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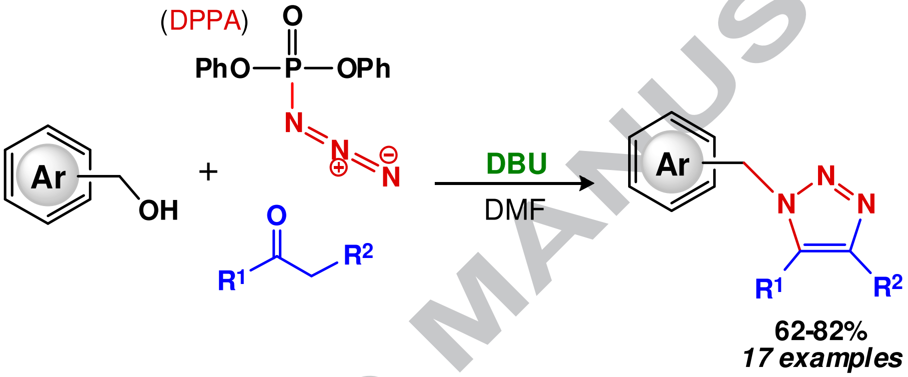

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A novel and facile synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from benzylic alcohols through a one-pot, three-component system

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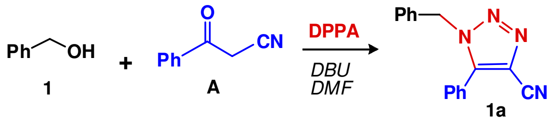
ABSTRACT

A simple one-pot procedure has been developed to efficiently prepare 1,4,5-trisubstituted 1,2,3-triazoles from benzylic alcohols. The presence of diphenylphosphoryl azide (DPPA) and active ketones allows for an azide-enolate [3+2] cycloaddition by use of DBU.

The triazole ring system is a key pharmacophore[1] for an increasingly important series of nitrogen heterocycles that display a wide range of therapeutic and biological activity.[2] Several methods for the synthesis of 1,4-disubstituted 1,2,3-triazoles[3] and 1,5-disubstituted 1,2,3-triazoles[4] have been described in literature. In the last decade, the *1,4,5-trisubstituted 1,2,3-triazole* framework has received much attention in medicinal chemistry due to its biological activity against cancer,[5] HIV-RT,[6] Cantagalo Virus,[7] and *Lachesis muta* snake venom,[8] as well as its use as an antiplatelet agent,[9] among other applications.[10] Hence, reports on synthetic methods to obtain 1,4,5-trisubstituted 1,2,3-triazole moieties are increasingly common in literature.[11] An outstanding synthetic method is azide-enolate [3+2] cycloaddition, best known as 'Dimroth Cycloaddition',[12] which has been improved[13] by several research groups. Recently, Cao *et al.* has given versatility to this method through an attractive three-component synthesis of 1,4,5-trisubstituted 1,2,3-triazoles, starting from primary alcohols and using a NaN_3/TsIm/TEA/TBAI/KOH system.[14] Thus, the development of an efficient synthesis of these valuable heterocycles —particularly from readily accessible and common substrates— is of ever increasing importance.

During one of our ongoing research projects, focused on the development of novel methodologies for the construction of triazole carbocyclic nucleosides,[15] we observed that an excess of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) in Thompson's azidation procedure[16] of benzyl alcohol **1** leads to the highly regioselective synthesis of 1,4,5-trisubstituted 1,2,3-triazole **1a** in the presence of *active* ketone benzoylacetonitrile **A** (78% yield) by a one-pot system.



Consequently, we decided to investigate the coupling of **1**, **A** and diphenylphosphoryl azide (DPPA) in greater detail, finding that triazolyzation was very inefficient using stoichiometric amounts of DBU. Moreover, the evident use of *only* benzylic alcohols when some alkylic alcohols (*e.g.* menthol, octyl alcohol, and phenethyl alcohol) failed under our procedure is in accordance with Thompson's discussion. Conventional heating (60–70 ºC upon adding ketone) and a 6 h reaction period were adopted as the standard. The coupling reactions of various benzylic alcohols in the presence of benzoylacetonitrile **A**, ethyl acetoacetate **B**, dibenzoylmethane **C**, and/or acetylacetone **D** as active ketones were then examined under these optimized conditions (Table 1).[17]

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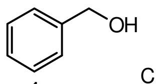
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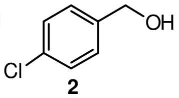
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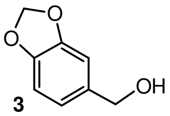
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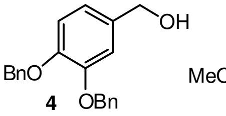
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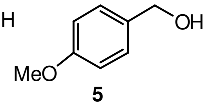
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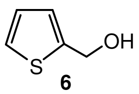
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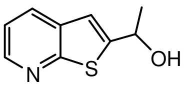
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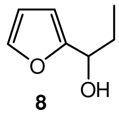
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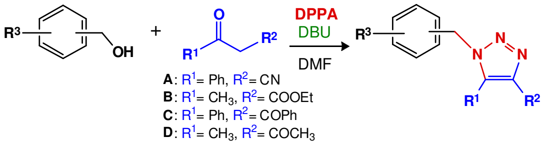
Table 1. Synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from benzylic alcohols by coupling with active ketones.



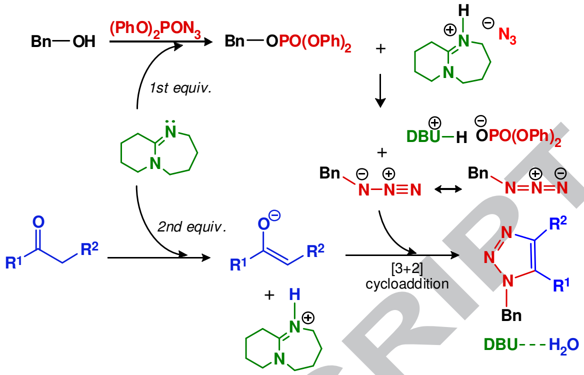
Entry	Benzyl Alcohol	Ketone	Triazole[a]	Yield (%)[b]
1	**1**	**A**	**1a**	78
2	**1**	**C**	**1c**	80
3	**2**	**D**	**2d**	82
4	**2**	**B**	**2b**	65[c]
5	**2**	**C**	**2c**	76
6	**3**	**D**	**3d**	75
7	**3**	**C**	**3c**	74
8	**4**	**D**	**4d**	77
9	**4**	**B**	**4b**	63[c]
10	**4**	**A**	**4a**	72
11	**5**	**D**	**5d**	76
12	**5**	**B**	**5b**	62[c]
13	**6**	**D**	**6d**	73
14	**6**	**B**	**6b**	66[c]
15	**7**	**D**	**7d**	82
16	**7**	**C**	**7c**	80
17	**8**	**A**	**8a**	75

[a] Confirmed by ^{1}H-NMR, ^{13}C-NMR and HRMS.
[b] Yields refer to chromatographically pure isolated compounds.
[c] In these cases, the reactions require longer times (36 h) upon adding ketone.

The presence of moderate EWG in the aromatic ring (*p*-Cl, entry 3) led to *slightly* higher yields than those observed for electron-rich benzylic alcohols (*p*-OCH$_3$, entry 11, considering acetylacetone **D** for these examples). However, the formation of a less stable enolate in the reaction (when ethyl acetoacetate **B** is used) leads to the synthesis of triazoles in low yields (entries 4, 9, 12, and 14). Furthermore, we have used the method with heterocycles (**6**, **7** and **8**) as aryl moieties. These results are consistent for both primary (**1**–**6**) and secondary (**7** and **8**) benzylic alcohols.

Mechanistically, we believe the reaction takes place in four discrete steps (Scheme 1). One DBU equiv. is necessary for an effective Thompson azidation. The enolate generated *in situ* by the action of a second DBU equiv. leads to azide-enolate [3+2] cycloaddition.

Scheme 1. Proposed plausible mechanism for azide-enolate [3+2] cycloaddition.



In summary, we developed a simple one-pot, three-component procedure for the direct conversion of alcohols to 1,4,5-trisubstituted 1,2,3-triazoles through highly regioselective synthesis under mild conditions.

Acknowledgments

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Supplementary Material

Supplementary material (characterization data of all compounds and copies of ^{1}H–NMR, ^{13}C–NMR and High Resolution Mass spectra) associated with this article can be found in the online version.

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17. *Experimental Procedure*: To a cold solution (0 ºC) of benzyl alcohol **1** (0.108 g, 1.0 mmol) and diphenylphosphoryl azide (0.236 mL, 1.1 mmol) in anhydrous DMF (2.5 mL) was added DBU (0.3 mL, 2.0 mmol). The solution was stirred for 15 min at 0 ºC under nitrogen atmosphere, and then brought to room temperature with continuous stirring for 3 h. Afterwards, TLC indicated the disappearance of the starting material. Benzoylacetonitrile **A** (0.145 g, 1.0 mmol) was then added to the reaction mixture, which was stirred for 3 h at 60–70 ºC. Brine (~40 mL) was added to the reaction mixture and washed with EtOAc (3×10 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography to give the brown highly viscous oil **1a** (0.2 g, 78%).