JOURNAL OF combinatorial CHEMISTRY

Report

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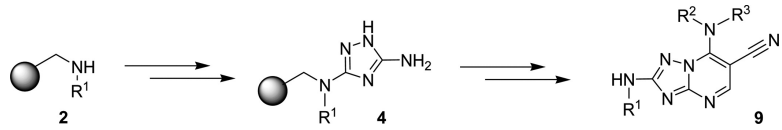
J. Comb. Chem., **2008**, 10 (1), 28-30• DOI: 10.1021/cc700161r • Publication Date (Web): 10 November 2007



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Preparation of 2,7-Diaminosubstituted-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-Carbonitriles by Solid-Phase Synthesis

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Received September 27, 2007

The biological importance of 1,2,4-triazolo[1,5-*a*]pyrimidines is well documented. Over the years, various substituted derivatives of these heterocycles have shown utility against a range of biological targets.[1] For example, they have demonstrated activity against malaria[2] and bronchospasm[3] and shown activity as coronary vasodilators,[4,5] antihypertensive agents,[5] leishmanicides,[6,7] antibiotics,[8] adenosine A_{2a} antagonists,[9] immunosuppressants,[10] antitumor agents,[11] fungicides,[12] xanthine oxidase inhibitors,[13] and phosphodiesterase inhibitors.[14] Although these papers describe 1,2,4-triazolo[1,5-*a*]pyrimidines with a number of substitution patterns, elaboration of this particular heterocyclic core has not been exhaustive. Herein, we disclose compounds containing a novel variation of this heterocycle, namely, 2,7-diamino-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitriles, synthesized by a solid-phase route. This approach is efficient and can potentially be used for the creation of combinatorial libraries based on the novel core structure.

Previous routes[1] to 1,2,4-triazolo[1,5-*a*]pyrimidines have primarily taken advantage of a solution phase reaction between 1,2,4-triazoles and myriad biselectrophiles[2,15] or, more recently, by using a multicomponent variation of this reaction.[16] We have taken a similar approach for the ring closure by condensing ethyl(ethoxymethylene)cyanoacetate with resin-bound diamino-1,2,4-triazoles. The resin-based approach detailed below provides a convenient route for library synthesis and eliminates the need for the purification of multiple intermediates.

The solid phase synthesis that was undertaken began with PL-FMP resin **1** (see Scheme 1), which was treated with sodium triacetoxyborohydride and a primary amine to provide resin **2**. Loadings were determined by benzoylation, cleavage, and gravimetric analysis, as well as by elemental analysis of the resin-bound intermediates. The amine resins **2** were treated with diphenoxycyanoimidate to give the corresponding phenyl isourea resin **3**. The progress of this reaction was monitored by LC-MS analysis of the cleaved intermediate, which was observed with a 4-hydroxy-2-methoxyphenyl substituent resulting from cleavage at the resin backbone instead of directly at the linker. Isourea resin **3** was treated with a benzoylation mixture, cleaved, and analyzed to ensure that there was no unreacted resin **2** remaining. Resin **3** was then cyclized with hydrazine to triazole resin **4**[17] and was also monitored by LC-MS analysis of the cleaved intermediate.

Michael addition of aminotriazole resin **4** to ethyl-(ethoxymethylene)cyanoacetate in the presence of acetic acid gave the resin bound Michael adduct **5**. The reaction was checked by cleavage of the intermediate and subsequent LC-MS analysis. It was observed that thorough washing of the resin was critical to remove polymeric impurities. Initial attempts to cyclize resin **5** with DMAP, DBU, or NaOMe were completely unsuccessful, even with heating at temperatures up to 100 °C. The cyclization of resin **5** was finally accomplished with potassium bis(trimethylsilyl)amide (KHMDS) in DMF at 100 °C to obtain the resin-bound triazolopyrimidinone **6**. Elevated temperature and strong base were required to push the reaction to completion because a significant amount of **5** still remained when KHMDS was employed at lower temperatures. Progress was monitored by LC-MS analysis of cleaved samples, and it was noted that the cleaved intermediate was not stable to methanolic TFA. Thus, it was necessary to cleave the intermediate with TFA and evaporate it to dryness prior to LC-MS analysis in methanol-containing mobile phases.

Treatment of resin **6** with phosphorus oxychloride in pyridine gave the resin-bound chlorotriazolopyrimidine **7**. The chlorine was then displaced by heating intermediate **7** in NMP with amines at 80 °C to obtain the resin-bound diamino triazolopyrimidines **8**. Both reactions were monitored by LC-MS analysis of the cleaved materials. Cleavage of resin **8** was accomplished by treatment with 30% TFA in DCM, thus providing the liberated triazolopyrimidines **9**.

The isolated yields of some representative compounds are shown in Table 1. All final products were purified by reverse-phase preparative HPLC. The isolated yields for these samples ranged from 7 to 25% for seven linear steps from the amine resin **2**. Yields are comparable when R^1 is an alkyl or benzyl amine.

Prior research on these heterocycles has shown that there are four possible regiochemical outcomes for the formation of the pyrimidine ring by this route. Literature precedents suggest that the exocyclic nitrogen of the triazole[16,18] will react first with the enol ether portion of the biselectrophile[19] and that ring closure will occur at N-2 of the triazole to provide the 1,2,4-triazolo[1,5-*a*]pyrimidine. Although the annulation is expected to occur by condensation with the ester,[15c,20] it should be noted that under certain conditions amino products resulting from addition to the nitrile have been reported.[7,20] Further support for the [1,5-*a*]-structures can also be found in observations that the [4,3-*a*]-isomers readily rearrange to the [1,5-*a*]-compounds;[18,21,22] therefore, any of the former isomer that is created should be converted to the latter.

In support of the first step of the pyrimidine formation, we were able to cleave resin **5a** ($R^1 = CH_2CH_2OMe$) and isolate the product. Mass spectral data for the intermediate

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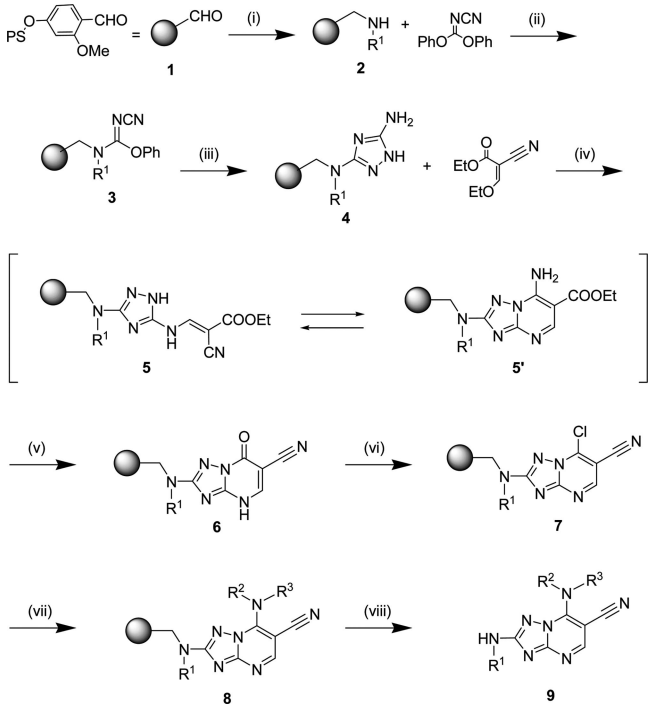
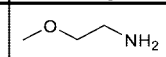
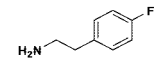
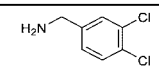
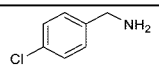
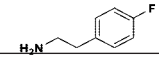
10.1021/cc700161r CCC: $40.75
Published on Web 11/10/2007

Scheme 1. Solid-Phase Synthesis of 1,2,4-Triazolo[1,5-*a*]pyrimidines[a]



[a] Reagents and conditions: (i) R^1NH_2, DMF, $NaBH(OAc)_3$, cat. AcOH; (ii) DIEA, DMAP, NMP, 75°C; (iii) N_2H_4, NMP, 75°C; (iv) 70% AcOH/NMP, 98°C; (v) potassium bis(trimethylsilyl)amide (0.5 M in toluene), DMF, RT for 3 h, then 100°C; (vi) $POCl_3$, pyridine, DCE, RT for 15 min, then 80°C; (vii) R^2R^3NH, NMP, 80°C; (viii) 30% TFA/DCE; R^1 = $MeOCH_2CH_2$ for **a** and 4-$ClPhCH_2$ for **b**.

Table 1. Yields for Some Representative 1,2,4-Triazolo[1,5-*a*]pyrimidines

Compound	R1 Reagent	R2/R3 Reagent	Crude Purity[a]	Yield[b]
9a-i			40%	**14%**
9a-ii	"		55%	**7%**
9a-iii	"		25%	**18%**
9a-iv	"		59%	**25%**
9b-i			65%	**19%**
9b-ii	"		43%	**17%**
9b-iii	"		59%	**18%**

[a] Purity of crude products after cleavage as determined by LC with UV detection at 220 nM. [b] Yields of isolated products after Prep LC purification; calculated based on initial resin loading of R^1.

supports displacement of an ethoxy group, and IR data obtained for resin **5a** confirmed the presence of the cyano substituent. However, IR data for the cleaved material lacked the definitive CN stretch, and H NMR data supported structure **5a′**. This leads one to speculate that the resin-bound material could be a mixture of **5a** and **5a′** that is converted to **5a′** under the acidic cleavage conditions. Reactions at the nitrile for this ring system have been reported under acidic conditions.[7,20]

Formation of triazolopyrimidinone **6a** was confirmed by the MS data and was consistent with the loss of an ethoxy group from **5**. As mentioned above, the initial failed attempts to cyclize this intermediate eventually necessitated the use of strongly basic conditions. This may be, at least in part, the result of the presence of **5a′**. Formation of the desired product from this intermediate would require retrocyclization to the nitrile and reclosure of the ring.

To show that the final products synthesized by the solid-phase route were the expected regioisomers, further structural work was undertaken. Because these compounds lack differentiating protons that can be used for a definitive structural assignment by ^1H NMR,[16a] structures were determined by comparison of UV absorption[23] and ^{13}C NMR data[23b,24,25] with that presented in the literature for several closely related analogs. As expected, the data for the methoxyethyl compound **6a** supported the assignment of the 1,2,4-triazolo[1,5-*a*]pyrimidine regioisomer shown. It displayed a downfield resonance in the ^{13}C NMR at 161.1 ppm, which agrees with related compounds in the literature, [23b,24] and UV absorptions at 233 and 298 nm, also in agreement with literature values.[23b,26] Data for the 4-chlorobenzyl analog **6b** also supported this assignment, with UV absorptions at 237 and 297 nm and a downfield resonance in the ^{13}C NMR at 163.8 ppm.

In conclusion, a robust solid-phase method has been developed that provides access to 2,7-diamino-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitriles. Furthermore, this methodology is amenable to library generation and is tolerant to various substitutions at the 2- and 7-positions. Spectroscopic data confirms that the products formed were 1,2,4-triazolo[1,5-*a*]pyrimidines. We continue to pursue the synthesis of combinatorial libraries based upon this chemistry, which will be disclosed separately.

Acknowledgment. We would like to thank Sharon Callahan and Sarah Traeger for NMR assistance, Peter Tidswell, Marianne Vath, Scott LaPaglia, Katy van Kirk, Art Miller, and Ruhui Qiu for providing analytical and purification support, and Rajeev Bhide for his careful observations and helpful discussions.

Supporting Information Available. General procedures for library synthesis and spectral data for key compounds. This information is available free of charge via the Internet at http: //pubs.acs.org.

References and Notes

(1) Fischer, G. *Adv. Heterocycl. Chem.* **1993**, *57*, 81–138.
(2) Werbel, L. M.; Elslager, E. F.; Chu, V. P. *J. Heterocycl. Chem.* **1973**, *10*, 631–635.
(3) Davies, G. E. J. *Pharm. Pharmacol.* **1973**, *25*, 681–689.
(4) Tenor, E.; Ludwig, R. *Pharmazie* **1971**, *26*, 534–539.
(5) Sato, Y.; Shimoji, Y.; Fujita, H.; Nishino, H.; Mizuno, H.; Kobayashi, S.; Kumakura, S. *J. Med. Chem.* **1980**, *23*, 927–937.
(6) Ram, V. J.; Srivastava, P.; Singh, S. K.; Kandpal, M.; Tekwani, B. L. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1087–1090.
(7) Ram, V. J. *Ind. J. Chem., Sect. B* **1988**, *27B*, 825–829.

(8) Abdelal, A. M.; Gineinah, M. M.; Kheira, S. M. M. *Med. Chem. Res.* **1999**, *9*, 277–290.

(9) (a) Peng, H.; Kumaravel, G.; Yao, G.; Sha, L.; Wang, J.; Van Vlijmen, H.; Bohnert, T.; Huang, C.; Vu, C. B.; Ensinger, C. L.; Chang, H.; Engber, T. M.; Whalley, E. T.; Petter, R. C. *J. Med. Chem.* **2004**, *47*, 6218–6229. (b) Vu, C. B.; Pan, D.; Peng, B.; Sha, L.; Kumaravel, G.; Jin, X.; Phadke, D.; Engber, T.; Huang, C.; Reilly, J.; Tam, S.; Petter, R. C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4831–4834. (c) Vu, C. B.; Shields, P.; Peng, B.; Kumaravel, G.; Jin, X.; Phadke, D.; Wang, J.; Engber, T.; Ayyub, E.; Petter, R. C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4835–4838.

(10) Kuramochi, H.; Masuda, A.; Shimizu, K.; Toyoda, E.; Tokunaka, K. Int. Patent WO 2005037837 A1, April 28, 2005.

(11) Zhang, N.; Ayral-Kaloustian, S.; Nguyen, T. H.; Wu, Y.; Tong, W. Int. Patent WO 2005030775 A1, April 7, 2005.

(12) For examples, see: (a) Pees, K.-J.; Becher, H.-M. Int. Patent WO 9420501 A1, September 15, 1994. (b) Wagner, O.; Grote, T.; Rheinheimer, J.; Nave, B.; Stierl, R. Int. Patent WO 2006066818 A2, June 29, 2006.

(13) Robins, R. K.; Revankar, G. R.; O'Brien, D. E.; Springer, R. H.; Novinson, T.; Albert, A.; Senga, K.; Miller, J. P.; Streeter, D. G. *J. Heterocycl. Chem.* **1985**, *22*, 601–634.

(14) Novinson, T.; Springer, R. H.; O'Brien, D. E.; Scholten, M. B.; Miller, J. P.; Robins, R. K. *J. Med. Chem.* **1982**, *25*, 420–426.

(15) For examples, see: (a) Bulow, C.; Haas, K. *Ber. Dtsch. Chem. Ges.* **1910**, *42*, 4638–4644. (b) Kano, H.; Makisumi, Y. *Chem. Pharm. Bull.* **1958**, *6*, 583–586. (c) Tominaga, Y.; Sakai, S.; Kohra, S.; Tsuka, J.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1985**, *33*, 962–970. (d) Petrich, S. A.; Qian, Z.; Santiago, L. M.; Gupton, J. T.; Sikorski, J. A. *Tetrahedron* **1994**, *50*, 12113–12124. (e) Almazroa, S.; Elnagdi, M. H.; El-Din, A. M. S. *J. Heterocycl. Chem.* **2004**, *41*, 267–272. (f) Černuchová, P.; Vo-Thanh, G.; Milata, V.; Loupy, A.; Jantová, S.; Theiszová, M. *Tetrahedron* **2005**, *61*, 5379–5387.

(16) (a) Chebanov, V. A.; Sakhno, Y. I.; Desenko, S. M.; Shishkin, S. V.; Musatov, V. I.; Shishkin, O. V.; Knyazeva, I. V. *Synthesis* **2005**, 2597–2601. (b) Chebanov, V. A.; Muravyova, E. A.; Desenko, S. M.; Musatov, V. I.; Knyazeva, I. V.; Shishkina, S. V.; Shishkin, O. V.; Kappe, C. O. *J. Comb. Chem.* **2006**, *8*, 427–434.

(17) Dodd D. S. Unpublished results.

(18) Allen, C. F. H.; Beilfuss, H. R.; Burness, D. M.; Reynolds, G. A.; Tinker, J. F.; Van Allan, J. A. *J. Org. Chem.* **1959**, *24*, 787–793.

(19) Milata, V. *Aldrichim. Acta* **2001**, *34*, 20–27.

(20) Reiter, J.; Pongo, L.; Dvortsak, P. *J. Heterocycl. Chem.* **1987**, *24*, 1149–1154.

(21) Novinson, T.; Okabe, T.; Robins, R. K.; Dea, P. *J. Heterocycl. Chem.* **1975**, *12*, 1187–1190.

(22) El Ashry, E. S. H.; El Kilany, Y.; Rashed, N.; Mousaad, A.; Assafir, H. *Z. Naturforsch., B: Chem. Sci.* **1998**, *5*, 1203–1212.

(23) (a) Allen, C. F. H.; Beilfuss, H. R.; Burness, D. M.; Reynolds, G. A.; Tinker, J. F.; VanAllan, J. A. *J. Org. Chem.* **1959**, *24*, 779–787. (b) Esses-Reiter, K.; Reiter, J. *J. Heterocycl. Chem.* **1987**, *24*, 1503–1508. (c) Reiter, J.; Pongo, L.; Dvortsak, P. *Tetrahedron* **1987**, *43*, 2497–2504.

(24) Reiter, J.; Pongo, L. *Org. Prep. Proced. Int.* **1989**, *21*, 163–171.

(25) Künstlinger, M.; Breitmaier, E. *Synthesis* **1983**, 44–47.

(26) Allen, C. F. H.; Beilfuss, H. R.; Burness, D. M.; Reynolds, G. A.; Tinker, J. F.; VanAllan, J. A. *J. Org. Chem.* **1959**, *24*, 779–787.

CC700161R