryl-4*H*-1,2,4-triazole-3,4-diamine, isocyanide and aldeyhde under solvent-free condition. The products are obtained in moderate to good yields and are in a state of high purity.



Keywords: Three-component reaction, *N*-Alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines, 5-aryl-4*H*-1,2,4-triazole-3,4-diamine, isocyanide, aldehyde

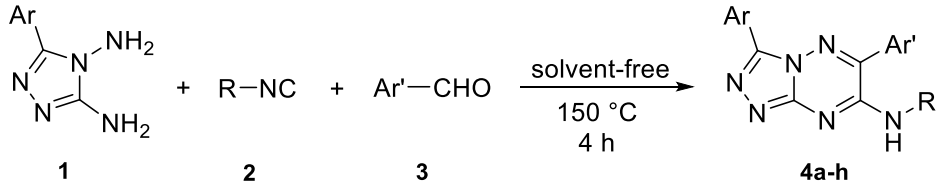
Introduction

The development of eco-friendly synthetic approaches is a major challenge for synthetic chemists. One of the most promising approaches is the solvent-free organic synthesis. These reactions may provide greater selectivity, precede with enhanced reaction rates, give cleaner products, and involve simple manipulation.[1-6] Nitrogen-containing heterocyclic compounds and their analogous are pharmaceutically attractive scaffolds and widely exist in naturally occurring and synthetic biologically active molecules.[7-11] Among them, fused polycyclic nitrogen-containing heteroaromatics have received much synthetic attention because of their high therapeutic values. These N-fused polycycles displayed a wide range of biological activities such as anticancer, antibacterial, antifungal, antiplasmodial, antineoplastic and DNA intercalators.[12-16] For instance, diverse compounds derived from 1,2,4-triazoles are well known as antibacterial, antifungal, antiviral, antiinflammatory, antihypertensive, and hypoglycemic agents.[17-23] They also show herbicidal and antimicrobial activities making them a popular target for new drug development.[24-26] Another example of *N*-containing biologically active heterocycles is 1,2,4-triazine-based derivatives which have been reported to possess anti-AIDS, antitumoural, anticancer, antiviral and antimicrobial activities.[27-31]

Owing to this broad range of properties of *N*-containing triazole and triazine heterocycles, it is also reasonable to expect that fused triazole-triazine derivatives have significant biological activity. So, in this paper, we intend to describe an efficient and eco-friendly approach for the synthesis of *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines under solvent-free condition. To date, this is the first report on the synthesis of this fused N-containing heterocyclic compounds.

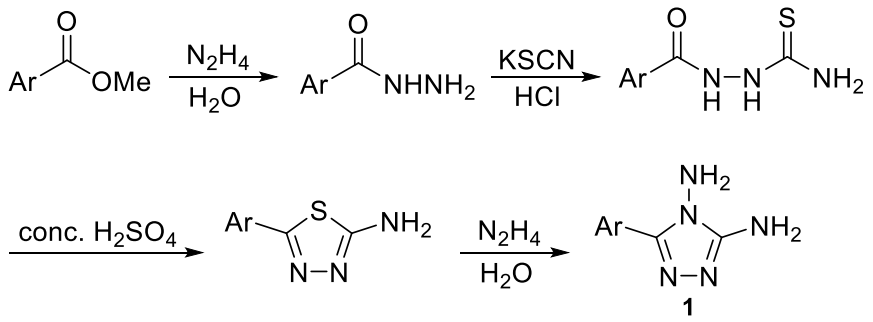
Results and Discussion

In continuation of our researches on preparation of N-containing organic compounds,[32-37] herein, we report a novel and efficient approach for the green synthesis of *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines **4a–h**, *via* three-component reaction of 5-aryl-4*H*-1,2,4-triazole-3,4-diamine **1**, isocyanide **2**, and aldeyhde **3**, under solvent-free condition at 150 °C (Scheme 1). The reactions went to completion within 4 hours and the corresponding products **4** were obtained in 68–82% yields. All the products were characterized by ^{1}H and ^{13}C NMR spectral data. No product other than **4** could be detected by NMR spectroscopy. The results are summarized in the Table 1.



Scheme 1. Three-component synthesis of the *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines.

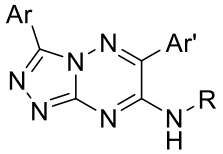
The 5-aryl-4*H*-1,2,4-triazole-3,4-diamines **1** were prepared based on four-step procedure reported by Gupta[38] shown in Scheme 2.



Ar = 4-NO_2-C_6H_4, 4-Cl-C_6H_4, 4-MeO-C_6H_4, 3,4-Cl_2-C_6H_3

Scheme 2. Three-component synthesis of the *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7-amines.

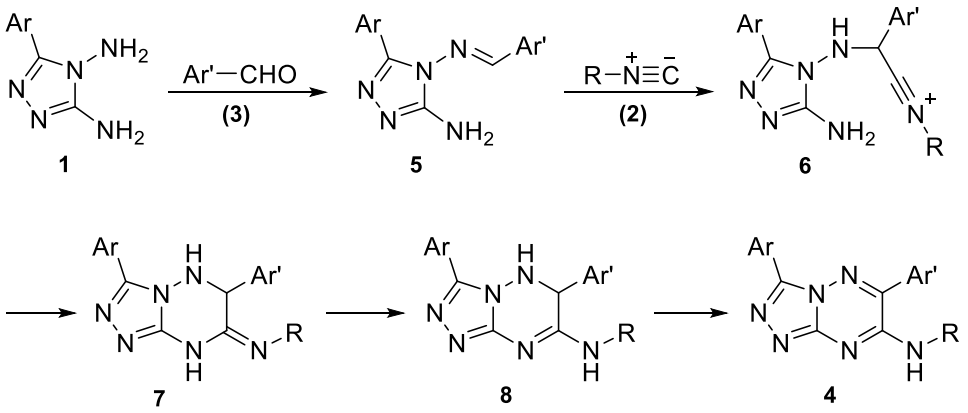
Table 1. Synthesis of *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines



Product	Ar	Ar′	R	Yield (%)[a]
4a	4-NO_2-C_6H_4	C_6H_5	*t*-Bu	72
4b	4-Cl-C_6H_4	2-CH_3-C_6H_4	*t*-Bu	75
4c	4-MeO-C_6H_4	3-NO_2-C_6H_4	Cyclohexyl	82
4d	4-Cl-C_6H_4	C_6H_5	Cyclohexyl	85
4e	4-Cl-C_6H_4	3-NO_2-C_6H_4	Cyclohexyl	78
4f	4-Cl-C_6H_4	2-Cl-C_6H_4	Cyclohexyl	74
4g	4-NO_2-C_6H_4	2-Cl-C_6H_4	Cyclohexyl	80
4h	3,4-Cl_2-C_6H_3	3-NO_2-C_6H_4	Cyclohexyl	78

[a] Yield of isolated products.

To explain the formation of *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines **4**, a plausible reaction mechanism is proposed in Scheme 3. Initially, due to the stronger nucleophilicity of the amino group at position 4 of the five-member ring in contrast to the amino group at position 3,[39,40] it is reasonable to assume that imine intermediate **5** is formed by condensation of 5-aryl-4*H*-1,2,4-triazole-3,4-diamine **1** with aldehyde **3**. Then, the nucleophilic addition of isocyanide **2** to this intermediate results in formation of intermediate **6**, which undergoes the intramolecular cyclization of amino group with triple bond followed by tautomerization and aerobic oxidation affords the *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines **4** (Scheme 2).



Scheme 3. Plausible mechanism for synthesis of the *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines.

Conclusions

In conclusion, a straightforward and eco-friendly approach for the synthesis of *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines based on three-component reaction between 5-aryl-4*H*-1,2,4-triazole-3,4-diamine, isocyanide and aldeyhde under solvent-free condition is described. The simplicity of starting materials, moderate to good yields of the products and use of solvent-free conditions are the main advantages of this method.

Experimental Section

General. All chemicals were purchased from Merck and Fluka companies. All yields refer to isolated products. IR spectra were recorded on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker, Rheinstetten, Germany (at 500 and 400 MHz) NMR spectrometer using tetramethylsilane (TMS) as internal standard. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. Melting points were determined in a capillary tube and are not corrected. The progress of reaction was followed with TLC using silica gel SILG/UV 254 and 365 plates. All products are known compounds and their structures were deduced by ^{1}H and ^{13}C NMR spectroscopy as well as elemental analysis.

General procedure for the preparation of products 4a–4h. A mixture of appropriate 5-aryl-4*H*-1,2,4-triazole-3,4-diamine **1** (1.0 mmol), isocyanide **2** (1.0 mmol), and aldeyhde **3** (1.0 mmol) was stirred in a sealed vessel at 150 °C under solvent-free condition for 4–9 h. After reaction completion (TLC), the reaction mixture was cooled to room temperature and the crude product was purified by column chromatography on silica gel using hexane–EtOAc (4:1) as eluent to afford products **4a–4h** (Table 1).

***N*-(*tert*-butyl)-3-(4-nitrophenyl)-6-phenyl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amine (4a).** White solid, mp 218–220 °C; IR (KBr): 3379, 2936, 2875, 1628, 1500, 1548, 1423, 1366cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.99 (s, 9H), 4.65 (s, 1H), 7.19–7.22 (m, 3H), 7.51 (d, *J* 9.0 Hz), 8.05 (d, *J* 8.0 Hz), 8.51 (d, *J* 8.0 Hz) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 29.9, 59.9, 118.2, 121.5, 121.7, 124.3, 124.5, 127.5, 127.6, 128.4, 128.5, 132.0, 136.3, 149.3 ppm; Anal. Calcd for $C_{20}H_{19}N_7O_2$: C, 61.69; H, 4.92; N, 25.18. Found: C, 61.61; H, 4.90; N, 25.16.

***N*-(*tert*-butyl)-3-(4-chlorophenyl)-6-(2-tolyl)-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amine (4b)**: White solid, mp224–226 °C; IR (KBr): 3370, 2930, 2852, 1601, 1570, 1565, 1489, 1382 cm-1. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.99 (s, 9H), 2.32 (s, 1H), 4.56 (s, 1H), 6.85 (t, *J* 7.0 Hz), 7.15 (t, *J* 7.0 Hz), 7.19 (d, *J* 8.0 Hz, 2H), 7.44 (d, *J* 7.0 Hz, 1H), 8.05 (d, *J* 8.0 Hz, 2H), 8.38 (d, *J* 7.0 Hz, 1H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 20.8, 30.0, 55.6,

116.3, 123.5, 123.8, 123.9, 124.0, 127.5, 127.6, 128.3, 128.4, 129.2, 132.4, 135.9, 137.9, 140.8 ppm; Anal. Calcd for $C_{21}H_{21}ClN_6$: C, 64.20; H, 5.39; Cl, 9.02; N, 21.39. Found: C, 64.11; H, 5.30; Cl, 8.96; N, 21.23.

***N*-cyclohexyl-3-(4-methoxyphenyl)-6-(3-nitrophenyl)-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amine (4c)**: Pale yellow solid, mp 188–190 °C; IR (KBr): 3277, 2944, 2856, 1654, 1527, 1530, 1428, 1338 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.08–1.70 (m, 10H), 2.81–2.84 (m, 1H), 4.00 (s, 3H), 4.79 (d, *J* 6.0 Hz, 1H), 7.17 (d, *J* 7.5 Hz, 1H), 7.28 (d, *J* 7.5 Hz, 1H), 7.40 (t, *J* 7.5 Hz, 1H), 7.51 (d, *J* 8.0 Hz, 2H), 8.13 (t, *J* 7.5 Hz, 1H), 8.33 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 24.3, 25.3, 33.4, 49.8, 56.2, 111.3, 111.5, 116.2, 123.2, 123.9, 124.9, 125.3, 127.7, 129.6, 130.0, 130.6, 134.2, 136.6, 143.1, 157.1 ppm; Anal. Calcd for $C_{23}H_{23}N_7O_3$: C, 62.01; H, 5.20; N, 22.01; Found: C, 61.92; H, 5.12; N, 21.93.

3-(4-chlorophenyl)-*N*-cyclohexyl-6-phenyl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amine (4d): White solid, mp 212–214 °C; IR (KBr): 3294, 2973, 2844, 1600, 1528, 1483, 1351cm-1. ^1H NMR (DMSO-d_6, 500 MHz): δ 0.91–1.59 (m, 10H), 2.68–2.73 (m, 1H), 4.53 (s, 1H), 7.16 (m, 2H), 7.39–7.44 (m, 2H), 7.50–7.58 (m, 3H), 8.43 (d, *J* 8.0 Hz, 2H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 24.0, 25.2, 32.9, 54.5, 118.6, 120.5, 120.7, 123.5, 126.5, 126.7, 127.4, 129.3, 132.3, 132.9, 133.8, 137.9 ppm; Anal. Calcd for $C_{22}H_{21}ClN_6$: C, 65.26; H, 5.23; Cl, 8.76; N, 20.76. Found: C, 65.21; H, 5.15; Cl, 8.70; N, 20.71.

3-(4-chlorophenyl)-N-cyclohexyl-6-(3-nitrophenyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7-amine (4e): White solid, mp 185–187 °C; IR (KBr): 3270, 2900, 2810, 1628, 1544, 1525, 1489, 1366cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.09–1.71 (m, 10H), 2.80–2.82 (m, 1H), 4.78 (d, *J* =6.0 Hz, 1H), 7.09 (d, *J* 7.5 Hz, 1H), 7.18–7.31 (m, 3H), 7.34 (d, *J* 7.5 Hz, 1H), 7.51 (d, *J* 8.0 Hz, 2H), 8.13 (d, *J* 7.5 Hz, 1H), 8.33 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 24.4, 25.3, 33.4, 52.8, 114.5, 117.2, 118.5, 120.8, 124.3, 124.6, 124.6, 127.7, 127.9, 128.1, 128.7, 157.3, 160.0 ppm; ; Anal. Calcd for $C_{22}H_{20}ClN_7O_2$: C, 58.73; H, 4.48; Cl, 7.88; N, 21.79. Found: C, 58.66; H, 4.41; Cl, 7.80; N, 21.71.

6-(2-chlorophenyl)-3-(4-chlorophenyl)-*N*-cyclohexyl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amine (4f): Yellow solid, mp 190–192 °C; IR (KBr): 3230, 2917, 2860, 1625, 1587, 1555, 1364 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.09–1.72 (m, 10H), 2.79 (m, 1H), 4.68 (d, *J* 6.0 Hz, 1H), 6.84 (t, *J* 7.5 Hz, 1H), 7.07 (d, *J* 7.5 Hz, 1H), 7.14 (t, *J* 7.5 Hz, 1H), 7.27 (d, *J* 8.0 Hz, 2H), 7.42 (d, *J* 7.5 Hz, 1H), 7.87 (d, *J* 8.0 Hz, 1H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 24.4, 25.3, 33.4, 52.0, 111.0, 114.4, 116.4, 121.3, 123.1, 123.4, 124.6, 127.7, 130.1, 131.6, 135.3, 140.3, 157.1 ppm; Anal. Calcd for $C_{22}H_{20}Cl_2N_6$: C, 60.14; H, 4.59; Cl, 16.14; N, 19.13. Found: C, 60.04; H, 4.43; Cl, 16.01; N, 19.02.

6-(2-chlorophenyl)-*N*-cyclohexyl-3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amine (4g): White solid, mp 202–204 °C; IR (KBr): 3285, 2900, 2827, 1615, 1577, 1515, 1479, 1365 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.12–1.79 (m, 10H), 2.85–2.90 (m, 1H), 4.98 (s, 1H), 7.23 (t, *J* 7.5 Hz, 1H), 7.52 (d, *J* 7.5 Hz, 1H), 7.73 (t, *J* 7.5 Hz, 1H), 8.11 (d, *J* 8.0 Hz, 2H), 8.36 (d, *J* 7.5 Hz, 1H), 8.66 (d, *J* 8.0 Hz, 2H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 24.4, 25.3, 33.5, 56.7, 116.8, 117.0, 121.1, 121.1, 123.5, 123.6, 124.4, 124.6, 129.7, 132.0, 132.2, 136.3, 140.7, 148.1 ppm; Anal. Calcd for $C_{22}H_{20}ClN_7O_2$: C, 58.73; H, 4.48; Cl, 7.88; N, 21.79. Found: C, 58.67; H, 4.40; Cl, 7.74; N, 21.68.

***N*-cyclohexyl-3-(3,4-dichlorophenyl)-6-(3-nitrophenyl)-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amine (4h)**: White solid, mp 217–219 °C; IR (KBr): 3280, 2925, 2847, 1615, 1577, 1535, 1479, 1360 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.11–1.78 (m, 10H), 2.84–2.88 (m, 1H), 5.05 (s, 1H), 7.26 (d, *J* 9.5 Hz, 1H), 7.58 (d, *J* 9.5 Hz, 1H), 7.74 (t, *J* 8.0 Hz, 1H), 8.14 (d, *J* 8.0 Hz, 1H), 8.57 (s, 1H), 8.63 (d, *J* 8.0 Hz, 1H) 9.09 (d, *J* 8.0 Hz, 1H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 24.5, 25.2, 33.5, 56.9, 119.0, 120.3, 120.6, 121.2, 121.3, 125.1, 127.8, 129.8, 132.0, 132.1, 132.7, 135.9, 139.0, 148.1 ppm; Anal. Calcd for $C_{22}H_{19}Cl_2N_7O_2$: C, 54.56; H, 3.95; Cl, 14.64; N, 20.24. Found: C, 54.48; H, 3.83; Cl, 14.53; N, 20.17.

Acknowledgements

This research was supported by a grant from Iran National Science Foundation (INSF).

Supplementary Material

General information, General procedure for the preparation of products **4a**-**4h**, Characterization data for compounds **4a**-**4h**, Copies of ^{1}H and ^{13}C NMR Spectra.

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