Tetrahedron Letters 50 (2009) 1667–1670

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Rapid, microwave-assisted synthesis of N1-substituted 3-amino-1,2,4-triazoles

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ARTICLE INFO

Article history:
Received 22 November 2008
Revised 8 December 2008
Accepted 9 December 2008
Available online 16 December 2008

ABSTRACT

A robust, regioselective synthesis of 3-amino-1,2,4-triazoles is described. This reaction employs a key intermediate **2**, which is coupled to carboxylic acids in good yields to afford intermediates **3a–d**. These entities, in turn, react with a variety of hydrazines or hydrazine hydrochlorides to provide proposed intermediates **4a–j**, which under microwave conditions cyclize to the desired 3-amino-1,2,4-triazoles (compounds **5a–j**). This approach permits the rapid synthesis of regioselective N1-substituted 3-amino-1,2,4-triazoles, and is shown to afford a variety of such compounds in 34–70% isolated yields.

N1-substituted 3-amino-1,2,4-triazoles have shown numerous beneficial pharmaceutical properties and have been utilized as antiviral agents,[1] CCK-A agonists,[2] and urinary tract antibacterial agents.[3] As part of our efforts to develop novel anticancer drugs, we required a rapid, divergent synthesis of such molecules which could be performed in a parallel manner and which would provide sufficient amounts of purified materials for multiple biological assessments (>100 mg). Unfortunately, none of the existing methods for 3-amino-1,2,4-triazole synthesis met our needs since they were (1) limited in scope,[4] (2) not regiospecific,[5] or (3) performed on solid phase which limited the scale of preparation.[6,7] Accordingly, we sought to develop a new method for the synthesis of the desired compounds which (1) would incorporate at least two diverse functional points on the triazole core, (2) would utilize commercially available starting materials, (3) would allow the parallel generation of a large number of triazole products in high yield, and (4) would provide the desired compounds in larger quantities (>100 mg). The results of our efforts are described below.

Commercially available carbonic acid benzyl ester 4-nitrophenyl ester (**1**) was reacted with *S*-methylisothiouronium sulfate to give the key intermediate **2** in 95% yield (Scheme 1).[8] Compound **2** was coupled with four different carboxylic acids using EDC/HOBt to give intermediates **3a–d**. These intermediates were purified by silica gel chromatography and were subsequently reacted with various hydrazines under microwave conditions to afford the triazole products. For example, condensation of **3a** with (4-fluorobenzyl)-hydrazine in a microwave at 160 °C for 30 min afforded a 70% isolated yield of compound **5a** (Table 1, entry 1).[9] The position of the 4-fluorobenzyl group present in compound **5a** was determined by 2D-NOESY-1H NMR (Fig. 1). This substitution position is consistent with a proposed triazole-forming reaction sequence in which the unsubstituted hydrazine nitrogen displaces the thioether present in compound **3a** to afford intermediate **4a**. Excess hydrazine then cleaves the carbamate group at the C3 amino moiety either before or after the intramolecular cyclization/dehydration[10] affords the observed amino-triazole product (route A, Scheme 1). This sequence of microwave-assisted chemical reactions is supported by the observation of **5a** in the crude reaction mixture by LC–MS with no detection of the other possible cyclized product (**6a**, route B, Scheme 1). Compounds **3a–d** reacted with (4-fluorobenzyl)-hydrazine to afford the corresponding amino-triazole products (**5a–d**) in 50–70% isolated yields following preparative reverse phase HPLC.

Six additional compounds containing a 2,4-dichloro-benzyl substituent at the C5 position were then synthesized using the method described above. The results of the yields for the last two steps and the analytical data (^{1}H NMR and microanalysis) for the final compounds are summarized in Table 2. Based on these results, independent of the nature of the hydrazines, this microwave-assisted cyclization reaction for the formation of N1-substituted 1,2,4-triazoles gave 34–70% isolated yields following preparative reverse phase HPLC.

In summary, we report a microwave-assisted synthesis of N1-substituted 1,2,4-triazoles in reasonable yields. This three-step methodology using commercially available carboxylic acids and hydrazines can generate regioselective N1-substituted 1,2,4-triazoles in an efficient way. In addition to these advantages, the triazoles synthesized can serve as starting materials for further acylation[11–13] or alkylation[14] to afford tri-substituted trizoles with regioselective substitution patterns.

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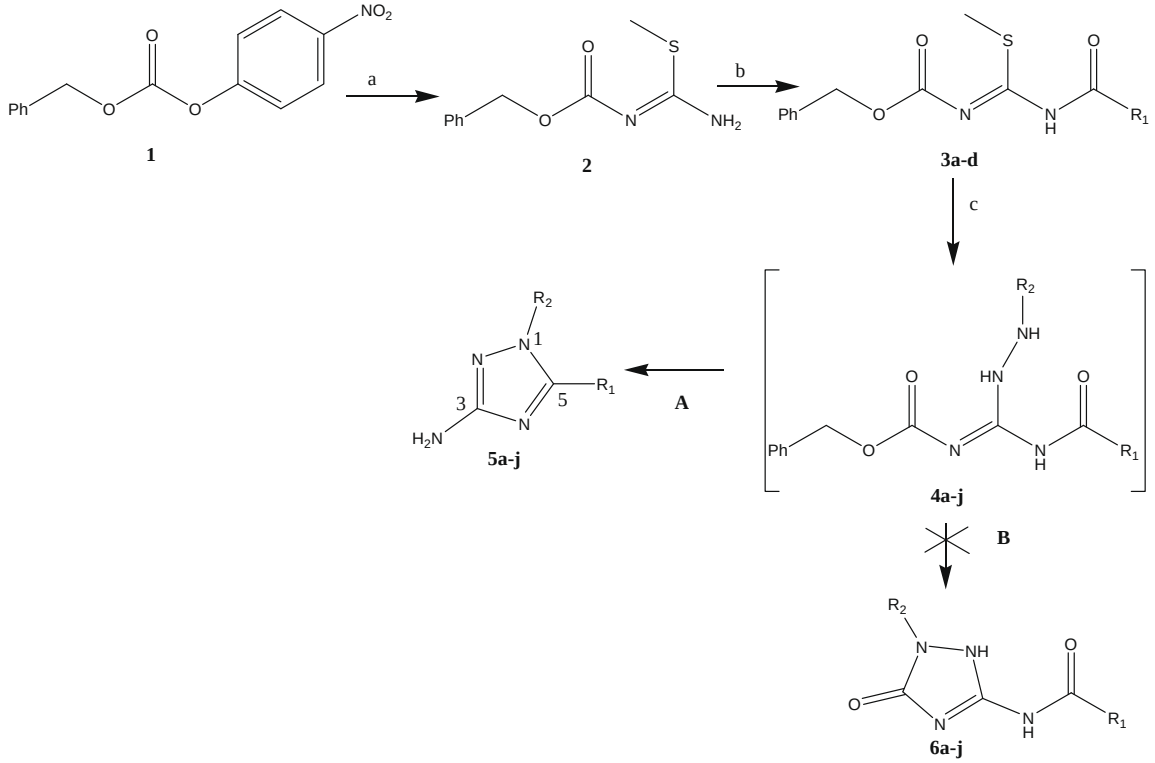
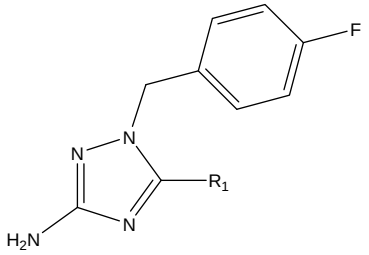
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.12.042



Scheme 1. Reagents and conditions: (a) 2-methyl-2-thiopseudourea sulfate, DMF, 23 °C, 12 h, 95%; (b) carboxylic acid, 4-methylmorpholine, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, 1-hydroxy benzotriazole, DMF, 23 °C, 12 h, 40%; (c) substituted hydrazine, triethylamine, microwave, 160 °C, 30 min, 34–70%.

Table 1



5a-d

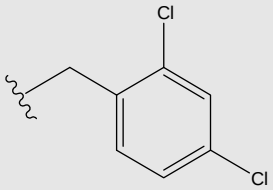
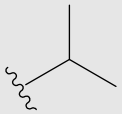
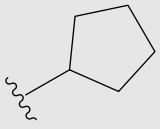
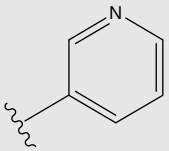
Entry	R_1	Isolated yield (%)	^{1}H NMR (DMSO-d_6) ppm	CHN
5a		70	4.19 (s, 2H) 5.19 (s, 2H) 7.12–7.19 (m, 2H) 7.24–7.31 (m, 2H) 7.31 (s, 1H) 7.34–7.39 (m, 1H) 7.58 (d, *J* = 2.02 Hz, 1H)	$C_{16}H_{13}Cl_2FN_4 \cdot 0.4H_2O$: C, 53.62; H, 3.88; N, 15.63. Observed: C, 53.58; H, 3.97; N, 15.63.
5b		48	1.10 (d, *J* = 6.82 Hz, 6H) 3.02–3.14 (m, 1H) 5.09 (s, 2H) 5.15 (s, 2H) 7.09–7.20 (m, 2H) 7.20–7.30 (m, 2H)	$C_{12}H_{15}FN_4 \cdot 0.33HOAc$: C, 59.84; H, 6.47; N, 22.05. Observed: C, 59.75; H, 6.52; N, 21.97.
5c		56	1.50–1.75 (m, 6H) 1.78–1.91 (m, 2H) 3.19 (t, *J* = 7.83 Hz, 1H) 5.10 (s, 2H) 5.15 (s, 2H) 7.12–7.21 (m, 2H) 7.22–7.28 (m, 2H)	$C_{14}H_{17}FN_4 \cdot 0.45H_2O$: C, 62.65; H, 6.72; N, 20.87. Observed: C: 62.65, H: 6.53, N: 20.53.

Table 1 (*continued*)

Entry	R_1	Isolated yield (%)	^{1}H NMR (DMSO-d_6) ppm	CHN
5d		56	5.50 (s, 2H) 5.81 (s, 2H) 7.08–7.20 (m, 2H) 7.26–7.36 (m, 2H) 7.44–7.53 (m, 1H) 7.92–8.01 (m, 1H) 8.00–8.08 (m, 1H) 8.70 (d, J = 4.04 Hz, 1H).	$C_{14}H_{12}FN_5 \cdot 0.39H_2O$: C, 60.86; H, 4.66; N, 25.35. Observed: C, 60.87; H, 4.78; N, 25.23.

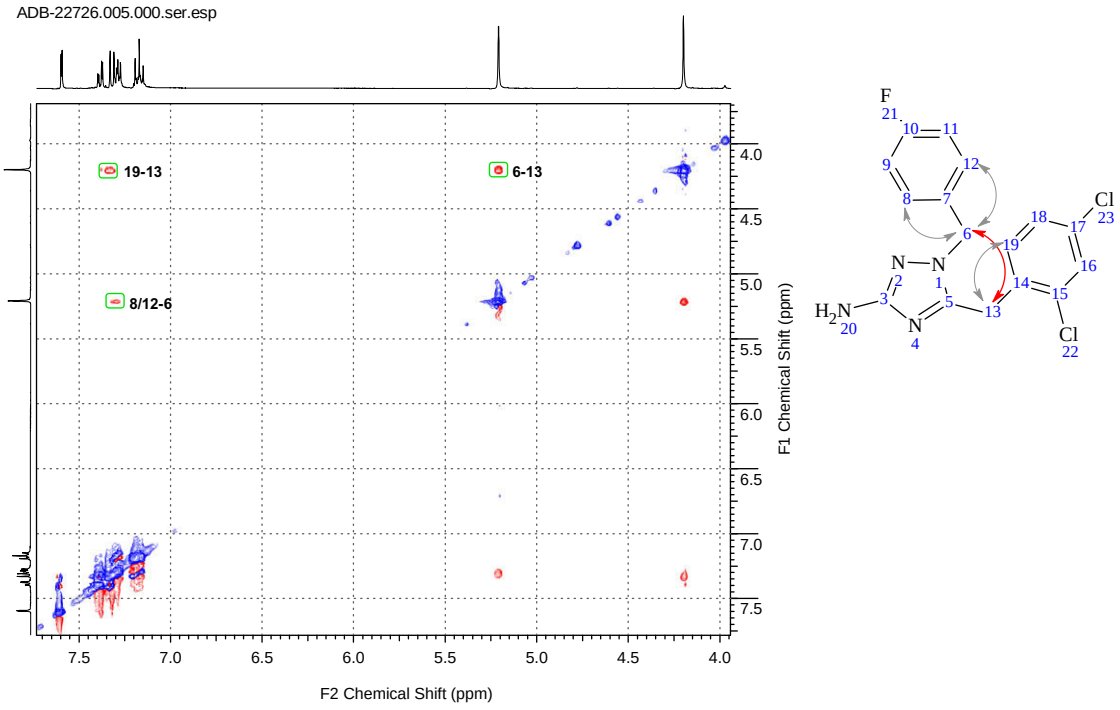
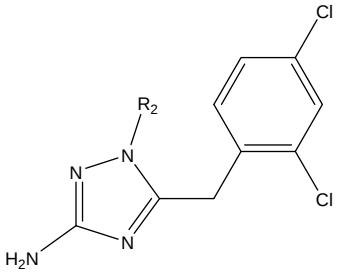
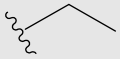


Figure 1. 2D-NOESY spectrum of **5a** (DMSO, 400 MHz). Arrows indicate observed NOEs. The NOE between two benzylic protons (#6 and #13, red arrow) confirmed that the benzylic substitution is at the N1 position, not at the N2 position. Other NOEs between benzylic protons (#6 and #13) and the phenyl protons (#8, #12, and #19, gray arrows) were also observed.

Table 2

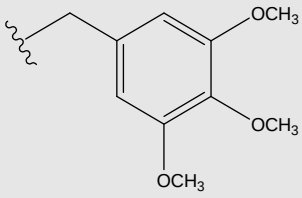
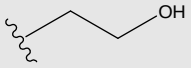
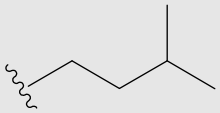
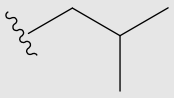
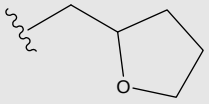


5e-j

Entry	R_2	Isolated yield (%)	^{1}HNMR (DMSO-d_6) ppm	CHN
5e		38	1.23 (t, J = 7.20 Hz, 3H) 3.92 (q, J = 7.33 Hz, 2H) 4.04 (s, 2H) 5.12 (s, 2H) 7.27–7.36 (m, 1H) 7.36–7.44 (m, 1H) 7.60 (d, J = 2.02 Hz, 1H)	$C_11H_{12}Cl_2N_4 \cdot 0.19HOAc$: C, 48.37; H, 4.55; N, 19.83. Observed: C, 48.32; H, 4.46; N, 20.04.

(*continued on next page*)

Table 2 (*continued*)

Entry	R_2	Isolated yield (%)	^{1}HNMR (DMSO-d_6) ppm	CHN
5f		34	3.56–3.62 (m, 3H) 3.67 (s, 6H) 4.11 (s, 2H) 5.20 (s, 2H) 5.74 (s, 2H) 6.46 (s, 2H) 7.22–7.28 (m, 1H) 7.31–7.37 (m, 1H) 7.52–7.59(m, *J* = 2.27 Hz, 1H)	$C_{19}H_{20}Cl_2N_4O_3 \cdot 0.74H_2O$: C, 52.27; H, 4.96; N, 12.83. Observed: C, 52.27; H, 4.57; N, 12.49.
5g		65	3.49–3.55 (m, 1H) 3.64 (q, *J* = 5.31 Hz, 2H) 3.94 (t, *J* = 5.43 Hz, 2H) 4.05 (s, 2H) 5.13 (s, 2H) 7.27–7.35 (m, 1H) 7.36–7.41 (m, 1H) 7.51–7.63(m, 1H)	$C_11H_{12}Cl_2N_4O \cdot 1.13HOAc$: C, 44.86; H, 4.69; N, 15.78. Observed: C, 45.22; H, 4.35; N, 15.78.
5h		34	0.78–0.91 (m, 6H) 1.20–1.34 (m, 1H) 1.45–1.59 (m, 2H) 3.82–3.94 (m, *J* = 6.06, 6.06 Hz, 2H) 4.04 (s, 2H) 5.12 (s, 2H) 7.28–7.35 (m, 1H) 7.35–7.43 (m, 1H) 7.60 (s, 1H)	$C_{14}H_{18}C_{l2}N_4 \cdot 0.43HOAc$: C, 52.64; H, 5.86; N, 16.52. Observed: C, 52.60; H, 5.93; N, 16.53.
5i		40	0.83 (d, *J* = 6.82 Hz, 6H) 1.92–2.16 (m, 1H) 3.15 (s, 2H) 3.70 (d, *J* = 7.33 Hz, 2H) 4.04 (s, 2H) 7.30–7.37 (m, 1H) 7.37–7.45 (m, 1H) 7.60 (d, *J* = 2.02 Hz, 1H)	$C_{13}H_{16}Cl_2N_4 \cdot 0.43HOAc$: C, 51.22; H, 5.55; N, 17.24. Observed: C, 51 21; H, 5 54; N, 17 12.
5j[a]		50	1.84–1.96 (m, 2H) 2.01–2.15 (m, 2H) 3.65–3.84 (m, 2H) 4.06–4.19 (m, 2H) 4.23–4.30 (m, 1H) 4.38 (d, *J* = 10.86 Hz, 2H) 7.33–7.40 (m, 2H) 7.55 (d, *J* = 2.02 Hz, 1H)	$C_{14}H_{16}C_{l2}N_4O \cdot 0.39HOAc$: C, 50.63; H, 5.05; N, 15.98. Observed: C, 50.65; H, 5.23; N, 16.02.

[a] Racemic.

Acknowledgments

We thank the Pfizer La Jolla analytical group for the analytical and spectral data. We also thank Dr. Martin Wythes for helpful discussions.

References and notes

1. Beria., I; Pesenti, E; Capolongo, L.; Mongelli, N.; Baraldi, P. PCT Intl. Appl. WO 9605196 A1, 1996.
2. Bignon, E.; Bras, J.-P.; De Cointet, P.; Despeyroux, P.; Frehel, D.; Gully, D. PCT Intl. Appl. WO 034729 A1, 2002.
3. Akerblom, E. B.; Campbell, D. E. S. *J. Med. Chem.* **1973**, *16*, 312.
4. Katritzky, A. R.; Rogovoy, B. V.; Vvednsky, V. Y.; Kovalenko, K.; Steel, P. J.; Markov, V. I.; Forood, B. *Synthesis* **2001**, 897.
5. Chen, C.; Dagnino, R.; Huang, C. Q.; McCarthy, J. R.; Grigoriadis, D. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3165.
6. Makara, G. M.; Ma, Y.; Margarida, L. *Org. Lett.* **2002**, *4*, 1751.
7. Yu, Y.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron Lett.* **2003**, *44*, 7841.
8. Yuan, C.; Williams, R. M. *Tetrahedron Lett.* **1996**, *37*, 1945.
9. Synthesis of compound (**5a**) 5-(2,4-dichloro-benzyl)-1-(4-fluoro-benzyl)-1*H*-[1,2,4]triazol-3-ylamine. A 3 mL microwave tube was charged with benzyl [(1*Z*)-{[(2,4-dichlorophenyl)acetyl]amino}(methylthio)methylene]carbamate (**3a**) (123 mg, 0.3 mmol). (4-Fluorobenzyl)hydrazine hydrochloride (318 mg, 1.8 mmol) and triethylamine (0.25 mL, 1.8 mmol) were added sequentially. The resulting mixture was heated in a microwave oven at 160 °C for 30 min (Biotage Initiator™ Sixty). Microwave reactions were performed in sealed tubes. Irradiation was automatically adjusted by the microwave software to maintain a constant 160 °C reaction temperature. The desired product was purified by reverse phase HPLC (using 0.1% acetic acid in H_2O and acetonitrile as eluents) to afford compound **5a** as a white solid (71 mg, 0.2 mmol, 70% yield). ^{1}H NMR (400 MHz, DMSO-d_6) ppm 4.19 (s, 2 H) 5.19 (s, 2 H) 7.12–7.19 (m, 2 H) 7.24–7.31 (m, 2H) 7.31 (s, 1H) 7.34–7.39 (m, 1H) 7.58 (d, *J* = 2.0 Hz, 1H). Calcd for $C_{16}H_{13}Cl_2FN_4 \cdot 0.4H_2O$ C: 53.62, H: 3.88, N: 15.63. Observed: C: 53.58, H: 3.97, N: 15.63.
10. El-Gendy, Z.; Abdel-Rahman, R. M.; Abdel-Malik, M. S. *Indian J. Chem., Sect. B* **1989**, *28*, 479.
11. Nettekoven, M.; Pullmann, B.; Schmitt, S. *Synthesis* **2003**, 1649.
12. Dzygiel, A.; Rzeszotarska, B.; Masiukiewicz, E.; Cmoch, P.; Kamienski, B. *Chem. Pharm. Bull.* **2004**, *52*, 192.
13. Zohdi, H. F. J. *Chem. Res., Synopses* **1998**, *9*, 536.
14. Medwid, J. B.; Paul, R.; Baker, J. S.; Brockman, J. A.; Du, M. T.; Hallett, W. A.; Hanifin, J. W.; Hardy, R. A.; Tarrant, M. E.; Torley, L. W.; Wrenn, S. *J. Med. Chem.* **1990**, *33*, 1230.