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Applications of solid supported azide anion: a one-pot, two-step preparation of functionalized 1,2,3-triazoles

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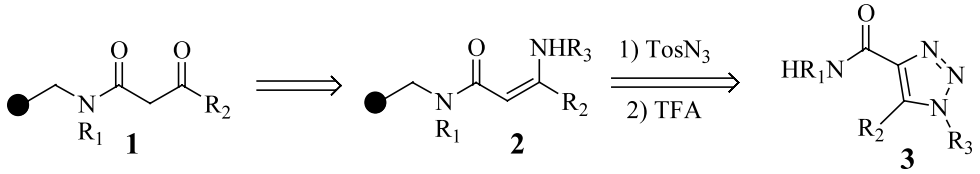
Abstract—Functionalized 1,2,3-triazoles were prepared in a one-pot, two-step synthesis from alkyl halides and alkynes using a polymer supported azide. Two different base resins were examined. The chemistry is suitable for the preparation of combinatorial libraries. © 2003 Published by Elsevier Science Ltd.

Over the past several years, the field of combinatorial chemistry has established itself as a valuable tool for drug discovery.[1] The synthesis of vast libraries based on heterocyclic scaffolds, including imidazoles, benzodiazepines, diketopiperazines, oxazolidinones, and quinolones have been reported. As part of our ongoing efforts to develop novel scaffolds for the preparation of combinatorial libraries, we have been investigating the preparation of functionalized 1,2,3-triazoles. Members of this class of compounds have been identified as adenosine antagonists, oxalic acid antagonists, metalloprotease inhibitors, antibacterials, β-lactamase inihibitors, antivirals and anticonvulsants.[2] A brief literature search identified two solid-phase syntheses of this class of compounds The first method employs functionalized, solid supported, β-ketoamides (**1**). Enamine formation (**2**), followed by ring closure with tosyl azide and TFA induced resin cleavage produced the desired 1,2,3-triazoles (**3**, Scheme 1).[3]

The second method, which has been recently disclosed, is an alternative solid phase method for the preparation of 1,2,3-triazoles from readily available bromo acids, alkynes, and Wang resin. Initial resin loading of an α-bromo acid (**4**) and modification to the resin bound azide (**5**) was followed by cycloaddition with a suitable alkyne to produce a resin bound triazole acid. Removal from the resin was then accomplished using standard conditions (Scheme 2).[4]

While both of these methods are effective for the production of functionalized triazoles, they both are limited by the required incorporation of a 'carboxyl' functionality to serve as the point of attachment for the resin. We felt that in order to increase the breadth of accessible library members of the triazole series, the presence of a required resin linker would need to be eliminated. Thus, we have developed a two-step preparation of substituted 1,2,3-triazoles based on the application of both resin bound reagent and cycloaddition chemistry. In this case, the use of a resin supported azide allows the use of an excess of this sometimes volatile reagent without requiring an aqueous work up to remove the excess azide. Simple filtration of the reaction removes the excess azide, and the next step can be performed without purification. Conversion of the alkyl bromide (**6**) to the necessary azide (**7**) can be



Scheme 1.

Keywords: solid supported azide; 1,2,3-triazoles; 2+3 cycloaddition.
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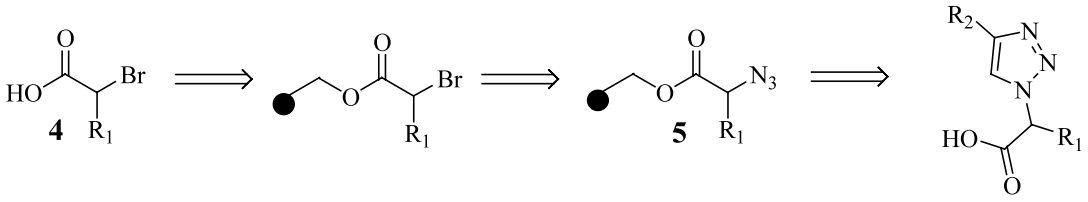
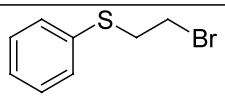
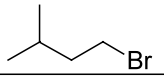
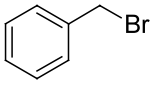
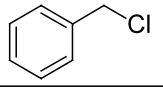
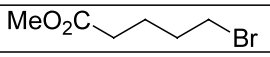
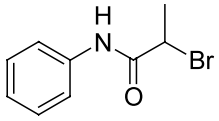
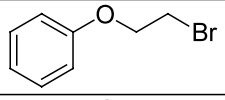
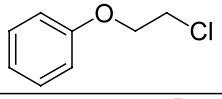
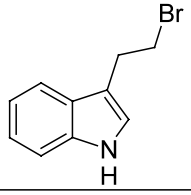
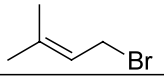
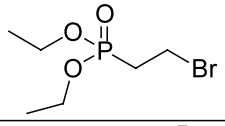
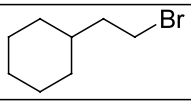


Scheme 2.

Table 1. Azide preparation and 2+3 cycloaddition with methyl propiolate

Entry	RBr (**6**)	Crude Yield **8**[a]	HPLC Purity (%)[b]	Crude Yield **8**[c]	HPLC Purity (%)[b]
1		84	86	82	80
2		48	93	73	99
3		85	89	98	97
4		86	60	98	95
5		98.5	81	99	85
6		99	62	99	64
7		92	63	100	75
8		0	NA	0	NA
9		95	77	97	84
10		41	76	88	84
11		35	58	90	87
12		89	95	99	95

[a] Using amberlite azide ion exchange resin.
[b] HPLC purity was measured at 220nm on a C18 symmetry column (4.6x 50 mm; 5um) using a linear gradient from 100% water to 100% acetonitrile over 8 minutes (2.5 ml/min flow rate).
[c] Using Merrifield resin supported tetra-alkyl ammonium azide.

Scheme 3.

accomplished with either Amberlite azide ion exchange resin[5] or the more conventional Merrifield resin supported tetra-alkyl ammonium azide (prepared from the commercially available polymer supported bromide)[6] in DMA over 72 hours. Removal of the resin by filtration and then heating the reaction to 80°C in the presence of 1.0 equiv. of methyl propiolate provided the desired 1,2,3-triazole (**8**) via a 2+3 cycloaddition reaction (Scheme 3). The products could then be isolated by simple evaporation of the solvents.[7] It is interesting to note that the while benzyl chloride provide the desired product in both reasonable yield and purity, the less reactive β-chlorophenetole did not provide detectable levels of the desired product. This is in direct contrast to β-bromophenetole, suggesting that alkyl chlorides that do not contain an additional activating feature are not reactive enough under the conditions examined. An examination of alternative solvents, such as EtOAc, THF, DMF and 1,4-dioxane, demonstrated that the reaction did occur, but the best results were obtained with DMA. Both of the azide resins provided the desired 1,2,3-traizoles in reasonable yields and purity, but the Merrifield resin bound azide showed superior swelling properties which may make it useful for additional chemistry that is not compatible with the Amberlite resin.

In summary, we have developed a simple, two step method for the preparation of libraries of functionalized 1,2,3-triazoles using a solid phase reagent. The products are obtained in reasonable yields and purity.

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6. Merrifield resin supported ammonium azide is prepared from the commercially available polymer supported bromide (3.5 mmol Br/g) as follows: 5.0 g of polymer supported bromide is suspended in 30 ml of DMA and 5.7 g of NaN_3 (5 equiv.) is added. After 48 h, the reaction is filtered, washed with methanol, and dried to a solid with IR showing a significant signal for azide at 2002 cm^{-1}.
7. Typical experimental procedure: To a suspension of azide bound resin (250 mg) in DMA (6 ml) is added a halide (50 mg). The mixture is then agitated for 72 h at room temperature. After the completion of the reaction (TLC), the resin is filtered off. To the solution is then added methyl propiolate (1 equiv.) and the reaction is stirred overnight at 80°C. The solvent is then evaporated and the desired product is isolated by reverse phase HPLC on a C18 symmetry column (20×100 mm; 5 μm) using a linear gradient from 100% water to 100% acetonitrile (0.02% TFA in both solvents) over 15 min (20 ml/min flow rate). Spectral data for Table 1: Entry **1** (^{1}H NMR, 300 MHz, CD_3OD): δ 3.30 (m, 2H), 3.75 (s, 3H), 4.50 (t, $J=6.50$ Hz, 2H), 7.09–7.20 (m, 5H), 8.33 (s, 1H). (M^+H) 264. Entry **2** (^{1}H NMR, 300 MHz, CD_3OD): δ 1.01 (d, $J=4.0$ Hz, 6H), 1.87 (q, $J=7.0$ Hz, 2H), 2.10 (m, 1H), 3.72 (m, 2H), 3.94 (s, 3H), 8.59 (s, 1H). (M^+H) 198. Entry **3** and **4** (^{1}H NMR, 300 MHz, CD_3OD): δ 3.90 (s, 3H), 5.66 (s, 2H), 7.31 (brs, 5H), 8.54 (s, 1H). (M^+H) 218. Entry **5** (^{1}H NMR, 300 MHz, CD_3OD): δ 1.69 (m, 2H), 2.02 (m, 2H), 2.49 (t, $J=7.30$ Hz, 2H), 3.73 (s, 3H), 3.82 (s, 3H), 4.39 (t, $J=7.00$ Hz, 2H), 8.46 (s, 1H). (M^+H) 242. Entry **6** (^{1}H NMR, 300 MHz, CD_3OD): δ 1.77 (d, $J=7.18$ Hz, 3H), 3.77 (s, 3H), 5.46 (m, 1H), 6.98 (t, $J=3.20$ Hz, 1H), 7.34 (t, $J=7.50$ Hz, 2H), 7.66 (d, $J=8.50$ Hz, 2H), 8.77 (s, 1H). (M^+H) 275. Entry **7** (^{1}H NMR, 300 MHz, CD_3OD): δ 3.84 (s, 3H), 3.70 (m, 2H), 4.40 (t, $J=5.0$ Hz, 2H), 6.82–6.89 (m, 3H), 7.17 (t, $J=5.30$ Hz, 2H), 8.55 (s, 1H). (M^+H) 247. Entry **9** (^{1}H NMR, 300 MHz, CD_3OD): δ 2.20 (m, 2H), 3.72 (t, $J=7.50$ Hz, 2H), 3.93 (s, 3H), 7.06 (m, 1H), 7.40 (d, $J=8.0$ Hz, 2H), 7.58 (m, 2H), 8.25 (s, 1H). (M^+H) 271. Entry **10** (^{1}H NMR, 300 MHz, CD_3OD): δ 1.97 (s, 6H), 3.79 (s, 3H), 4.30 (m, 2H), 5.36 (m, 1H), 8.33 (s, 1H). (M^+H) 196. Entry **11** (^{1}H NMR, 300 MHz, CD_3OD): δ 1.15 (m, 6H), 3.61 (m, 4H), 3.80 (s, 3H), 3.94 (m, 2H), 4.58 (m, 2H), 8.50 (s, 1H). (M^+H) 292. Entry **12** (^{1}H NMR, 300 MHz, CD_3OD): δ 1.30–1.46 (m, 11H), 1.88 (m, 2H), 3.83 (s, 3H), 4.38 (t, $J=7.50$ Hz, 2H), 8.38 (s, 1H). (M^+H) 238.