Tetrahedron Letters 51 (2010) 3907–3909

Contents lists available at ScienceDirect

Tetrahedron Letters

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

[1,3]Oxazolo[3,2-*b*][1,2,4]triazoles: a versatile synthesis of a novel heterocycle

Catherine Ball, David K. Dean *, Olivier Lorthioir, Lee W. Page, Charlotte L. Smith, Stephen P. Watson

GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK

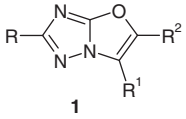
ARTICLE INFO

Article history:
Received 6 April 2010
Revised 30 April 2010
Accepted 21 May 2010
Available online 26 May 2010

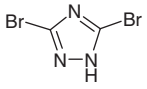
ABSTRACT

An efficient one-pot microwave approach for the synthesis of novel [1,3]oxazolo[3,2-*b*][1,2,4]triazoles is described.

The synthesis of novel heterocycles is of ongoing interest to the medicinal chemistry and pharmaceutical communities because heterocycles are ubiquitous in drugs and biologically active molecules. Indeed, a recent review by Pitt et al. at UCB[1] highlighted the large number of potential heterocycles that have to be yet exemplified. In our laboratories we recently had need to prepare compounds based on the hitherto unprecedented [1,3]oxazolo[3,2-*b*][1,2,4]triazole heterocyclic system for one of our drug discovery programmes. Herein, we describe an expedient and versatile one-pot synthesis of the novel [1,3]oxazolo[3,2-*b*][1,2,4]triazole template **1** from 3,5-dibromo-1,2,4-triazole (**2**).

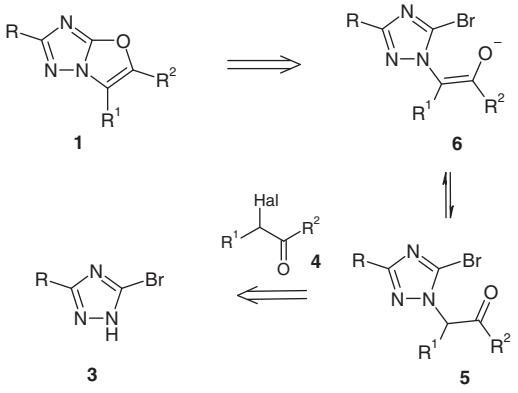


1

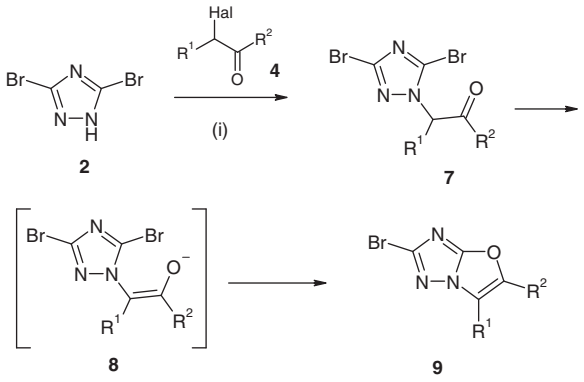


2

In designing a synthetic approach, we anticipated that [1,3]oxazolo[3,2-*b*][1,2,4]triazoles **1** could be constructed by way of a tandem alkylation-displacement reaction of 3-bromo-1,2,4-triazoles **3** and α-haloketones **4**, via intermediate enolate **6** (Scheme 1). Whilst alkylation of 1,2,4-triazoles typically occurs at N-1(2) rather than N-4, reflecting the higher nucleophilicity of N–N systems,[2] the envisaged synthetic scheme also required triazole alkylation on the N-1(2) nitrogen atom adjacent to the bromine atom. However, dependent on the nature of the other ring substituent, alkylation of triazoles **3** could occur predominantly (or exclusively) at the nitrogen remote from the bromine atom, which would preclude cyclisation. We consequently reasoned that the use of symmetrical 3,5-dibromo-1,2,4-triazole (**2**) would overcome such regiochemical difficulties, by forcing alkylation adjacent to a bromine atom and allowing subsequent cyclisation, to afford the overall strategy outlined in Scheme 2. The residual bromine atom could then be removed (having functioned as a 'dummy atom') or used for further functionalisation as appropriate. Furthermore,



Scheme 1. [1,3]oxazolo[3,2-*b*][1,2,4]triazoles—retrosynthesis.



Scheme 2. Reagents and conditions: (i) Base (see Table 1), 100 °C, microwave, 10–20 min.

* Corresponding author. Tel.: +44 1279 627687; fax: +44 1279 622260.
E-mail addresses: david.k.dean@gsk.com, deandandr@aol.com (D.K. Dean).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.05.100

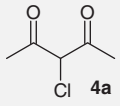
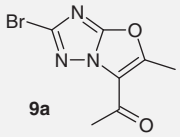
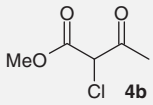
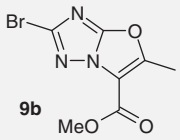
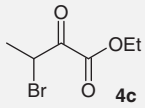
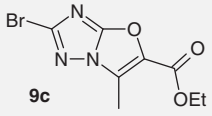
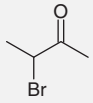
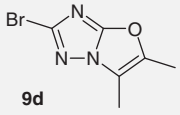
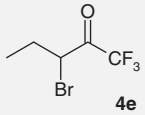
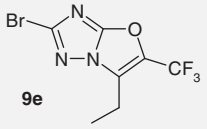
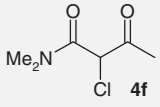
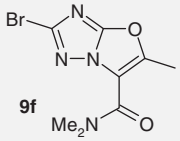
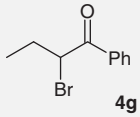
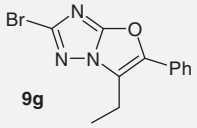
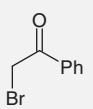
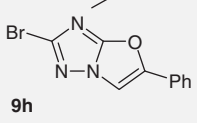
nucleophilic substitution is fast at the 5-position of 1-alkyl-1*H*-[1,2,4]triazoles and very slow at the 3-position,[3] therefore the alkylation at N-1 was also anticipated to activate the triazole to facilitate the subsequent intramolecular nucleophilic substitution/cyclisation.

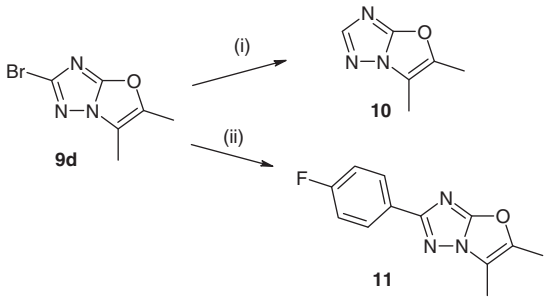
To implement this strategy we first alkylated 3,5-dibromo-1,2,4-triazole (**2**) to afford intermediate **7** and, in preliminary experiments, were gratified to find substantial amounts of the spontaneously cyclised [1,3]oxazolo[3,2-*b*][1,2,4]triazole final product **9**. Rapid optimisation of the reaction conditions transformed this two-step scheme into a convenient one-pot reaction, made even more expeditious by the use of microwave heating (Scheme 2).

Detailed investigation revealed this tandem alkylation/cyclisation reaction (Scheme 2) to be versatile and tolerant of diverse functionalities (Table 1). While α-haloketones **4a** and **4b**, activated by an additional α-carbonyl group, underwent cyclisation to **9a,b** in the presence of DIPEA, reaction of α-haloketone **4c** required a stronger base, presumably to facilitate the formation of a less-stabilized enolate intermediate **8**.

In view of the apparent ease of the ring formation we further investigated the scope of this procedure and were interested in whether it could be extended to α-haloketones lacking further activation towards enolisation, using 3-bromo-2-butanone (**4d**) as a model substrate. Thus, reaction of 3,5-dibromo-1,2,4-triazole (**2**) with **4d** in the presence of 3 equiv of DBU at 100 °C in a microwave reactor gave 2-bromo-5,6-dimethyl[1,3]oxazolo[3,2-*b*][1,2,4]triazole (**9d**) as the exclusive reaction product (60%). The regiochemistry of compound **9d** was confirmed by X-ray crystallography.[4] Alkylation of 3,5-dibromo-1,2,4-triazole (**2**) with DBU and **4d** at room temperature allowed isolation of the intermediate ketone (**7d**, $R^1 = R^2 = Me$) in 75% yield and subsequent microwave heating with DBU at 100 °C afforded **9d** as the exclusive product (69%). DBU is required in this step to facilitate enolisation and subsequent cyclisation to the [1,3]oxazolo[3,2-*b*][1,2,4]triazole ring system.

Table 1
Synthesis of [1,3]oxazolo[3,2-*b*][1,2,4]triazoles[5]

α-Haloketone	Base	Product	Yield (%)
 **4a**	DIPEA	 **9a**	81
 **4b**	DIPEA	 **9b**	68
 **4c**	NaH	 **9c**	60
 **4d**	DBU	 **9d**	60
 **4e**	DIPEA	 **9e**	43
 **4f**	DIPEA	 **9f**	39
 **4g**	DBU	 **9g**	9
 **4h**	DBU	 **9h**	29



Scheme 3. Reagents and conditions: (i) H_2, 10% Pd/C, Et_3N (2 equiv), MeOH, (61%); (ii) 4-$FC_6H_4B(OH)_2$, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, DME, H_2O 100 °C (67%).

Finally, the remaining 'dummy' bromine atom in compound **9d** was readily removed by catalytic hydrogenation[6] to afford the expected [1,3]oxazolo[3,2-*b*][1,2,4]triazole **10**. The typical reactivity of the bromo group in **9d** for further functionalisation was demonstrated by Suzuki coupling with 4-fluorobenzene boronic acid giving the corresponding 2-aryl[1,3]oxazolo[3,2-*b*][1,2,4]triazole **11** (Scheme 3).

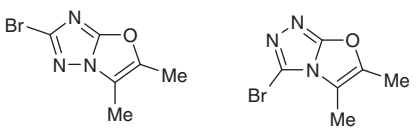
In summary, we have developed an expedient synthesis of [1,3]oxazolo[3,2-*b*][1,2,4]triazoles via a tandem alkylation/cyclisation reaction, exploiting a facilitating 'dummy' bromine atom. The synthesis affords easy entry into a previously unreported fused heterocyclic system and allows for subsequent elaboration of the template via the 5-Br atom or other functionalities (such as esters) of which the synthesis is tolerant.

Acknowledgements

We thank Professor W. Clegg and Dr. L. Russo (University of Newcastle) for the GSK-funded X-ray crystallographic analysis.

References and notes

1. Pitt, W. R.; Parry, D. M.; Perry, B. G.; Groom, C. R. *J. Med. Chem.* **2009**, *52*, 2952–2963.
2. So called 'α effect', see: Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Publishing, 2000. p 506.
3. Zumbrunn, A. *Synthesis* **1998**, 1357–1361.
4. X-ray crystallography of **9d** confirmed that regioisomer **X** and not **Y** was obtained exclusively, as predicted on steric and electronic (α-effect) grounds



.

Crystallographic data (excluding structural factors) for compound **9d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 771885. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or email: deposit@ccdc.cam.ac.uk).

5. Preparation of 1-(2-bromo-5-methyl[1,3]oxazolo[3,2-*b*][1,2,4]triazol-6-yl)ethanone (**9a**). To a stirred suspension of 3,5-dibromo-1,2,4-triazole (**2**) (1.134 g, 5.0 mmol) in MeCN (20 mL) were added DIPEA (1.75 mL, 10 mmol) and 3-chloro-2,4-pentanedione (**4a**) (0.57 mL, 5.0 mmol), and the reaction mixture was heated for 20 min at 100 °C in a microwave reactor (Biotage Initiator 2.5). The solvent was evaporated and the residue was partitioned between CH_2Cl_2 (100 mL) and aqueous 1 M HCl (100 mL). The layers were separated and the organic phase was evaporated to dryness. The crude product was purified by silica gel chromatography eluting with 0–70% EtOAc in isohexane to give the title compound **9a** as a white solid (980 mg, 81%). Mp 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.765 (s, 3H), 2.759 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.4, 30.0, 121.9, 142.5, 155.7, 157.9, 187.2. LC/MS $[M+H]^+$ 244/246. IR (solid): ν 1701 cm^{-1}.

2-Bromo-5,6-dimethyl[1,3]oxazolo[3,2-*b*][1,2,4] triazole (**9d**). To a suspension of 3,5-dibromo-1,2,4-triazole (**2**) (500 mg, 2.20 mmol) in MeCN (8 mL) were added DBU (0.33 mL, 2.20 mmol) and then 3-bromo-2-butanone (**4d**) (0.29 mL, 2.76 mmol). The mixture was stirred at room temperature for 10 min and then heated for 5 min at 100 °C in a microwave reactor. Additional DBU (0.66 mL, 4.4 mmol) was added and the mixture was heated for 10 min at 100 °C in the microwave. The solvent was evaporated, CH_2Cl_2 (25 mL) and 1 M HCl (25 mL) were added to the residue, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The organic layers were combined, dried and evaporated. The crude product was purified by silica gel chromatography eluting with 0–70% EtOAc in isohexane to give the title compound **9d** as a white solid (284 mg, 60%). Mp 72–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 2.37 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): 7.1, 11.0, 117.3, 141.5, 144.0, 158.4. LC/MS $[M+H]^+$ 216/218.

3-(3,5-Dibromo-1*H*-1,2,4-triazol-1-yl)-2-butanone (**7d**). A suspension of 3,5-dibromo-1,2,4-triazole (**2**) (567 mg, 2.5 mmol) in MeCN (5 mL) was stirred at room temperature, DBU (0.415 mL, 2.75 mmol) was added, and the resulting solution was stirred for 10 min. A solution of 3-bromo-2-butanone (**4d**) (0.29 mL, 2.75 mmol) in MeCN (1 mL) was added dropwise and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc (30 mL) and 2 M HCl (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (20 mL). The organic extracts were combined and the solution was washed with 2 N HCl (15 mL), H_2O (20 mL) and brine (20 mL), dried and evaporated. The residue was triturated with cold Et_2O/isohexane (1:4) and the resulting solid was collected and dried to give the title compound **7d** as a white solid (554 mg, 75% yield). Mp 82–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (3H, d, J = 7.2 Hz), 2.18 (s, 3 H), 5.43 (1H, q, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 14.9, 26.3, 63.7, 131.8, 139.3, 202.2. LC/MS $[M+H]^+$ 296/298/300. IR (solid): ν 1715 cm^{-1}.

5,6-Dimethyl[1,3]oxazolo[3,2-*b*][1,2,4]triazole (**10**). White solid. Mp 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, s), 2.37 (3H, s), 7.88 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 7.2, 11.1, 117.0, 144.5, 154.0, 159.6. LC/MS $[M+H]^+$ 138.

6. Libnow, S.; Wille, S.; Christiansen, A.; Hein, M.; Reinke, H.; Kockerling, M.; Miethchen, R. *Synthesis* **2006**, 496–508.