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Traceless Solid-Phase Synthesis of 1,2,4-Triazoles Using a Novel Amine Resin

Scott D. Larsen* and Brian A. DiPaolo

Combinatorial and Medicinal Chemistry Research, Pharmacia Corporation, Kalamazoo, Michigan 49007

scott.d.larsen@pharmacia.com

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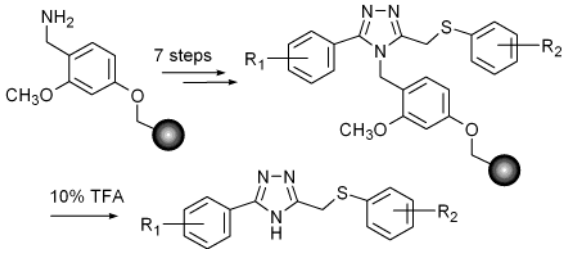
ABSTRACT

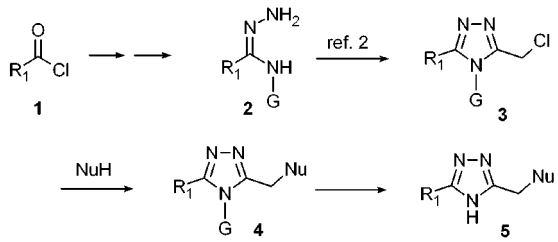


A solid-phase route to 5-aryl-3-arylthiomethyl-1,2,4-triazoles has been developed that permits the incorporation of two elements of diversity. The heterocycle was constructed upon a novel 4-benzyloxy-2-methoxybenzylamine (BOMBA) resin, from which traceless cleavage could be effected with dilute TFA. A library of 96 triazoles was produced with an average yield of 26% (84% yield per step) and an average purity of 80%. In a direct comparison, the new BOMBA resin proved to be markedly superior to Rink Amide resin for this application.

In conjunction with an ongoing therapeutic effort, we required the development of a library synthesis of 1,2,4-triazoles that would permit facile variation at the 3 and 5 carbons. 1,2,4-Triazoles have been prepared by a number of routes, but only a couple have been adapted to solid phase.[1] The most commonly employed approach entails the direct condensation of thioamides with hydrazides, but this was not appealing because these starting materials are not commercially available in sufficient diversity. An alternative strategy was thus considered that was less concise but more flexible (Scheme 1). Amidrazones **2** (*G* = aryl), readily derived from acid chlorides **1**, have been reported by Thiel to react with chloroacetyl chloride to afford 3-chloromethyl-1,2,4-triazoles **3**,[2] intermediates that seemed ideal for the subsequent introduction of diversity via nucleophilic addition. Replacement of the G group on the nitrogen of **2** with a resin linker offered the prospect for a solid-phase synthesis that would culminate in the traceless cleavage of triazoles **5**.

The success of this approach relied upon the selection of an appropriate resin linker that would permit the release of the triazoles under mild conditions. An excellent precedent was provided by Bilodeau, who used a 2-methoxy-4-alkoxybenzyl linker for preparing imidazoles on resin, which were subsequently cleaved with acetic acid.[3] Assuming that

Scheme 1



(1) (a) Katritzky, A. R.; Qi, M.; Feng, D.; Zhang, G.; Griffith, M. C.; Watson, K. *Org. Lett.* **1999**, *1*, 1189−91. (b) Wilson, M. W.; Hernandez, A. S.; Calvet, A. P.; Hodges, J. C. *Mol. Diversity* **1998**, *3*, 95−112.

(2) Thiel, W. *Z. Chem.* **1990**, *30*, 365−367.

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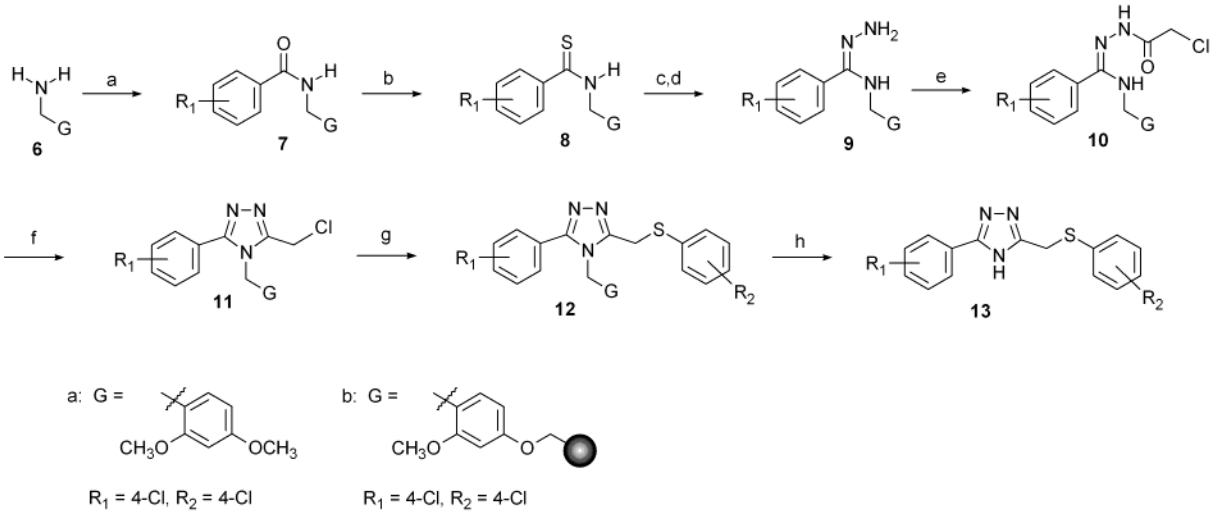
Scheme 2[a]



[a] Reagents and conditions: (a) $R_1PhCOCl$, Et_3N, CH_2Cl_2; (b) Lawesson's reagent, pyr, 85 °C; (c) MeOTf, CH_2Cl_2, rt; (d) hydrazine, 2-methoxyethanol, rt; (e) $ClCOCH_2Cl$, CH_2Cl_2, rt; (f) 1:1 DMF/HOAc, rt; (g) R_2PhSH, KOH, 2-methoxyethanol; (h) 10% TFA/CH_2Cl_2.

triazoles would be released at least as readily as imidazoles, this linker seemed ideal for our application.

Chemistry was developed initially in solution, using 2,4-dimethoxybenzylamine (**6a**) as a model for the eventual resin linker (Scheme 2). Anticipating that eventual library production would be executed in IRORI MiniKans, conditions were limited to those compatible with Kan integrity. Acylation with 4-chlorobenzoyl chloride to make amide **7a** (62%) was straightforward. Conversion to thioamide **8a** (90%) was effected with Lawesson's reagent in hot pyridine. Direct conversion of the thioamide to amidrazone **9a** by heating with hydrazine was not successful, so **8a** was first converted to the corresponding thioimidate via alkylation with methyl triflate, which subsequently reacted smoothly with hydrazine at room temperature to afford **9a** (54% overall). Acylation with chloroacetyl chloride then produced acylated amidrazone **10a** (94%), which was isolated as a mixture of regio- and/or stereoisomers.

The key cyclization of **10a** required some development. Direct heating, as reported by Thiel,[2] provided the desired triazole **11a** but was accompanied by significant cleavage of the dimethoxybenzyl group. However, when the crude amidrazone **10a**, isolated as the HCl salt, was first neutralized by washing with dilute aqueous NaOH, cyclization in DMF/HOAc proceeded smoothly (92%) at room temperature with no detectable debenzylation. Reaction of the resulting chloromethyltriazole **11a** with 4-chlorothiophenol in alkaline 2-methoxyethanol then provided the desired thiomethyltriazole **12a** (80%). The key model cleavage of the benzyl group was effected in 90 min at room temperature with 50% TFA in methylene chloride, affording **13a** in 85% yield.

With a viable solution-phase route in hand, we turned our attention to translating the chemistry onto resin. To our surprise, we could find no literature precedent for the requisite polystyrene amine resin **6b**, despite the fact that the corresponding benzyl alcohol resin is commercially available (SASRIN).[4] Related commercial amine resins, including Rink, PAL and Knorr, were rejected on the basis of excessive steric bulk, extreme acid sensitivity, or the presence of incompatible functionality (carboxamide).[5] Closely related literature resin BOBA[6] (**14**, Figure 1) was deemed insufficiently reactive to release triazoles under mild acidic conditions, and the 2-methoxy-4-benzyloxy resin **15**[7] (Figure 1), derived from (HMPB)-MBHA resin, also possessed an incompatible butyramide linkage.

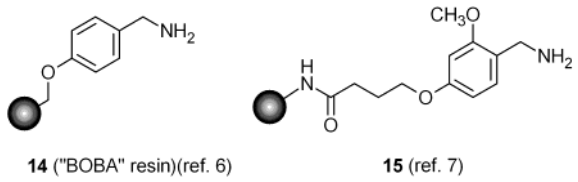


Figure 1. Literature benzylamine resins.

A number of routes to resin **6b** were examined, only one of which proved reliable upon scale-up (Scheme 3). AMEBA resin **16**,[8] prepared from Merrifield resin (IRORI Unisphere 200), was converted to oxime resin **17** with hydroxylamine

(3) Bilodeau, M. T.; Cunningham, A. M. *J. Org. Chem.* **1998**, *63*, 2800−2801.

(4) Registered trademark of BACHEM.

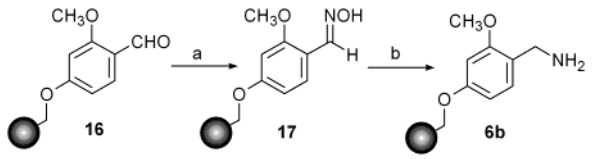
(5) For an excellent recent review on resin linkers, see: Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091−2157.

(6) Kobayashi, S.; Aoki, Y. *Tetrahedron Lett.* **1998**, *39*, 7345−7348.

(7) Cho, C. Y.; Youngquist, R. S.; Paikoff, S. J.; Beresini, M. H.; Hebert, A. R.; Berleau, L. T.; Liu, C. W.; Wemmer, D. E.; Keough, T.; Schultz, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 7706−7718.

(8) Fivush, A. M.; Willson, T. M. *Tetrahedron Lett.* **1997**, *38*, 7151−7154.

Scheme 3[a]



[a] Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, pyr, rt, 30 h; (b) 1 M $LiAlH_4$, THF, rt, 24 h.

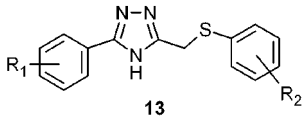
hydrochloride in pyridine. Reduction to amine resin **6b** was then effected with 1 M $LiAlH_4$ in THF at room temperature.[9] The overall yield of **6b** from Merrifield resin was 28% (final loading = 0.44 mmol/g, determined by FMOC quantitation).

The solution-phase route depicted in Scheme 2 translated onto solid phase with remarkable ease (**6b**−**13a**). The only variable that consistently needed to be changed was reaction time. One notable exception was the key cyclization of **10b** to triazole **11b**. Whereas neutralization of **10a** was critical for success in solution, we observed no apparent need for neutralizing resin **10b**. Cyclization to **11b** occurred with equal yield and purity regardless of whether **10b** was used directly or first washed with triethylamine. One possible explanation is that cleavage from the resin is simply not as facile as the solution-phase debenzylation. Final cleavage from resin **12b** proceeded under mild conditions (10% TFA/CH_2Cl_2, rt, 1 h), affording **13a** in 65% overall yield (*ca. 95% yield per step*) and 78% purity (HPLC at 210 nm).

Rink amide resin (IRORI Unisphere 200) was also evaluated as a support in this synthesis in a direct side by side comparison with **6b** in which 60 mg of each resin was placed in separate IRORI MiniKans and subjected to the eight-step sequence in Scheme 2. In this experiment, resin **6b** afforded 7.8 mg of **13** (88% overall yield) in 85% purity, while Rink amide resin provided only 4.4 mg (23% overall yield) in <80% purity. Despite its considerably lower loading (0.44 mmol/g **6b** vs 0.94 mmol/g Rink amide), the new resin **6b** actually afforded nearly double the mass of **13a**, indicating a clear superiority for this particular application.

To gauge the generality of the solid-phase synthesis in Scheme 2, a two-dimensional library of triazoles was prepared. Eight aroyl chlorides and 12 aryl thiols were combined to construct a 96-member library, using the IRORI AccuTag-100 system. Following cleavage, HPLC/MS analysis of the entire library (data not shown) indicated that every analogue had been successfully prepared in purities ranging from 20% to 99%. Specific yield and purity data for representative analogues (at least one example of each diversity element) are compiled in Table 1. The average yield for the entire library was 26%, with an average purity of 80%. Because the library analogue yields were lower than expected from the development work, a second cleavage was performed, resulting in an additional average of 5.0 mg (50% yield) for each analogue that was of slightly lower average purity (71%). Thus the actual average yield for the library was closer to 75%, although optimum purity was achieved by performing a single lower-yielding cleavage operation.

Table 1. Yield and Purity Data for Representative Analogues from Triazole Library



13

cmpd	R_1	R_2	purity[a] (%)	yield[b] (%)
13a	4-Cl	4-Cl	83	33
13c	2,4-diOMe	4-Cl	37	13
13d	4-OMe	4-Cl	85	24
13e	4-Cl	4-OMe	83	25
13f	H	4-Cl	82	36
13g	4-Cl	H	89	31
13h	4-Cl	3,4-diOMe	85	28
13i	4-Cl	pentafluoro	71	23
13j	4-Cl	4-AcNH	85	23
13k	4-Cl	3,4-diCl	86	34
13l	4-Cl	2-naphthyl[c]	96	29
13m	4-Cl	4-Me	85	29
13n	4-Cl	4-Br	58	29
13o	3,4-diCl	4-Cl	81	28
13p	4-Cl	2-CH_2OH	83	27
13q	2-naphthyl[c]	4-Cl	87	33
13r	4-Me	4-Cl	80	33
13s	4-CF_3	4-Cl	84	36
13t	4-Cl	4-NH_2	83	25

[a] Determined by HPLC/MS (210 nm). [b] Overall unpurified yield from resin **6b**. [c] Denotes R_1 or R_2 being fused phenyl ring.

To expand the scope of our triazole synthesis, two alkanethiols (3-phenyl-1-propanethiol and benzyl mercaptan) were successfully reacted with resin **11b**, affording the corresponding triazoles **13** in 71% and 74% purities, respectively, after TFA cleavage. Attempts to incorporate an alkyl acid chloride into Scheme 2 were less promising, however. At the acyl amidrazone formation stage, the

(9) Pietta, P. G.; Cavallo, P. F.; Takahashi, K.; Marshall, G. R. *J. Org. Chem.* **1974**, *39*, 44−48.

(10) **Synthesis of BOMBA Resin 6b.** To a suspension of IRORI Unisphere 200 Merrifield resin (1.10 g, 1.58 mmol/g) in DMF (25 mL) was added sodium methoxide (0.293 g, 5.43 mmol), followed by 4-hydroxy-2-methoxybenzaldehyde (0.828 g, 5.44 mmol). The mixture was heated to 65 °C for 24 h, after which time the resin was filtered and washed successively with DMF, MeOH, H_2O, MeOH, CH_2Cl_2, and MeOH. The resin was dried in vacuo; **16** was obtained as an off-white resin (1.05 g). FTIR indicated aldehyde formation with a strong absorption peak at 1678 cm^{-1}. AMEBA resin **16** (1.05 g) and hydroxylamine hydrochloride (0.70 g, 10.08 mmol) were suspended in pyridine (10 mL). After agitating for 30 h at room temperature, the resin was filtered and washed with 1:1 pyridine/H_2O, H_2O, MeOH, CH_2Cl_2, and MeOH. FTIR analysis indicated complete disappearance of the carbonyl peak at 1678 cm^{-1}; **17** was obtained as an off-white resin (1.04 g). To a suspension of oxime resin **17** (0.50 g, 0.64 mmol) in THF (3.8 mL) was added 1 M lithium aluminum hydride in THF (1.3 mL). The mixture was stirred for 24 h at room temperature, after which time the reaction mixture was cooled to 0 °C. The excess lithium aluminum hydride was slowly quenched with EtOH, and the aluminum salt byproducts were then dissolved with a minimal amount of 10% HCl. Once dissolved, the resin was filtered and washed with MeOH and CH_2Cl_2 (alternating, three cycles), followed by washing with 10% triethylamine in CH_2Cl_2 to neutralize the amine. Following a final wash with CH_2Cl_2, the resin was dried in vacuo. **6b** was obtained as a brownish-yellow resin (0.50 g). Loading of resin, determined by FMOC quantitation, was 0.44 mmol/g.

solution-phase chemistry became very complex, discouraging us from expanding the solid-phase chemistry in this direction.

In conclusion, we have developed a novel benzylamine resin (4-benzyloxy-2-methoxybenzylamine, BOMBA)[10] on which a de novo solid-phase synthesis[11] of disubstituted 1,2,4-triazoles was successfully demonstrated. To the best of our knowledge, this is the first reported synthesis of 1,2,4-triazoles entailing tethering of the nascent heterocycle to the resin through a ring nitrogen, thereby permitting a "traceless" synthesis. The construction of heterocycles on solid phase via linkage directly to the ring has proven in general to be a valuable strategy because it permits facile variation of substituents.[12] The overall yields and purities realized in the production of a 96-member library suggest that the chemistry is sufficiently general to accommodate a variety of substituents, although clearly diversity would be expected to be tolerated to the greatest degree in the nucleophilic addition step. It is worth noting that the success of this synthetic route was greatly facilitated by the IRORI AccuTag technology,[13] which is able to conveniently accommodate the introduction of diversity early in a synthetic sequence.

Supporting Information Available: Full experimental details for the solution-phase synthesis of **13a** from **6a**, including analytical and spectroscopic data for each intermediate, and procedures for the synthesis of the 96-member triazole library with the IRORI AccuTag-100 system. This material is available free of charge via the Internet at http://pubs.acs.org. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **Procedures for the Solid-Phase Synthesis of 5-(4-Chlorophenyl)-3-{[(4-chlorophenyl)thio]methyl}-1*H*-1,2,4-triazole (13a) from Resin 6b.** Six IRORI MiniKans, filled with BOMBA resin **6b** (60 mg in each), were placed in a 100-mL round-bottom flask, to which were added CH_2Cl_2 (30 mL) and triethylamine (2.09 mL, 15.0 mmol). The MiniKans were degassed. After cooling to 0 °C, 4-chlorobenzoyl chloride (1.90 mL, 15.0 mmol) was added and the MiniKans were stirred at 0 °C for an additional 30 min. Once warmed to room temperature, the MiniKans were stirred for another 6 h. The reaction solution was then decanted off, and the MiniKans were washed with CH_2Cl_2 and MeOH (alternating, three wash cycles). Following a final wash with pyridine, the MiniKans containing resin **7b** were dried in vacuo. To a solution of Lawesson's reagent (1.60 g, 3.96 mmol) in pyridine (25 mL) was added **7b**. The MiniKans were degassed, and the reaction mixture was heated to 85 °C. After heating for 24 h, the reaction solution was decanted, and the MiniKans were washed with CH_2Cl_2 and MeOH (three alternating cycles). After a final wash with pyridine, the MiniKans were resubjected to the reaction conditions for an additional 24 h. Once again the reaction solution was decanted, and the MiniKans were washed with 1:1 pyridine/H_2O, followed by CH_2Cl_2 and MeOH (three alternating cycles). After a final CH_2Cl_2 wash, the MiniKans were dried in vacuo. To the six IRORI MiniKans, now containing thioamide resin **8b**, in a 100 mL round-bottom flask was added CH_2Cl_2 (20 mL). The mixture was degassed before the addition of methyl triflate (0.907 mL, 8.00 mmol). After agitating overnight at room temperature, the reaction solution was decanted, and the MiniKans were washed with CH_2Cl_2 and acetonitrile (alternating, three cycles). After a final wash with 2-methoxyethanol in preparation for the next step, the MiniKans were dried in vacuo. The MiniKans containing thioimidate resin were submersed in 2-methoxyethanol (25 mL), degassed, and mechanically agitated for 10 min before hydrazine monohydrate (1.21 mL, 25.0 mmol) was added. After agitating for 24 h at room temperature, the reaction solution was decanted, and the MiniKans were washed with CH_2Cl_2 and acetonitrile (three alternating wash cycles). After a final wash with 2-methoxyethanol, the MiniKans were resubjected to the reaction conditions for an additional 24 h. The reaction solution was again decanted, and the MiniKans were washed with CH_2Cl_2 and acetonitrile (alternating, three cycles). After the final wash with CH_2Cl_2, the MiniKans were dried in vacuo. To the MiniKans containing amidrazone resin **9b** was added CH_2Cl_2 (25 mL). The mixture was degassed before the addition of chloroacetyl chloride (2.00 mL, 25.0 mmol). After the reaction was capped and mechanically shaken at room temperature for 24 h, the reaction solution was decanted, and the MiniKans were washed with CH_2Cl_2 and MeOH (three alternating cycles). Finally, the MiniKans were washed with DMF and dried in vacuo. Acylated resin **10b**, in IRORI MiniKans, was submersed in 1:1 DMF/AcOH (30 mL), degassed, and mechanically agitated at room temperature for 20 h. The reaction solution was decanted, and the MiniKans were washed with CH_2Cl_2 and MeOH (alternating, three wash cycles). The MiniKans were dried in vacuo. A small sample of the resin was then cleaved with 10% TFA in CH_2Cl_2. HPLC/MS analysis at this step indicated a purity of 96% at 254 nm and 87% at 210 nm. In a 50-mL round-bottom flask, potassium hydroxide (1.68 g, 30 mmol) was dissolved in 1:1 THF/2-methoxyethanol (30 mL). After the solution was degassed, 4-chlorothiophenol (4.34 g, 30 mmol) was added, and the solution was stirred for 10 min. Triazole resin **11b**, in IRORI MiniKans, was added, and the reaction mixture was once again degassed. After stirring at room temperature for 24 h, the reaction solution was decanted, and the MiniKans were washed with CH_2Cl_2 and MeOH (three alternating wash cycles). After drying in vacuo, one of the MiniKans, originally loaded with 60 mg of resin **6b**, was cleaved with 10% TFA/CH_2Cl_2 (rt, 1 h), affording 5.7 mg of **13a** (65% overall yield from **6b**). Purity of the final product was 89% at 254 nm, and 78% at 210 nm. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (s, 2 H), 7.26 (d, J = 8.1 Hz, 2 H), 7.31 (d, J = 8.5 Hz, 2 H), 7.43 (d, J = 8.3 Hz, 2 H), 7.95 (d, J = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.87, 126.58, 127.94, 128.75, 129.28, 129.36, 129.54, 130.56, 131.27, 134.48, 134.77. MS (ES+) m/z 336 (100), 338 (72).

(12) (a) Backes, B. J.; Ellman, J. A. *Curr. Opin. Chem. Biol.* **1997**, *1*, 86−93. (b) For a recent review on solid-phase heterocycle syntheses, see: Franzen, R. G. *J. Combi. Chem.* **2000**, *2*, 195−214.

(13) Mendonca, A. J. *Am. Lab.* **1998**, *30*, 46−47.