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Aluminium(III) Chloride-Catalyzed Three-Component Condensation of Aromatic Aldehydes, Nitroalkanes and Sodium Azide for the Synthesis of 4-Aryl-*NH*-1,2,3-triazoles

Qinquan Hu,[a] Yi Liu,[a] Xiaocong Deng,[a] Yanjun Li,[b,]* and Yunfeng Chen[a,]*

[a] School of Chemistry and Environmental Engineering, Wuhan Institute of Technology, Wuhan 430073, People's Republic of China
E-mail: yfchen@wit.edu.cn
[b] Department of Chemistry, Wuhan University of Science and Technology, Wuhan 430081, People's Republic of China
E-mail: yanwatercn@wust.edu.cn

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Abstract: An aluminium(III) chloride-catalyzed three-component reaction of aromatic aldehydes, nitroalkanes, and sodium azide has been developed; this reaction sequence can be applied to a broad substrate scope and affords the corresponding 4-aryl-*NH*-1,2,3-triazoles in good to excellent yields. The milder reaction conditions and easier operation make this $AlCl_3$-catalyzed protocol more advantageous for the synthesis of 4-aryl-*NH*-1,2,3-triazoles.

Keywords: aluminium(III) chloride catalysis; *NH*-1,2,3-triazoles; sodium azide; three-component reaction

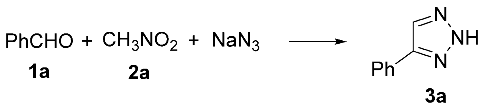
1,2,3-Triazoles are one of the most significant classes of heterocyclic compounds, and they have found widespread applications in diverse areas, such as medicinal chemistry,[1] materials chemistry[2] and synthetic organic chemistry.[3] In the past decades, many approaches for the synthesis of 1,2,3-triazoles have been developed. The most popular method is the Cu-catalyzed azide-alkyne cycloaddition (Cu-AAC),[4] which gives the 1,4-disubstituted 1,2,3-triazoles with high efficiency. Complementarily, other transition metal-catalyzed click protocols such as Ru-AAC,[5] Ir-[6] and Ag-AAC[7] have allowed the synthesis of 1, 5-disubstituted or 1,4,5-trisubstituted 1,2,3-triazoles. Recently, several other methods for the synthesis of different 1,2,3-triazole derivatives were reported, including organocatalyzed azide-ketone cycloaddtions,[8] three-component reactions,[9] metal-free and azide-free methods.[10] Within the 1,2,3-triazole categories, the *NH*-1,2,3-triazole is an important class which has shown wide applications in many fields, especially in the synthesis of diverse 1,2,3-triazoles by post-*N*-functionalizations, such as post-alkylation or arylation of *NH*-1,2,3-triazole for synthesis of N^2-substituted 1,2,3-triazoles.[11] However, to a certain extent, the synthesis of *NH*-1,2,3-triazole is still a challenge in contrast to the direct synthesis of substituted 1,2,3-triazoles. Methods for the synthesis of 4-aryl-*NH*-1,2,3-triazoles are usually confined to the cycloaddition of alkynes and $TMSN_3$ followed by deprotection of the TMS group.[12] A direct Pd-catalyzed cyclization of vinyl bromides and NaN_3 was also developed, which did not need the deprotection step.[13] The condensation of nitroalkenes and NaN_3 is a popular method for the synthesis of *NH*-1,2,3-triazoles. Zefirov initially reported the reaction of sodium azide with nitrostyrenes to synthesize *NH*-triazoles.[14] Then the method was revised by Zard with improved yields, but was still limited by potential substrate polymerization.[15] Recently, Guan has made an adventurous breakthrough by introducing PTSA (*p*-methylbenzenesulfonic acid) to this cycloaddition reaction, which inhibited the cyclotrimerization of the nitroolefins and promoted the cycloaddition effectively.[16]

Multicomponent reactions are a kind of powerful tool for the assembly of different molecules in a single synthetic operation, which not only is high step-economical, but also avoids the separation of the reaction intermediates.[17] In 2008, the Shi group reported a proline-catalyzed three-component reaction of aldehyde, β-alkylnitroalkene, and NaN_3 to synthesize 4,5-disubstituted-1,2,3-*NH*-triazoles.[18] Then, a three-component reaction based upon the Julia reagent, aldehyde, and NaN_3 was conducted by the Chu group.[19] Lately, Lin developed another three-component reaction based upon aldehyde, nitroalkane and NaN_3.[20] However, the reaction efficiency was hindered by the requirement of slow addition of nitroalkane and excess amounts of $NaHSO_3/Na_2SO_3$ (2 equivalents) and NaN_3 (4 equivalents) under an argon atmosphere. At the same time, the overall yields were not high, especially those with aromatic aldehydes bearing either strongly electron-donating or electron-withdrawing groups gave lower yields.

We are interested in the synthesis and properties of new 1,2,3-triazoles and related heterocycles.[21] The development of a more simple and efficient method for the synthesis of *NH*-1,2,3-triazoles is one of the major goals for us. In this paper, we report an $AlCl_3$-catalyzed three-component condensation of aromatic aldehydes, nitroalkanes and NaN_3 for the synthesis of 4-aryl-*NH*-1,2,3-triazoles. This reaction proceeds under mild conditions and affords the products with high yields and reaction efficiency. Benzaldehyde and nitromethane were selected for the initial conditions screening. The results are summarized in Table 1.

Initially we proposed that the condensation of benzaldehyde with nitromethane would occur smoothly under acid conditions, such as AcOH to afford the nitroalkene intermediate, then the nitroalkene could subsequently react with NaN_3[22] to give the *NH*-1,2,3-triazole. Firstly, the reaction was carried out using AcOH as catalyst and DMSO as solvent at 110 °C, the desired 1,2,3-triazole **3a** was obtained in 63% yield (entry 1). Then other sets of conditions were screened based on the initial test, as shown in Table 1. In the absence of catalyst, **3a** could be also isolated in 58% yield (entry 2). It seemed that the NaN_3 served as both base and reaction component to promote formation of the nitroalkene, and further react with nitroalkene to give the target product. When PTSA was used as catalyst, a slight improvement was observed. Furthermore, on lowering the reaction temperature to 70 °C, the yield of **3a** could be increased to 78% (entry 5). We proposed that the low reaction temperature could prevent NaN_3 from decomposition under acidic conditions, however, an increase in the amount of NaN_3 did not improve the product yield obviously (entry 6), at the same time, the reaction only gave 72% yield without any catalyst at 70 °C (entry 7), indicating that the acid catalyst was still playing the key role in the reaction. So the catalyst was changed to a Lewis acid. The reaction gave **3a** in 72% yield when $FeCl_3$ was used as catalyst (entry 8), while $ZnBr_2$ and $CuCl_2$ as catalysts did not give better results. It was gratifying that a 95% isolated yield was obtained (entry 11) when $AlCl_3$ served as catalyst. The subsequent screening of different solvents (entries 11–13) revealed DMSO as the optimal solvent. Further lowering of the temperature (50 °C, entry 15) significantly decreased the reaction rate, while a higher temperature (110 °C, entry 16) was not advantageous for the yield either.

Table 1. Optimization of the reaction conditions.[a]



Entry	Cat.	Solvent	Temp. [°C]	Yield [%][b]
1	AcOH	DMSO	110	63
2		DMSO	110	58
3	TsOH	DMSO	110	67
4	TsOH	DMSO	90	72
5	TsOH	DMSO	70	78
6[c]	TsOH	DMSO	70	80
7		DMSO	70	72
8	$FeCl_3$	DMSO	70	72
9	$ZnBr_2$	DMSO	70	68
10	$CuCl_2$	DMSO	70	66
11	$AlCl_3$	DMSO	70	95
12	$AlCl_3$	DMF	70	70
13	$AlCl_3$	CH_3CN	70	NR
14	$AlCl_3$	DMSO	r.t.	NR
15[d]	$AlCl_3$	DMSO	50	41
16	$AlCl_3$	DMSO	110	78

[a] *Reaction conditions:* benzaldehyde (212 mg, 2 mmol), nitromethane (183 mg, 3 mmol), NaN_3 (156 mg, 2.4 mmol), and catalyst (0.2 mmol), solvent (8 mL); reaction time, overnight, in air.

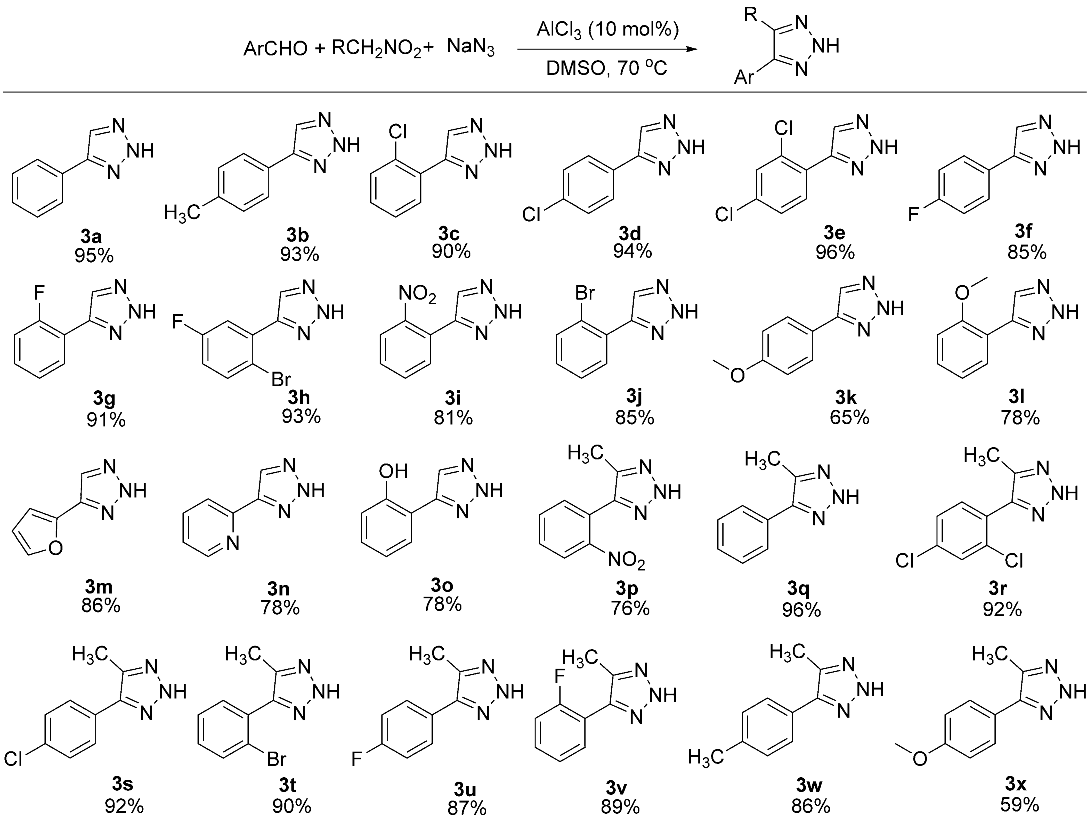
[b] Yields of isolated products.

[c] 3 mmol (1.5 equiv.) NaN_3 were used.

[d] 32% unreacted benzaldehyde was recovered.

With the optimized reaction conditions established, we then explored the substrate scope. The results are summarized in Scheme 1. The $AlCl_3$-catalyzed three-component reaction showed good functional group tolerance and has proved to be a general method for the synthesis of 4-aryl-*NH*-1,2,3-triazoles. Irrespective of whether the functional groups on aryl rings are electron-withdrawing, or electron-donating, they all gave excellent yields. By contrast, hydroxy, methoxy and nitro substituted aromatic aldehydes gave relatively lower yields than other groups due to their potential for coordinating with $AlCl_3$, which were different with the PTSA-catalyzed results.[16] Aliphatic aldehydes, such as phenylacetaldehyde and butyraldehyde, were also tested for this three-component reaction, however, these reactions could not give desired products.

Generally, the condensation of NaN_3 with nitroalkenes was a popular method for synthesis of 4-aryl-*NH*-1,2,3-triazoles. However, some nitroalkenes were, to some extent, hard to be obtained, for example, ester group-substituted nitroalkenes were obtained usually with lower yields or under harsh reaction conditions.[9b,23] Based on these considerations, the 2-ethyl nitroacetate has been chosen for this three-component reaction (Scheme 2). It was exciting that the reactions resulted in high efficiency, which gave the ester group-substituted *NH*-1,2,3-triazoles with high



Scheme 1. Substrate scope of the reaction. *Reaction conditions:* aromatic aldehydes (2 mmol), nitroalkanes (3 mmol), NaN_3 (2.4 mmol), and $AlCl_3$ (0.2 mmol), DMSO (8 mL); overnight, in air. Yields of isolated products are given.

yields. So far, this method is the optimal way to synthesize ester group-substituted *NH*-1,2,3-triazoles.[19,24]

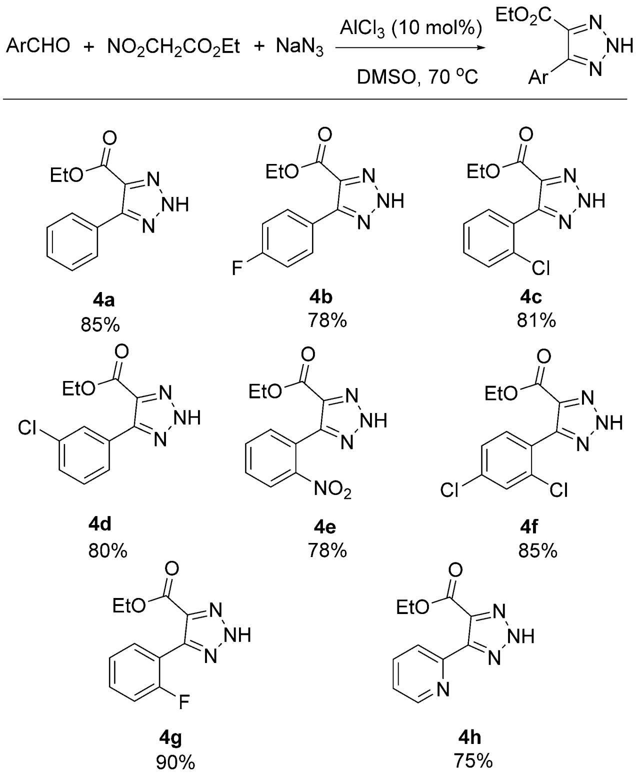
To further identify the reaction process and understand the efficiency of this three-component reaction, certain control experiments were performed (Scheme 3). The condensation of benzaldehyde and nitromethane barely occurred when $AlCl_3$ was used as catalyst at 70 °C (Scheme 3a). At the same time, the condensation of nitroalkene with NaN_3 by using $AlCl_3$ as catalyst at room temperature could also give **3a** with 96% yield in 2 h (Scheme 3b), which revealed that the formation of *NH*-1,2,3-triazole was a fast process. These results indicated that the fast formation of triazole could drive the initial slow Henry reaction, which potential inhibited the polymerization tendency of nitroalkene intermediate. To further identify the role of $AlCl_3$, 2-pyridine-carboxaldehyde was chosen as the substrate, when the $AlCl_3$ was changed to PTSA, the triazole **3n** was obtained in only 47% yield (Scheme 3c), indicating that the $AlCl_3$ should be a Lewis acid to activate the nitro group to benefit the azide nucleophilic addition.[25]

In conclusion, we have developed an efficient and convenient $AlCl_3$-catalyzed three-component condensation reaction of aromatic aldehydes, nitroalkanes and sodium azide. The reactions gave 4-aryl-*NH*-1,2,3-triazoles with excellent yields under operationally convenient conditions and showed a toleration of a wide range of functional groups. Besides the easily available reaction materials, this method avoided the separation of the nitroalkene intermediates, especially those with sensitive functional groups like nitrovinylpyridine, thus improved the overall yields. Further application of the simple protocol for synthesis of functional 4-aryl-*NH*-1,2,3-triazoles with unique properties are under investigation in our group.

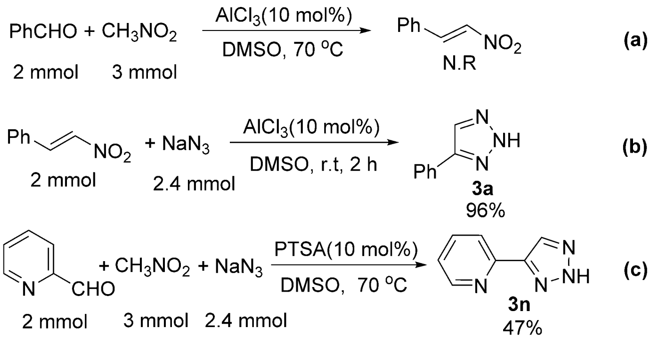
Experimental Section

Typical Procedure for the Synthesis of 3a

The mixture of benzaldehyde (**1a**, 212 mg, 2 mmol), nitromethane (**2a**, 183 mg, 3 mmol), NaN_3 (156 mg, 2.4 mmol), and $AlCl_3$ (27 mg, 0.2 mmol), were stirred in 8 mL DMSO at 70 °C under air. After 5–8 h (as monitored by TLC), the solution was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The resulting mixture was chromatographed on silica gel by eluting with ethyl acetate/petroleum ether to afford **3a** as a white solid; yield: 276 mg (95%).



Scheme 2. Synthesis of carboxylated *NH*-1,2,3-triazoles. *Reaction conditions:* aromatic aldehydes (2 mmol), 2-ethyl nitroacetate (3 mmol.), NaN$_3$ (2.4 mmol.), and AlCl$_3$ (0.2 mmol), DMSO (8 mL); overnight, in air. Yields of isolated products are given.



Scheme 3. Some control experiments.

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