ORGANIC LETTERS

1999
Vol. 1, No. 8
1189−1191

Synthesis of 1,2,4-Triazole-Functionalized Solid Support and Its Use in the Solid-Phase Synthesis of Trisubstituted 1,2,4-Triazoles[†]

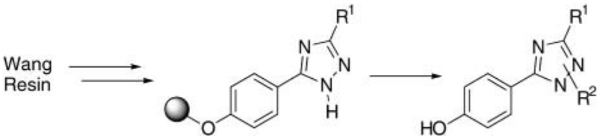
Alan R. Katritzky,*,[‡] Ming Qi,[§,‡] Daming Feng,[‡] Guifeng Zhang,[‡]
Michael C. Griffith,[§] and Karen Watson[§]

Center for Heterocyclic Compounds, Department of Chemistry,
University of Florida, Gainesville, Florida 32611-7200, and Trega Biosciences Inc.,
9880 Campus Point Drive, San Diego, California 92121

katritzky@chem.ufl.edu

Received July 26, 1999

ABSTRACT



1,2,4-Triazoles were synthesized on a solid support in three steps, with excellent yields and purities. The utility of this triazole-functionalized solid support was demonstrated by the solid-phase synthesis of various trisubstituted 1,2,4-triazoles.

In the past decade, research from our laboratory has demonstrated that benzotriazole is a versatile synthetic auxiliary in the syntheses of many structurally diverse, useful organic compounds.[1] The benzotriazole methodology has the advantages of (i) easy introduction of the benzotriazolyl moiety into various starting materials and (ii) versatile cleavage of benzotriazole from the products.[1,2] Meanwhile, combinatorial chemistry, particularly solid-phase synthesis, has emerged as an important method for the construction of organic compound libraries.[3] This advance prompted us to apply well-established solution-phase benzotriazole-mediated synthetic methodologies to solid-phase combinatorial chemistry, allowing us to take advantage of both areas. The most direct realization of this would be the development of a solid support with a terminal *N*-unsubstituted benzotriazolyl group. As 1,2,4-triazole possesses similar reactivity to that of benzotriazole,[4] and because of its easier accessibility, we set as our first goal the synthesis of a 1,2,4-triazole-functionalized solid support and the further investigation of its potential use in combinatorial synthesis.[5] Herein, we disclose the successful preparation of the 1,2,4-triazole linker on

---

[†] Some of this work is covered in a patent application.

[‡] University of Florida.

[§] Trega Biosciences, Inc.

(1) (a) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409. (b) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683.

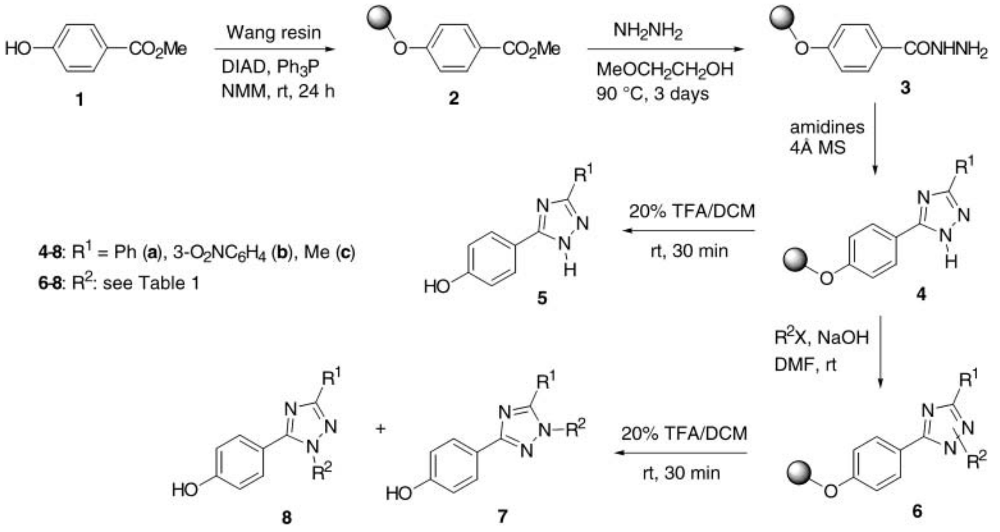
(2) (a) Katritzky, A. R.; Qi, M. *J. Org. Chem.* **1997**, *62*, 4116. (b) Katritzky, A. R.; Qi, M.; Feng, D.; Nichols, D. A., *J. Org. Chem.* **1997**, *62*, 4121.

(3) (a) Balkenhohl, F.; Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2289. (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (c) *Acc. Chem. Res.* **1996**, *29*, 111 (Special Issue on Combinatorial Chemistry; Czarnik, A. W., Ellman, J. A., Eds.). (d) *Chem. Rev.* **1997**, *97*, 347 (Combinatorial Chemistry; Szostak, J., Ed.). (e) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643. (f) Wilson, S. R., Czarnik, A. W., Eds. *Combinatorial Chemistry, Synthesis and Application*; John Wiley & Sons: New York, 1997.

(4) (a) Katritzky, A. R.; Jozwiak, A.; Lue, P.; Yannakopoulou, K.; Palenik, G. J.; Zhang, Z.-Y. *Tetrahedron* **1990**, *46*, 633. (b) Katritzky, A. R.; El-Zemity, S.; Lang, H.; Kadous, E. A.; El-Shazly, A. M. *Synth. Commun.* **1996**, *26*, 357. (c) A model study using 3,5-diphenyl-1,2,4-triazole instead of benzotriazole in the synthesis of 1,3-aminoether [cf. Katritzky, A. R.; Rachwal, S.; Rachwal, B.; Steel, P. J. *J. Org. Chem.* **1992**, *57*, 4932] has been carried out successfully in this laboratory.

10.1021/ol990186a CCC: $18.00

Scheme 1



Wang resin and its preliminary use in the synthesis of a variety of trisubstituted 1,2,4-triazoles.

Synthesis of 1,2,4-Triazole Linker on Wang Resin. Several synthetic routes for the preparation of 1,2,4-triazoles in the solution phase are documented.[6] Considering the relatively milder reaction conditions and greater availability of starting materials, we utilized Meckler et al.'s method[6b] as a three-step procedure (Scheme 1). Acid-labile Wang resin was selected as the solid support. After each step, the product was cleaved from the resin and analyzed by HPLC, GCMS, or NMR to determine the reaction process.[7]

Resin **2** was easily prepared from Wang resin and methyl *p*-hydroxybenzoate (**1**), via a Mitsunobu reaction (Scheme 1),[8] in quantitative yield and 100% purity (according to GC analysis of the mixture after cleavage). Both diisopropyl azodicarboxylate (DIAD) and diethyl azodicarboxylate (DEAD) were used successfully in this reaction.

Conversion of ester resin **2** into acyl hydrazide resin **3**[9] was attempted under various reaction conditions, including (i) neat hydrazine hydrate (99%) at room temperature, (ii) hydrazine hydrate (99%) in dioxane (15% v/v) or (iii) glycol (1:1) at 90 °C, (iv) hydrazine hydrate (99%) in DMF (1:1) at room temperature. Of all the conditions tried, hydrazine hydrate (99%) in 2-methoxyethanol (1:1) at 90 °C gave the best result in terms of yield (>95%), purity (93−97%), and reproducibility. The reaction is usually complete after 3 days; however, we obtained almost the same results for the 7 day reaction, which demonstrates that the reaction products are stable on the resin under these conditions.

Resin **3** was reacted with benzamidine, using sodium methoxide as catalyst in 2-methoxyethanol at 100 °C to produce triazole resin **4a**. Samples of the resin were frequently cleaved, and the resulting mixture was analyzed by HPLC (comparing to authentic sample made via solution-phase chemistry[6b]) and LC/MS (ESI). It was found that adding 4 Å molecular sieves as a water scavenger facilitates the cyclization process.[10] Under these conditions, the expected triazole **5a** was obtained in a quantitative overall mass yield of product mixture based on the original loading of the Wang resin, in 85% purity. We also found that the use of freshly made acyl hydrazide resin **2** (less than 2 days old) gave much better results than using resin stored for a longer time (about 2 weeks). In a similar manner, 3-nitrobenzamidine was treated with acyl hydrazide resin **3** to give

---

[5] While this paper was in the internal review process, our group and others prepared benzotriazole on solid support, as well as the solid-phase synthesis of 3-thio-1,2,4-triazoles, see: (a) Katritzky, A. R.; Belyakov, S. A.; Tymoshenko, D. O. *J. Comb. Chem.* **1999**, *1*, 173. (b) Schiemann, K.; Showalter, H. D. H. *J. Org. Chem.* **1999**, *64*, 4972. (c) Paio, A.; Zaramella, A.; Ferritto, R.; Conti, N.; Marchioro, C.; Seneci, P. *J. Comb. Chem.* **1999**, *1*, 317. (d) Wilson, M. W.; Hernandez, A. S.; Calvet, A. P.; Hodges, J. C. *Mol. Diversity* **1998**, *3*, 95.

[6] (a) Temple, C., Jr. *The Chemistry of Heterocyclic Compounds*, Vol. 37; Montgomery, J. A., Ed.; 1981; p 41. (b) Francis, J. E.; Gorczyca, L. A.; Mazzeuga, G. C.; Meckler, H. *Tetrahedron Lett.* 1987, *28*, 5133. (c) Kosmrlj, J.; Kocevar, M.; Polanc, S. *Synlett* **1996**, 652.

[7] Resin cleavage conditions: 20% TFA/CH$_2$Cl$_2$ (v/v) at room temperature for 30 min. HPLC conditions: reverse phase column (ODS-3); UV detector at 210 nm. Mobile phase: 70% CH$_3$CN−30% H$_2$O−0.1% TFA.

[8] (a) Hughes, D. L. *Org. React.* **1992**, *42*, 355. (b) Richter, L. S.; Gadek, T. R. *Tetrahedron Lett.* **1994**, *35*, 4705. (c) Rano, T. A.; Chapman, K. T. *Tetrahedron Lett.* **1995**, *36*, 3789. (d) Krchnak, V.; Flegelova, Z.; Weichsel, A. S.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 6193.

[9] An alternative route for the synthesis of resin **3** was also tried. However, the Mitsunobu reaction between Wang resin and 4-hydroxybenzoic hydrazide in DMSO/NMM gave a complex mixture, according to HPLC analysis.

[10] **Preparation of Triazole Resin 5a**. (i) Twenty bags of Wang resin (loading 0.86 mmol/g, 100 mg/bag) were suspended in *N*-methylmorpholine (NMM, 160 mL). Methyl *p*-hydroxybenzoate (40 mmol) was added and dissolved in NMM, followed by Ph$_3$P (40 mmol) and DIAD (40 mmol) at 0 °C. After the mixture was shaked at room temperature for 24 h, the tea bags were washed with DMF (2 × 50 mL), MeOH (50 mL), DMF (50 mL), MeOH (50 mL), CH$_2$Cl$_2$ (50 mL), MeOH (50 mL), and CH$_2$Cl$_2$ (2 × 50 mL) and dried under vacuum to give ester resin **2**. (ii) Ten bags of resin **2** and NH$_2$NH$_2$·H$_2$O (99%, 30 mL) in 2-methoxyethanol (30 mL) were stirred at 90 °C for 3 days. The resin was then washed with MeOH (2 × 50 mL), CH$_2$Cl$_2$ (50 mL), MeOH (50 mL), and CH$_2$Cl$_2$ (2 × 50 mL) and dried under vacuum to afford acyl hydrazide resin **3**. (iii) Ten bags of resin **3** were added to a solution of benzamidine (40 mmol) in 2-methoxyethanol (80 mL), followed by 4 Å molecular sieves (7 g). The tea bags were heated at 100 °C for 7 days, washed as for resin **2**, and dried to give triazole resin **4a**.

triazole resin **4b**. After cleavage, triazole **5b** was obtained in 90% purity and 95% yield. The structure of **5b** was confirmed by LC/MS and MS/MS analysis.

The synthesis of methyl-substituted triazole resin **4c** was also attempted (Scheme 1). It has been reported[6b] that acetamidine reacts with acyl hydrazides at room temperature to form acyl amidirazones, which could be isolated and further cyclized to triazoles upon heating (solution phase). Knowing that free acetamidine decomposes even on slight heating, we reacted acetamidine with resin **3** in 2-methoxyethanol at room temperature for 2 days to form the intermediate, which was then heated in the presence of 4 Å molecular sieves at 100 °C. The desired methyltriazole **5c** was obtained, after cleavage in 90% yield and 75% purity.

Preparation of Trisubstituted Triazoles. To introduce another substituent group into the triazole ring, we tried the reaction of triazole resins **4** with various alkyl halides (Scheme 1). The solution-phase reactions of 1,2,4-triazole and alkyl halides is well-developed.[11] We found the solid-phase reaction gave good results (70−90% purity in almost quantitative yields) for both primary and secondary alkyl bromides (Table 1). All of these reactions employed a DMF solution of R^2X (0.25 M, ∼30 equiv) and NaOH (0.8 M, ∼100 equiv, ground under the protection of nitrogen). Except in two cases, all trisubstituted triazoles contain two regioisomers in 60:40 to 40:60 ranges. For the products from resin **4b**,**c**, one isomer was the major isomer, presumably due to the steric effect differences from the two substituents on the ring.

In most cases, the corresponding alkyl *p*-hydroxybenzoate is the major byproduct. Apparently, this byproduct is formed from the hydrolysis of the impurities (unreacted ester, acyl hydrazide, or other intermediates) present on the resin in the same tea bag[12] with the triazole linker **5** and esterfication of the resulting *p*-hydroxybenzoic acid.

Table 1. Preparation of Trisubstituted Triazoles **7** and **8**[a]

resin **4**	R^1	R^2X	time (h)	purity[b]	isomer ratio[c]
4a	Ph	*n*-BuBr	7	82	56/44
4a	Ph	*i*-PrBr	15	90	48/52
4a	Ph	c-C_5H_9Br	15	71	51/49
4a	Ph	$CH_2{=}CHCH_2Br$	5	78	50/50
4a	Ph	$C_6H_5CH_2Br$	5	54[d]	64/36
4a	Ph	*n*-$C_6H_{13}CHBrCH_3$	5	88	49/51
4a	Ph	$C_6H_5CHBrCH_3$	15	70	40/60
4a	Ph	c-$C_3H_5CH_2Br$	5	77	38/62
4b	3-$O_2NC_6H_4$	*n*-BuBr	12	37[e]	18/82
4c	Me	*n*-$C_6H_{13}CHBrCH_3$	5	90	94/6

[a] An almost quantitative overall mass yield of product mixtures based on the original loading of the Wang resin was obtained in each case. [b] Qualitative purity based on GCMS, LCMS, or HPLC. [c] It has not been determined whether isomer **7** or **8** corresponds to the major isomer. [d] Determined by HPLC and NMR; the product was contaminated with 39% of starting material **5a**. [e] The resin used only consists of 53% of the expected resin **4b**.

In solution-phase reactions, when the benzotriazole or triazole moiety is removed in the last stage, most often it is displaced by substitution.[1a,4] This means that the triazole linker would be acting as a traceless linker[13] for solid-phase synthesis. Further work on this area will be reported in due course.

In conclusion, we devised a synthetic method for the effective construction of 1,2,4-triazoles on solid support and utilized these novel triazole linkers for the synthesis of trisubstituted 1,2,4-triazoles.

OL990186A

---

(11) (a) Zhang, H.; Liao, L.; Guo, Q. *Houji Huaxue*, **1986**, 108; *Chem. Abstr*. **1986**, *105*, 226456. (b) Katritzky, A. R.; Kuzmierkiewicz, W.; Greenhill, J. V. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 369.

(12) Houghten, R. A. U.S. Patent 4,631,211, 1986.

(13) (a) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171. (b) Chenera, B.; Finkelstein, J. A.; Veber, D. F. *J. Am. Chem. Soc.* **1995**, *117*, 11999. (c) Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1997**, *38*, 211.