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Highly efficient and mild synthesis of variously 5-substituted-4-carbaldehyde-1,2,3-triazole derivatives

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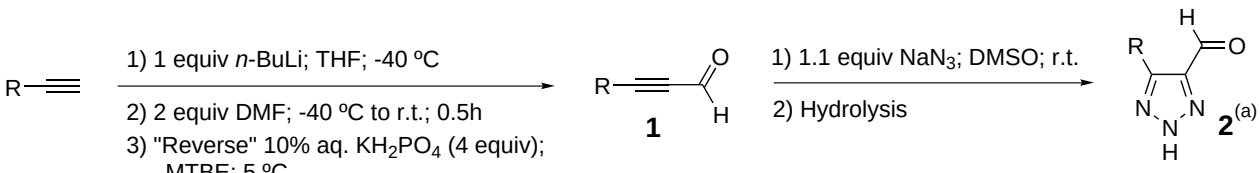
Abstract—Synthesis of variously 5-substituted-4-carbaldehyde-1,2,3-triazole derivatives **2** was accomplished by reacting sodium azide with α,β-acetylenic aldehydes **1** in DMSO at room temperature. Therefore, the reaction remains basic avoiding the generation of the hazardous explosive HN_3, resulting in a safe process. This mild and general reaction was instantaneous and was essentially quantitative.

The 1*H*-1,2,3-triazole heterocyclic entity is a very interesting component in terms of biological activity. Indeed, the 1,2,3-triazole moiety is present in a number of drugs such as the β-lactam antibiotic Tazobactam or the cephalosporine Cefatrizine just to name a few. As part of an ongoing program in our laboratories, we became interested in preparing a 1,2,3-triazole aldehyde derivative as a key building block in the synthesis of a drug candidate.[1] The 1,3-dipolar cycloaddition[2] reaction is a well-established and general method for the construction of five-membered ring heterocycles. In particular, addition of azides to acetylenes has been a method of choice for the synthesis of 1,2,3-triazoles.[3] Consequently, performing reactions with azides has become a useful tool in industrial organic synthesis.[4] Cycloaddition of azides with an activated triple bond has been investigated primarily with acetylenic esters.[5] Surprisingly, upon checking the literature, we found very few examples of the cycloaddition between azides and acetylenic aldehydes,[5b,6] and the synthesis of 1,2,3-triazole-4-carbaldehydes had not been studied extensively.[7] A recent example was reported using an acetylenic silyl ketone run at high temperatures in refluxing toluene for several hours albeit in moderate yields.[8] Subsequent desilylation provided 4-carbaldehyde-1,2,3-triazoles, however lacking substitution at the 5-position. In our case it was also important to use sodium azide instead of an alkyl azide since no substitution on the nitrogen was desired. Also, the reportedly used hydrazoic acid[6b,c] was not an option for us for obvious safety reasons.



Entry	R	Yield (%)
a	Ph	>98
b	$TBSO(CH_2)_3$	
c	$THPO(CH_2)_2$	
d	$THPOCH_2$	
e	$TBSOCH_2$	
f	n-C_4H_9	

(a) Position of the triazole NH is arbitrarily assigned since we cannot differentiate reliably between NH tautomers.

Scheme 1.

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Herein, we wish to report the efficient preparation of variously 5-substituted-4-carbaldehyde-1,2,3-triazole derivatives under mild conditions. Since the ease of the azide cyclization is governed by polarization of the acetylene, we thought that α,β-acetylenic aldehydes would be highly reactive towards sodium azide. Therefore, we first designed an efficient synthesis of α,β-acetylenic aldehydes **1** by simple formulation of acetylides with DMF.[9] As expected, they reacted instantaneously with sodium azide in DMSO at room temperature to give the corresponding triazoles **2** in essentially quantitative yield (Scheme 1). In addition, it is noteworthy that the reaction remains basic avoiding the generation of the hazardous explosive HN_3, resulting in a safe process. The mode of addition as well as good mixing were important to achieve a clean reaction. Indeed, acetylenic aldehydes **1a–f** must be reverse-added[10] into a vigorously stirred DMSO solution containing 1.1 equiv. of sodium azide[11] leading to the 1,2,3-triazole aldehydes **2a–f**.[12]

General procedure: To a vigorously stirred solution of dissolved[10] sodium azide (3.57 g, 55 mmol) in DMSO (110 mL) was added a DMSO solution of the aldehyde **1** (50 mmol in 35 mL of DMSO) over 10 min maintaining the temperature between 20 and 25°C over an ice-water bath. The resulting reaction mixture was stirred at room temperature for 30 min and was poured into a vigorously stirred biphasic solution prepared from a 15% aqueous solution of KH_2PO_4 (300 mL, 300 mmol) and MTBE (350 mL) at room temperature. Layers were separated and the organic extract was washed with water (2×250 mL). Combined aqueous layers were back extracted with MTBE (100 mL). Combined organic layers were dried over MgSO4, filtered and concentrated to give the crude triazole aldehyde derivative in >98% yield with no purification needed.

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7. Rearrengements of 1*H*-1,2,3-triazole-4-carbaldehydes to replace the 1-aryl substituent have been studied started from the known 1-phenyl-1,2,3-triazole-4-carbaldehyde (Ref. 6a): (a) L'abbé, G.; Bruynseels, M.; Delbeke, P.; Toppet, S. *J. Heterocyclic Chem*. **1990**, *27*, 2021; (b) L'abbé, G.; Bruynseels, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1492.
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10. Starvation of azide during addition led to decomposition. We believe that in the absence of sodium azide, the triazole aldehyde anion added onto **1** triggering its polymerization.
11. Since the excess azide in the waste stream can be a potential hazard, 1.0 equiv. of azide can be used still leading to a quantitative yield of the triazole and keeping the azide level $\leq$30 ppm into the aqueous. Sodium azide was assayed by reverse phase HPLC: C-18 Metachem inertsil ODS-3 column (250×4.6 mm, 5 μm) with a flow rate of 0.75 mL/min (UV detection @ 200 nm). Elution: gradient using a 10/90 mixture of CH_3CN/H_2O (0.1% H_3PO_4) to 30/70 in 20 min. t_R for azide was 7.35 min.
12. ^1H NMR (400 MHz, $CDCl_3$) for 1,2,3-triazole aldehydes **2**. Compound **2a**: registry no. 2579-22-8. Compound **2b**: δ 10.22 (s, 1H), 3.75 (t, $J=5.8$ Hz, 2H), 3.16 (t, $J=7.0$ Hz, 2H), 1.96 (quin., $J=7.0$ Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H). Compound **2c**: δ 10.23 (s, 1H), 4.65 (br s, 1H), 4.05–4.12 (m, 1H), 3.79–3.86 (m, 2H), 3.50–3.53 (m, 1H), 3.34–3.38 (m, 2H), 1.63–1.78 (m, 2H), 1.49–1.56 (m, 4H). Compound **2d**: δ 10.24 (s, 1H), 5.21 (br d, $J=15.3$ Hz, 1H), 5.03 (d, $J=15.3$ Hz, 1H), 4.74 (br t, $J=3.8$ Hz, 1H), 3.98–4.03 (m, 1H), 3.57–3.63 (m, 1H), 1.84–1.90 (m, 2H), 1.56–1.65 (m, 4H). Compound **2e**: δ 10.23 (s, 1H), 5.13 (s, 2H), 0.95 (s, 9H), 0.17 (s, 6H). Compound **2f**: δ 10.23 (s, 1H), 3.07 (t, $J=7.7$ Hz, 2H), 1.70 (quin., $J=7.6$ Hz, 2H), 1.35 (hex., $J=7.7$ Hz, 2H), 0.88 (t, $J=7.5$ Hz, 3H).