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An efficient protocol for domino one pot synthesis of 1,2,3-triazoles from natural organic acids and phenols

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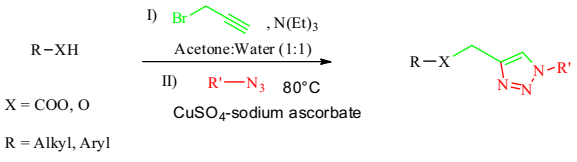
ABSTRACT

An efficient three-component protocol was developed for the one-pot synthesis of 1,2,3-triazoles from natural product based acids and phenols, using $CuSO_4$–sodium ascorbate catalyst system. The method is general and showed considerable synthetic advantage giving products in excellent yields with a wide substrate scope.

Five membered heterocyclic compounds like triazoles have the ability to bind to a variety of enzymes and receptors in biological systems and thus exhibit diverse biological activities like anti-HIV,[1] antimicrobial,[2] anticancer[3] and b3-adrenergic receptor agonist.[4] These are useful in the field of material sciences and molecular structure design as well.[5–7] Triazoles are important and frequently occurring structural motifs in various pharmaceuticals, agrochemicals and chemical reagents.[8–11] Various drug-like properties including potency and selectivity through replacements, lipophilicity, polarity and solubility can be modulated by a strategic insertion of a heterocyclic moiety into the parent molecule.[12–16] Owing to their emerging importance, spectacular interest has been paid for the development of new and efficient methods for the one-pot synthesis of 1,2,3-triazoles. Huisgen 1,3-dipolar cycloaddition reaction between azide and terminal alkyne is one of the most extensively used protocols for the preparation of 1,2,3-triazoles.[17–19] However, earlier methods were associated with numerous drawbacks such as, the reactions were conducted at high temperature for a prolonged time period, and usually led to the formation of a mixture of 1,4 and 1,5-disubstituted-1,2,3-triazoles and hence decreased the synthetic efficiency.[20] It is always desirable to develop a new, cleaner, safer and more efficient and ecofriendly protocol by modernizing old procedures. Some new strategies and transition-metal catalysts have been introduced to overcome the drawbacks associated with earlier methods for the synthesis of triazoles.[18,19,21,22]

Exhaustive literature survey revealed that O-substituted 1,2,3-triazoles have more potential biological activities than simple 1,2,3-triazole derivatives.[3,23] Since limited number of alkynes and azides is available commercially, the complex triazoles are usually synthesized in multi-step sequences, thereby decreasing synthetic efficiency. On the other hand, multi-component reactions (MCRs) provide an easy and rapid way to access complex structures from simpler units. MCRs generally afford excellent yields and are fundamentally different from simple reactions in many aspects.[24,25] Several methods of Huisgen cycloaddition reaction using one-pot procedure to prepare 1,2,3-triazole derivatives have been reported.[26–33]

In continuation of our previous communication where we reported the synthesis of natural product based O-substituted 1,2,3-triazole derivatives in two steps from natural organic acids,[3] we herein report a general and easy procedure for the one-pot syntheses of 1,2,3-triazoles. To the best of our knowledge there



Scheme 1.

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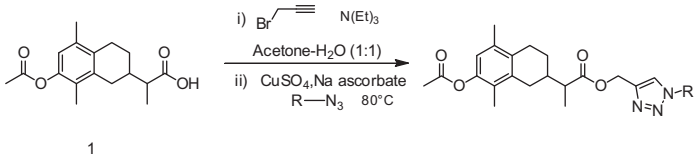

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Scheme 2. One pot synthesis of triazoles from natural organic acids catalysed by $CuSO_4$–sodium ascorbate catalytic system.

are no reports available in the literature regarding direct one pot synthesis of triazoles using acids or phenols as starting materials. In this protocol natural organic acids/phenols reacted with propargyl bromide to generate their terminal alkynes in situ, which are then reacted with organic azides (Scheme 1).

At the onset of this work, reaction of acid substrate **1**, propargyl bromide and 4-azidobenzonitrile was selected as template reaction (Scheme 2). Using $CuSO_4{\cdot}5H_2O$–sodium ascorbate catalyst system in a 2:1 mixture of water and tert-butanol, only 50% conversion was observed and the desired compound **1a** was obtained in 47% yield in 48 h at room temperature (Table 1, entry 1).

Optimum reaction conditions were then explored using various solvent combinations, catalyst concentrations, time and temperature. For successful one-pot protocol, full conversion of **1** to the corresponding propargyl was essential to avoid side reactions. Since it was known that, in the presence of a base and Cu(I) catalysts, terminal acetylenes could be converted to the corresponding alkynylides through the Glaser coupling.[34] In continuation of our work on one pot synthetic procedures,[35] we decided that it could be better to perform the one-pot reaction in a sequential manner to achieve complete conversion of reactants to the final triazole product. Initially the model reaction of acid **1** with propargyl bromide at room temperature in water–tert-butanol (2:1) medium showed incomplete (almost 60–65%) conversion of acid **1** to its propargyl product (monitored by TLC) even if long reaction time was employed. Consequently, the reaction demanded higher temperatures for complete conversion of **1** to its propargyl product. Complete conversion of **1** to propargyl product was observed in 3.5 h when 80 °C was applied and upon addition of azide and $CuSO_4$–sodium ascorbate (10 mol % each), the reaction proceeded cleanly and the desired triazole **1a** was obtained in 89% overall yield in a total reaction time of 8.5 h. Upon investigating the effect of temperature, we found that there was no significant increase in the product yield beyond 80 °C (Table 1, entries 2 and 3). When all the components were mixed at the same time, poor yields were obtained even if 2 equiv of propargyl bromide and heating were applied.

With 10 mol % of catalyst and 80 °C reaction temperature, a series of solvents were screened for reaction between substrate **1**, propargyl bromide and 4-azidobenzonitrile, (the model reaction). Solvent systems like *t*-butanol–water, ethanol–water, THF–*t*-Butanol–H_2O and DMF–*t*-Butanol–H_2O gave good yields but required longer reaction time (Table 2 entries 1, 2, 6 and 7). In water–THF, the corresponding triazole was formed with 90% yield in 8.5 h (Table 2, entry 4). Relatively poor yields were obtained in solvents like ethanol, THF, DMF and water (Table 2, entries 8–10). Methanol and ethanol as solvents also produced good yields particularly in case of acids, but comparatively longer reaction time was required (Table 2 entries 11 and 12). The optimum solvent system for this reaction was found to be the acetone–water (1:1) system in which reaction proceeded cleanly and 92% yield was obtained within 8 h (Table 2, entry 3).

We examined the influence of the $CuSO_4$–sodium ascorbate catalyst system on the model reaction using various catalyst concentrations (Table 3). $CuSO_4$–sodium ascorbate (10 mol % each) was found to be the most effective in catalysing the three-component reaction in terms of yield and reaction time. Increasing the catalyst amount or catalyst loading could not improve the product yield of this model reaction (Table 3, entries 7–10). We also examined the influence of various bases on the model reaction. Some inorganic and organic bases were investigated. Triethylamine showed better yields and no byproducts were observed. Potassium

Table 1
Screening of catalyst conditions[a]

Entry	Catalyst	Temperature (°C)	Time (h)	Yield[b] (%)
1	$CuSO_4$–sodium ascorbate (1:1)	rt	24	47
2	$CuSO_4$–sodium ascorbate (1:1)	80	8.5	89
3	$CuSO_4$–sodium ascorbate (1:1)	100	8.5	89
4	$CuSO_4$	80	24	<10
5	None	80	48	Traces

[a] All the reactions were performed with 1.0 equiv of acid, 1.5 equiv of $N(Et)_3$, 15 mL of solvent (2:1 water–tert-butanol), 1.2 equiv of propargyl bromide, 1.0 equiv of azide.
[b] Isolated yield of the triazole.

Table 2
Screening of various solvent combinations for $CuSO_4$ catalysed one pot triazole synthesis[a]

Entry	Solvents	Time (h)	Yield[b] (%)
1	*t*-Butanol–H_2O (2:1)	8.5	89
2	Ethanol–H_2O (1:1)	8.5	79
3	Acetone–H_2O (1:1)	8	92
4	THF–H_2O (1:1)	8.5	90
5	DMF–H_2O (1:1)	8.5	89
6	THF–*t*-Butanol–H_2O (1:1:1)	8	78
7	DMF–*t*-Butanol–H_2O (1:1:1)	8	83
8	THF	8	63
9	DMF	8	58
10	H_2O	12	49
11	Methanol	10	68
12	Ethanol	10	63

[a] All reactions were performed with 1 equiv of acid, 1.5 equiv of $N(Et)_3$, 15 mL of solvent, 1.2 equiv of propargyl bromide, 1.0 equiv of azide, $CuSO_4$–sodium ascorbate (10 mol % each) at 80 °C.
[b] Isolated yield of the triazole.

Table 3
Optimization for the $CuSO_4$–sodium ascorbate concentration[a]

Entry	Catalyst (mol %)	Time (h)	Yield[b] (%)
1	1.5	12	42
2	2	12	53
3	3	10	58
4	5	10	62
5	7	8.5	76
6	10	8	92
7	12	8	92
8	15	8	93
9	20	8	89
10	No catalyst	48	N.D.

[a] All reactions were performed with 1.0 equiv of acid, 1.2 equiv of $N(Et)_3$, 20 mL of solvent, 1.2 equiv of propargyl bromide, 1.0 equiv of azide with 10 mol % sodium ascorbate.
[b] Isolated yield of the triazole.