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One-Pot Synthesis of 4-Aryl-*NH*-1,2,3-Triazoles through Three-Component Reaction of Aldehydes, Nitroalkanes and NaN_3

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A one-pot three-component reaction of aldehydes, nitroalkanes and NaN_3 for the synthesis of *NH*-1,2,3-triazoles has been developed. The reaction provides a safe, efficient and step-economic approach for the synthesis of various *NH*-1,2,3-triazoles in good to excellent yields.

Keywords aldehydes, sodium azide, one-pot, three-component reaction, *NH*-1,2,3-triazoles

Introduction

Owing to the unique chemical structures and properties, substituted triazoles have been widely used in material science, agricultural chemistry and bio-pharmaceutical.[1] Particularly, large numbers of 1,2,3-triazoles have recently been discovered to have remarkable bioactivity, such as IDO1 inhibitor, antiviral agent, Src kinase inhibitor and HDAC inhibitor (Figure 1, a—d). In the past few decades, a variety of methods have been developed for the construction of 1,2,3-triazoles.[2,3] The common approaches rely on the classical Cu(I)-, Ru(II)- or Ir-catalyzed azide-alkyne cycloadditions.[4-7] Recently, organo-catalyzed 1,3-dipolar cycloaddition of organic azides with α,β-unsaturated acyl azoliums,[8] and condensation of *N*-tosylhydrazones with anilines,[9] have been developed for the synthesis of 1,2,3-triazoles.

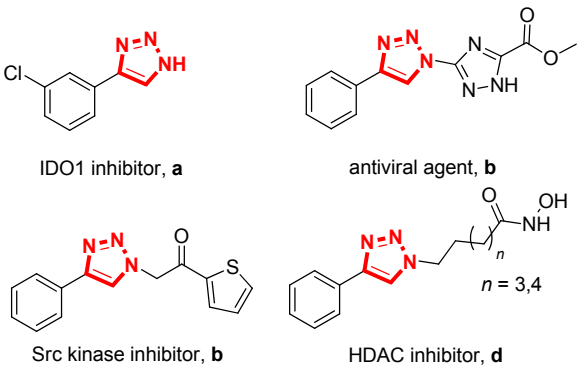

Figure 1 Selected examples of biologically active 1,2,3-triazoles.

Organo-catalyzed three-component condensation reaction to synthesize 1,4,5-trisubstituted 1,2,3-triazoles has also been developed.[10] However, most of these strategies are restricted to employing terminal alkynes and organic azides as the substrates to synthesize *N*-substituted 1,2,3-triazoles. Versatile and practical methods for the synthesis of valuable *NH*-1,2,3-triazoles remain highly desirable.

In 2014, we developed an efficient 1,3-dipolar cycloaddition of nitroolefins and inorganic NaN_3 for the synthesis of 4-aryl-*NH*-1,2,3-triazoles (Scheme 1a).[11] To suppress the undesired cyclotrimerization of nitroolefins, the reaction was conducted under *p*-TsOH-mediated acidic conditions. To our knowledge, the reaction was one of the most effective methods for the synthesis of 4-aryl-*NH*-1,2,3-triazoles to date. However, the explosive and toxic hydrazoic acid was released inevitably under the acidic conditions.[12] This safety issue of the reaction prompted us to develop a safe protocol for the synthesis of *NH*-1,2,3-triazoles. Since the nitroolefins could be easily synthesized by condensation of aldehydes and nitroalkanes,[13] we hypothesized that 1,3-dipolar cycloaddition of in situ generated nitroolefins and inorganic NaN_3 for the synthesis of *NH*-1,2,3-triazoles might be achieved under neutral conditions.[14] In this case, the undesired cyclotrimerization of nitroolefins might be inhibited through rapid cycloaddition of in situ generated nitroolefins and NaN_3. Therefore, in this paper, we described the development of an one-pot reaction of aldehydes, nitroalkanes, and NaN_3 for the safe and step-economic synthesis of 4-aryl-*NH*-

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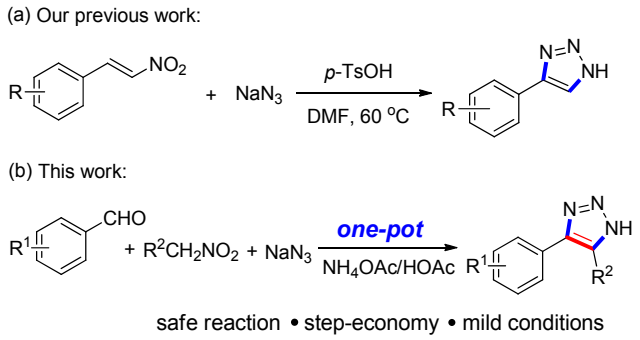
1,2,3-triazoles (Scheme 1b).

Scheme 1 Synthesis of 4-aryl-*NH*-1,2,3-triazoles



Experimental

General information

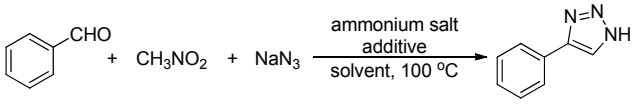
Column chromatography was carried out on silica gel. ^{1}H NMR spectra were recorded at 400 MHz in DMSO-d_6 and ^{13}C NMR spectra were recorded at 100 MHz in DMSO-d_6. All new products were further characterized by HRMS; copies of their ^{1}H NMR and ^{13}C NMR spectra are provided in Supporting Information. Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and used without further purification.

Typical procedure for the synthesis of 4-aryl-*NH*-1,2,3-triazoles: Aldehydes **1** (0.3 mmol), nitroalkanes **2** (0.9 mmol), NaN_3 (0.75 mmol), HOAc (0.15 mmol), NH_4OAc (0.3 mmol) and DMF (3 mL) were charged in a 10 mL round bottom flask. Then, the reaction mixture was stirred at 100 ℃. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (10 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4 and then evaporated *in vacuo*. The corresponding triazoles were obtained after purification by flash chromatography on silica gel with hexane/ethyl acetate (*V*/*V*＝5∶1) as the eluent.

Results and Discussion

Initially, benzaldehyde **1a**, nitromethane **2a** and NaN_3 were selected as model substrates to optimize the reaction conditions. Considering that the condensation of aldehydes and nitroalkanes was conventionally proceeded in the presence of NH_4OAc in HOAc solvent,[13a] we began our investigation with NH_4OAc in DMF. Gratifyingly, the desired 4-phenyl-*NH*-1,2,3-triazole **3a** was obtained in 54% yield at 100 ℃ (Table 1, Entry 1). Then, various ammonium salts such as $(NH_4)_2CO_3$, NH_4HCO_3, NH_4Cl and $HCOONH_4$ were screened (Table 1, Entries 2—5). However, no further improvement was observed. Optimization of different solvents such as DMAC, DMSO and NMP, suggested that DMF was still the best reaction media for this transformation (Table 1, Entries 6—8). Inspired by the pioneer copper(I)-catalyzed cycloaddition reaction for the synthesis of 2-substituted-1,2,3-triazoles,[15] we envisioned that a buffer reaction system might prompt this one-pot three-component reaction. Therefore, PivOH and HOAc were tested as the additives (Table 1, Entries 9—10). The yield of **3a** was dramatically improved to 72% in the presence of 0.5 equivalent of PivOH (Table 1, Entry 9). Indeed, this safe buffer reaction conditions show great effectivity for the one-pot three-component reaction, and 93% yield of **3a** was obtained when 0.5 equivalent of HOAc was used as the additive (Table 1, Entry 10). Finally, the reaction temperature was also varied, and 100 ℃ was still the best choice (Table 1, Entries 11 and 12).

Table 1 Optimization of reaction conditions[a]



1a **2a** **3a**

Entry	Ammonium salt	Additive	Solvent	Yield[b]/%
1	NH_4OAc		DMF	54
2	$(NH_4)_2CO_3$		DMF	41
3	NH_4HCO_3		DMF	43
4	NH_4Cl		DMF	48
5	$HCOONH_4$		DMF	39
6	NH_4OAc		DMAC	49
7	NH_4OAc		DMSO	47
8	NH_4OAc		NMP	35
9	NH_4OAc	PivOH	DMF	72
10	**NH_4OAc**	**HOAc**	**DMF**	**93**
11[c]	NH_4OAc	HOAc	DMF	66
12[d]	NH_4OAc	HOAc	DMF	72

[a] Reaction conditions: benzaldehyde **1a** (0.3 mmol), nitromethane **2a** (3.0 equiv.), NaN_3 (2.5 equiv.), ammonium salt (1.0 equiv.), and additive (0.5 equiv.) in solvent (3 mL) at 100 ℃ under air. [b] Isolated yield. [c] The reaction was performed at 80 ℃. [d] The reaction was performed at 110 ℃.

With the optimized reaction conditions in hand, a series of aldehydes **1** were investigated for extending the substrate scope (Table 2). This transformation proved to be a general method for the preparation of 4-aryl-*NH*-1,2,3-triazoles. In all cases examined, the *para*-, *meta*- and *ortho*-substituted aromatic aldehydes were all converted into substituted 1,2,3-triazoles in good to excellent yields. Aryl aldehydes with electron-donating substituents on aryl rings, such as methyl and methoxyl, proceeded smoothly and resulted in the desired triazoles **3b—3f** in 88%—96% yields. Furthermore, salicylalde-

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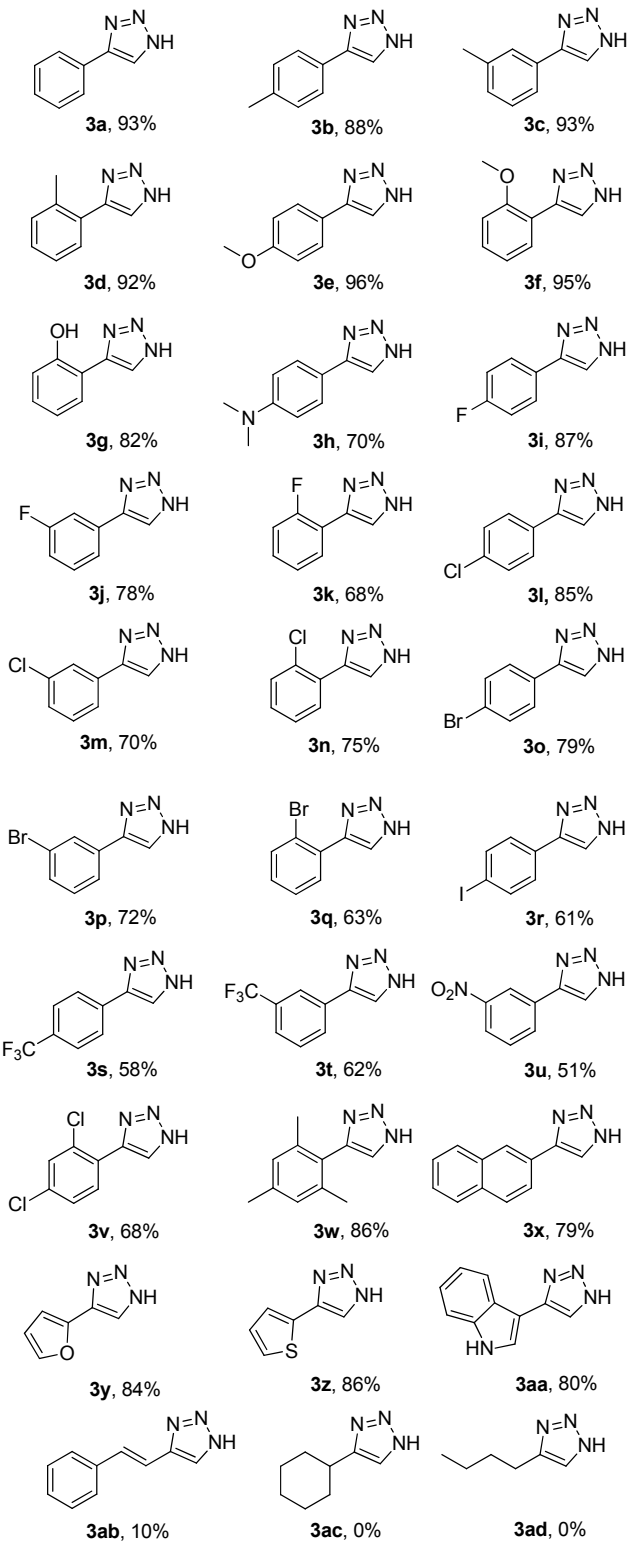
Table 2 Reaction scope of aldehydes **1**, nitromethane **2a** and NaN_3[a]

1 3

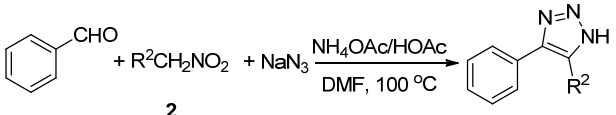


[a] Reaction condition: **1** (0.3 mmol), nitromethane **2a** (3.0 equiv.), NaN_3 (2.5 equiv.), NH_4OAc (1.0 equiv.), HOAc (0.5 equiv.), DMF (3 mL) at 100 ℃, isolated yield.

hyde and 4-(dimethylamino)benzaldehyde also exhibited good reactivity and gave the triazoles **3g**—**3h** in 82% and 70% yields, respectively. To further investigate the scope of this reaction with regard to other functional groups, substrates containing halo substituents such as fluoro, chloro, bromo, and iodo were tested. The corresponding triazoles **3i**—**3r** were afforded in good to high yields. Aryl aldehydes with strong electron-withdrawing groups such as trifluoromethyl and nitro, afforded the triazoles **3s**—**3u** in moderate yields, implying that the electronic nature of the substrates has slight influence on the reaction. Furthermore, when 2,4-dichlorobenzaldehyde and 2,4,6-trimethylbenzaldehyde were employed as multisubstituted substrates, the reaction reacted well to give the corresponding triazoles **3v**—**3w** in good yields. 2-Naphthylbenzaldehyde participated in the reaction smoothly and afforded the desired triazole **3x** in 79% yield. Heterocyclic substituted aldehydes such as furyl, thienyl, and indolyl, were well tolerated in the reaction to give the corresponding triazoles **3y**—**3aa** in 80%—86% yields. In addition, the desired triazole **3ab** was obtained in only 10% yield when cinnamaldehyde was employed as the vinyl substituted aldehyde. However, no reaction occurred when aliphatic aldehydes such as cyclohexanecarbaldehyde and pentanal were used as the substrates.

In an attempt to provide access to a broader range of triazoles, the reaction with different nitroalkanes was investigated under the standard conditions (Scheme 2). Gratifyingly, nitroethane and 1-nitropropane **2b**—**2c** proceeded smoothly to give the corresponding triazoles **4b**—**4c** in 91%—97% yields. Moreover, ester substituted *NH*-1,2,3-triazole **4d** could also be synthesized in 36% yield.

Scheme 2 Reaction scope of benzaldehyde **1a**, nitroalkanes **2** and NaN_3



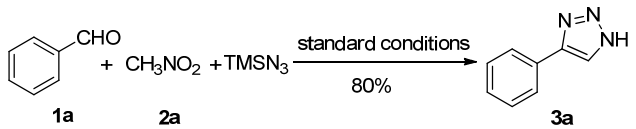
1a 2 4

2b: R^2 = Me
2c: R^2 = CH_2CH_3
2d: R^2 = CO_2Et

4b: R^2 = Me 91%
4c: R^2 = CH_2CH_3 97%
4d: R^2 = CO_2Et 36%

It should be noted that alkyl azides were also tolerated in this three-component reaction. Interestingly, 4-phenyl-*NH*-1,2,3-triazole **3a** was obtained in 80% yield when azidotrimethylsilane ($TMSN_3$) was used as the substrate (Scheme 3).

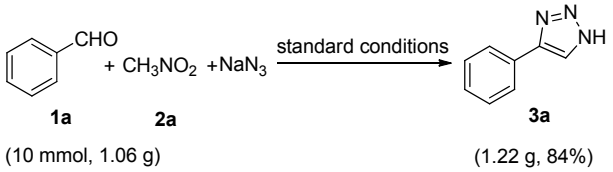
Scheme 3 Three-component reaction of benzaldehyde **1a**, nitromethane **2a** and $TMSN_3$



1a 2a 3a

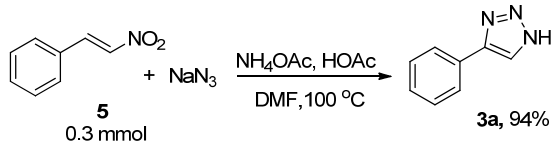
To demonstrate the synthetic utility of this reaction, a gram-scale (10 mmol, 1.06 g) reaction was performed under the standard conditions. Expectedly, the 4-phenyl-*NH*-1,2,3-triazole **3a** was obtained in 84% yield (Scheme 4).

Scheme 4 Gram scale reaction

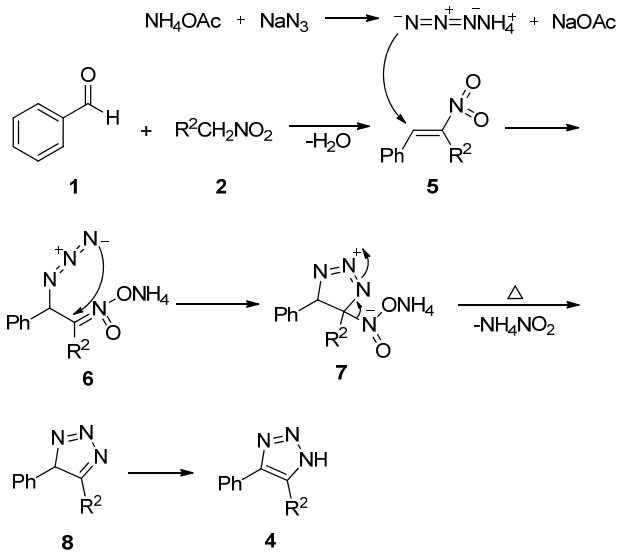


To further gain insights into the reaction mechanism, nitroalkene **5a** was synthesized to undergo the cycloaddition reaction with NaN_3 under the standard conditions. As expected, the desired 4-phenyl-*NH*-1,2,3-triazole **3a** was obtained in 94% yield (Scheme 5). The results further confirm the proposed reaction mechanism which is shown in Scheme 6.[16] Firstly, the nitroolefin **5** was easily synthesized by condensation of benzaldehyde **1** and nitroalkane **2**. At the same time, the reaction between ammonium acetate and sodium azide afforded ammonium azide. Then, the nucleophilic addition of ammonium azide to nitroolefin **5** afforded the intermediate **6**. An intramolecular nucleophilic cyclization of intermediate **6** gave the intermediate **7**. Next, elimination of a molecule of NH_4NO_2 generated the intermediate **8**. Finally, isomerization of the intermediate **8** produced the 1,2,3-triazole **4**.

Scheme 5 1,3-Dipolar cycloaddition of nitroolefin with NaN_3



Scheme 6 Plausible reaction mechanism



Conclusions

In summary, a safe, facile and step-economic three-component reaction of aldehydes, nitroalkanes and inorganic NaN_3 for the synthesis of 4-aryl-*NH*-1,2,3-triazoles has been developed in the paper. NH_4OAc/HOAc plays a crucial role in the reaction. The reaction employs readily available starting materials, tolerates a wide range of functional groups, thus providing an efficient method for the synthesis of valuable *NH*-1,2,3-triazoles in high to excellent yields. Further reaction scope and applications are underway in our lab.

Acknowledgement

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