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Solid-phase synthesis of functionalized 1,2,3-triazoles

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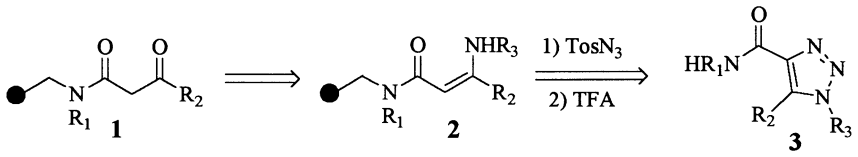
Abstract—Functionalized 1,2,3-triazoles are prepared by 2+3 cycloaddition of resin bound α-azido esters with substituted alkynes. The reaction is regioselective when the electron-deficient alkyne methyl propiolate is used.

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 on solid support, we have been investigating the resin-based synthesis 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 one solid-phase synthesis of this class of compounds employing 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]

We decided to explore an alternative route for the preparation of 1,2,3-triazoles from readily available bromo acids, alkynes, and Wang resin. Thus, initial resin loading of an α-bromo acid (**4**) and modification to the resin-bound azide (**5**) could be followed by cycloaddition with a suitable alkyne to produce a resin-bound triazole acid which could then be released from the resin with appropriate reagents (Scheme 2).

Resin loading of α-bromo acids has been reported using mild conditions (DIC, DMAP, DCE) to produce the desired resin bound esters (**6**) in high yield.[4] Conversion to the necessary azide (**5**) was readily accomplished using either sodium azide or TMS azide in dimethylacetamide (DMA) at room temperature (Scheme 3). Formation of the azido ester was easily monitored by IR, as a characteristic peak at ca. 2100 cm^{-1} appears and increases in intensity as the bromide is converted to the azide. Cycloaddition with an alkyne was then attempted under a variety of conditions. The electronic nature of the alkyne used was of critical importance to the outcome of the chemistry. The electron-poor alkyne methyl propiolate produces the desired resin bound triazole from the azide at 60°C in DMA or DMF after 72 h (Table 1). Progress of the reaction was again easily monitored by loss the characteristic azide peak at ca. 2100 cm^{-1}. Resin cleavage using standard TFA cleavage methods provided the free acid in reasonable yield and as a single regioisomer (**7a**). In contrast, phenyl acetylene, a more electron-rich alkyne, showed no loss of the azide resonance under the same conditions. Cycloaddition was, however, achieved at 120°C in DMA after 72



Scheme 1.

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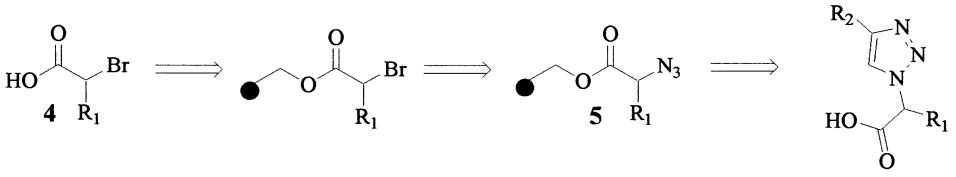
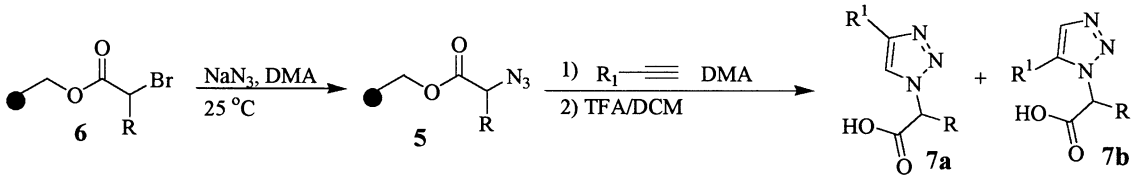


Scheme 2.



Scheme 3.

Table 1. 2+3 Cycloaddition of resin bound azides with terminal alkynes[5]

Entry	R	R^1	Temp. (°C)	Yield **7a**[a] (%)	Yield **7b**[a] (%)	Ratio **7a**/**7b**[b]
1	H	CO_2Me	60	27	0	NA
2	Me	CO_2Me	60	19	0	NA
3	Et	CO_2Me	60	17	0	NA
4	*n*-Hex	CO_2Me	60	20	0	NA
5	CH_2-2-Nap	CO_2Me	60	4	0	NA
6	H	Ph	120	11	12	1/1
7	Me	Ph	120	12	13	1/1
8	Et	Ph	120	11	11	1/1
9	*n*-Hex	Ph	120	12	12	1/1

[a] Yields are reported over four steps.
[b] Product ratios were determined by HPLC.

h to provide a mixture of the two possible regioisomers after TFA cleavage. While 2+3 cycloaddition reaction can be accomplished in DMF, premature resin cleavage occurs due to the presence of free amines generated by decomposition of DMF at elevated temperature during the course of the reaction. HPLC separation of the two regioisomers was accomplished using reverse phase conditions, and the regioisomers were assigned by X-ray crystallography.

In summary, we have developed a novel method for the solid-phase synthesis of functionalized 1,2,3-triazoles.

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5. Typical experimental procedure: 300 mg of Wang resin (1.0 mmol/g) is suspended in 10.0 ml of dichloroethane, 125.1 mg (0.9 mmol, 3.0 equiv.) of α-bromoacetic acid and 36.6 mg (0.3 mmol) of DMAP are added, followed by 226.8 mg (158 μl, 1.8 mmol) of diisopropylcarbodiimide. The reaction is allowed to shake for 24 h, and then the suspension is filtered. The resin is washed with methylene chloride and methanol and dried under vacuum. The resin is suspended in 5.0 ml of DMA, 200 μl of DIPEA is added, followed by 39 mg (0.6 mmol, 2.0 equiv.) of NaN_3, and the reaction is shaken for 24 h. The reaction is then filtered, the resin is washed with methylene chloride and methanol, and dried under vacuum. The resin is then suspended in 5.0 ml of DMA, and 97 mg (102 μl, 1.15 mmol, 3.8 equiv.) of methyl propiolate is added, and the reaction is heated to 60°C. After 72 h, the reaction is filtered and the resin is washed with methylene chloride and methanol, and dried under vacuum. The resin is then suspended in 7.0 ml of 15% trifluoroacetic acid in methyl-

ene chloride and shaken for 18 h. The reaction is then filtered and the resin is rinsed with methanol. The solvent is then stripped to yield and oil which upon HPLC purification yields 15.0 mg of **7a** (27%). The reaction conditions for phenyl acetylene are identical, except the cycloaddition step. This step is done at 120°C instead of 60°C. **7a-1**: ^{1}H NMR (300 MHz, CD_3OD) 8.57 (1H, s), 5.36 (s, 2H), 3.93 (3H, s). Mass spectrum m/z (%): 185 (M+1, 100%). **7a-2**: ^{1}H NMR (300 MHz, CD_3OD) 8.67 (s, 1H), 5.65 (q, 1H, J=7.5 Hz), 3.92 (s, 3H), 1.88 (d, 3H, J=7.5 Hz). Mass spectrum m/z (%): 200 (M+1, 100%). **7a-3**: ^{1}H NMR (300 MHz, CD_3OD) 8.67 (s, 1H), 5.37 (q, 1H, J=5.25 Hz), 3.87 (s, 3H), 2.31 (m, 2H, J=5.25, 7.16 Hz), 0.90 (t, 3H, J=7.16 Hz). Mass spectrum m/z (%): 214 (M+1, 100%). **7a-4**: ^{1}H NMR (300 MHz, CD_3OD) 8.71 (s, 3H), 5.46 (q, 1H, J=6.6 Hz), 3.94 (s, 3H), 2.31 (m, 2H), 1.30 (m, 6H), 1.15 (m, 2H), 0.89 (t, 3H, J=6.78 Hz). Mass spectrum m/z (%): 270 (M+1, 100%). **7a-5**: ^{1}H NMR (300 MHz, CD_3OD) 8.59 (s, 1H), 7.73 (m, 3H), 7.57 (s, 1H), 7.44 (m, 2H, J=6.78 Hz), 7.29 (d, 1H, J=6.78 Hz), 5.94 (dd, 1H, J=6.03, 10.93 Hz), 3.85 (s, 3H), 3.77 (m, 2H, J=6.03, 10.93 Hz). Mass spectrum m/z (%): 326 (M+1, 100%). **7a-6**: ^{1}H NMR (300 MHz, CD_3OD) 8.34 (s, 1H), 7.84 (d, 2H, J=7.16 Hz), 7.44 (t, 2H, J=7.53 Hz), 7.37, (d, 2H, J=7.53 Hz), 5.33 (s, 2H). Mass spectrum m/z (%): 204 (M+1, 100%). **7b-6**: ^{1}H NMR (300 MHz, CD_3OD) 7.83 (s, 1H), 7.53 (m, 5H), 5.25 (s, 2H). Mass spectrum m/z (%): 204 (M+1, 100%). **7a-7**: ^{1}H NMR (300 MHz, CD_3OD) 8.46 (s, 1H), 7.86 (d, 2H, J=7.1 Hz), 7.45 (t, 2H, J=7.54 Hz), 7.36 (t, 1H, J=7.53 Hz), 5.58 (q, 1H, J=7.54 Hz), 1.92 (d, 3H, J=7.54 Hz). Mass Spectrum m/z (%): 218 (M+1, 100%). **7b-7**: ^{1}H NMR (300 MHz, CD_3OD) 7.82 (s, 1H), 7.56 (m, 5H), 5.31 (q, 1H, J=7.16 Hz), 1.89 (d, 3H, J=7.16 Hz). Mass spectrum m/z (%): 218 (M+1, 100%). **7a-8**: ^{1}H NMR (300 MHz, CD_3OD) 8.50 (s, 1H), 7.84 (d, 2H, J=6.41 Hz), 7.48 (t, 2H, J=7.16 Hz), 7.38 (t, 1H, J=7.54 Hz), 5.38 (dd, 1H, J=4.90, 10.2 Hz), 2.41 (m, 2H, J=4.90, 10.2, 7.54 Hz), 0.97 (t, 3H, J=7.54 Hz). Mass spectrum m/z (%): 232 (M+1, 100%). **7b-8**: ^{1}H NMR (300 MHz, CD_3OD) 7.82 (s, 1H), 7.55 (m, 3H), 7.48 (m, 2H), 5.05 (q, 1H, J=6.03, 9.42 Hz), 2.38 (m, 2H, J=6.03, 9.42, 7.54 Hz), 0.81 (t, 3H, J=7.54 Hz). Mass spectrum m/z (%): 232 (M+1, 100%). **7a-9**: ^{1}H NMR (300 MHz, CD_3OD) 8.48 (s, 1H), 7.87 (d, 2H, J=7.16 Hz), 7.45 (t, 2H, J=7.15 Hz), 7.36 (t, 1H, J=7.6 Hz), 5.45 (q, 1H, J=5.65, 10.4 Hz), 2.31 (m, 2H), 1.30 (m, 8H), 0.89 (t, 3H, J=6.78 Hz). Mass spectrum m/z (%): 288 (M+1, 100%). **7b-9**: ^{1}H NMR (300 MHz, CD_3OD) 7.84 (s, 1H), 7.58 (m, 3H), 7.49 (m, 2H), 5.15 (dd, J=6.15, 9.5 Hz), 2.34 (m, 2H), 1.21 (m, 8H), 0.87 (t, 3H, J=6.78 Hz). Mass spectrum m/z (%): 288 (M+1, 100%).