

# One-Pot, Three-Component Reaction Using Modified Julia Reagents: A Facile Synthesis of 4,5-Disubstituted 1,2,3-(NH)-Triazoles in a Wet Organic Solvent

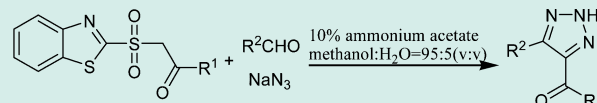
Huihui Chai, Ruiqiang Guo, Wei Yin, Lingping Cheng, Renhua Liu, and Changhu Chu\*

School of Pharmacy, Shanghai Key Laboratory of New Drug Design, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, P. R. China

## Supporting Information

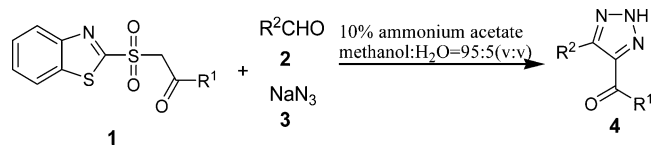
**ABSTRACT:** A new one-pot, three component reaction involving the use of Julia reagent, aldehyde, and sodium azide was developed for the efficient synthesis of *N*-unsubstituted 1,2,3-triazoles. This reaction could be carried out under mild reaction conditions without any precaution, and broad scope of substrates, both respect to Julia reagents and aldehydes, could be applied in this reaction system in generation of a small library of title compounds.

**KEYWORDS:** multicomponent reaction, Julia reagent, 1,2,3-triazoles, sodium azide, one pot



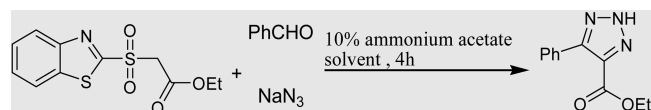
1,2,3-Triazole derivatives are attractive target compounds, which have been utilized as dyes, photostabilizers, agro-

## Scheme 1. One-Pot Multicomponent Synthesis of 4,5-Disubstituted-(NH)-1,2,3-triazole



chemicals, pharmaceutically active ingredients, and biochemicals, as well as intermediate in chemical synthesis.<sup>1</sup> So far, many synthetic methods for achieving this ring system have been developed for different purposes. Among these methods, a typical click reaction, copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) is undoubtedly the most powerful strategies.<sup>1,2</sup> Besides Cu(I) catalysts, other transition metal catalysts, such as ruthenium,<sup>3</sup> palladium<sup>4</sup> and zinc<sup>5</sup> in combination with different reaction systems, have also been utilized to promote the formation of 1,2,3-triazoles. Furthermore, other protocols, including the use of nontransition metal catalysts, such as tetrabutylammonium fluoride (TBAF),<sup>6</sup> tetraalkylammonium hydroxide, or potassium *tert*-butoxide,<sup>7</sup> small organic molecules and organic bases,<sup>8</sup> even heat promoted [3+ 2] cycloaddition reactions<sup>9</sup> and catalyst free strain-promoted alkyne–azide cycloaddition (SPAAC) have been developed.<sup>10</sup> However, most of these methods afforded 1-substituted 1,2,3-triazoles, and only a few of them gave *N*-unsubstituted 1,2,3-triazoles, which could be further derivatized to 2-substituted 1,2,3-triazoles.<sup>11</sup> On the other hand, a multicomponent reaction (MCR), which was first reported in 1838 by Laurent and Gerhardt, is an attractive synthetic strategy in drug discovery research, since it provides easy and rapid access to large libraries of organic compounds with

Table 1. Screening of Reaction Solvent<sup>a</sup>



entry	solvent	conversion (%)	selectivity (%) <sup>b</sup>	yield (%)
1	EtOH	100	87	87
2	MeOH	100	95	95
3	MeOH/H <sub>2</sub> O(95:5)	100	98	98
4	DMSO	100	45	45
5	H <sub>2</sub> O	0	0	0
6	DMA	100	51	51
7	DMF	100	33	33
8	THF	70	53	37
9	CH <sub>2</sub> Cl <sub>2</sub>	0	0	0
10	CHCl <sub>3</sub>	0	0	0
11	EtOAc	40	28	11
12 <sup>c</sup>	MeOH/H <sub>2</sub> O(95:5)	90	51	45

<sup>a</sup>Reaction conditions: benzaldehyde (58 mg, 0.55 mmol), Julia reagent (143 mg, 0.5 mmol), sodium azide (49 mg, 0.75 mmol), ammonium acetate (4 mg, 0.05 mmol); reaction time, 4 h; temperature, 30 °C; 2 mL of commercial solvent was used directly without any further purification. Conversion, selectivity, and yield are determined by GC.

<sup>b</sup>Selectivity is the percent of target compound in all of products.

<sup>c</sup>Ammonium acetate was not used.

diverse substitution patterns. Since the Strecker amino-acid synthesis reaction in 1850, many named reactions, such as Mannich, Hantzsch, Biginelli, Tietze, Robinson–Schopf, Grieco, Ugi, etc., were incorporated into MCRs,<sup>12</sup> and some MCRs were developed for obtaining 1,2,3-triazoles.<sup>11a,13</sup> It still

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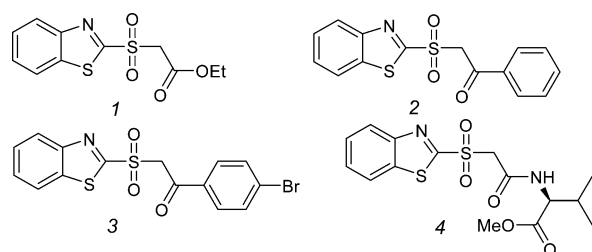


Figure 1. Diversity of Julia reagents 1{1–4}.

is of great importance to develop new MCRs, which may offer greater possibilities for molecular diversity per step with a minimum of synthetic time and effort. Furthermore, the efficient construction of the ring structure without using transition metal catalysts is also an essential issue both in pharmaceutical synthesis and bioconjugation. Therefore, construction of heterocyclic systems with simple organic molecules by MCRs is highly desired.

In our previous work, a type of substituted vinyl sulfones were prepared through the  $\text{Ti}(\text{O}i\text{-Pr})_4$  mediated Knoevenagel condensation between benzothiazol-2-yl sulfones (BT sulfone, Julia reagent) and aldehydes with good yields and exclusively *E* isomers, which could rapidly react with sodium azide to afford 4,5-disubstituted-(*NH*)-1,2,3-triazoles with high yield.<sup>14</sup> However, this (*NH*)-1,2,3-triazoles synthesis procedure was time-consuming requiring two independent steps. Furthermore, the  $\text{Ti}(\text{O}i\text{-Pr})_4$  is a moisture sensitive reagent, thus the Knoevenagel condensation reaction should be run in a dry solvent under an inert atmosphere. In addition, a laborious workup is required because of the amorphous precipitate of titanous acid formed upon hydrolysis. In spite of these disadvantages, it was noticeable that the irreversible 1,3-dipolar cycloaddition reaction between vinyl sulfones and sodium azide in polar solvents and can be carried out under mild condition without any precautions. Likewise, the Knoevenagel condensation can be catalyzed by ammonium salts in alcoholic solvent. Furthermore, Julia reagents can be readily prepared. Based on the facts mentioned above, it was assumed that an ammonium catalyzed Knoevenagel condensation between aldehyde and BT sulfone could give a vinyl sulfone, which subsequently would react with sodium azide by an irreversible 1,3-dipolar cycloaddition and elimination the benzothiazol sulfonyl group to drive the preceding equilibrium to the product side (of course, the elimination of the sulfone part of the group in the Julia reagent is not atom efficient). Our interest in developing a new, more efficient method for the synthesis of functional 4,5-disubstituted-(*NH*)-1,2,3-triazoles encouraged us to test the

three component reaction between Julia reagents, aldehydes and sodium azide with ammonium acetate as the catalyst. Herein, we would like to describe an efficient method for obtaining 4,5-disubstituted-(*NH*)-1,2,3-triazoles (Scheme 1). This process, which has a broad scope both in respect to the Julia reagents and aldehydes, is experimentally simple, and affords the target compounds in moderate to excellent yield without a complicated purification step. Different ammonium salts, such as ammonium acetate, ammonium chloride, ammonium carbonate, ammonium formate, ammonium nitrate, etc., could be used for this reaction. Additionally, alcoholic solvents, such as methanol and ethanol are preferred solvents (Table 1, entries 1 and 2). Polar aprotic solvents, including *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), tetrahydrofuran (THF), ethyl acetate (EtOAc), and dimethyl sulfoxide (DMSO) can also be used in this reaction as well; however, neither the selectivity nor conversion is satisfactory (Table 1, entries 4, 6, 7, 8, and 11). When chloroform, dichloromethane and water were used as solvent, no reaction was detectable (Table 1, entries 5, 9, and 10). In addition, since the reaction is not sensitive to moisture, a small amount of water (about 5%) accelerates it due to sodium azide's high aqueous solubility (Table 1, entry 3), 95% aqueous methanol was used in all the rest of multicomponent reactions. A control experiment was also carried out without using ammonium acetate as the catalyst resulting in a lower selectivity and yield (Table 1, entry 12).

After various combinations of reagents were screened, an optimized procedure for obtaining 4,5-disubstituted-(*NH*)-1,2,3-triazoles was achieved. The Julia reagents contain three diverse functionalities, an ester, a ketone, and an amide (Figure 1), aldehydes include aromatic aldehydes with electronic-donating and electron-withdrawing groups, heterocyclic aldehyde and alkyl aldehydes (Figure 2). As depicted in Table 2, the reactions preceded in moderate to excellent yield (55–99%). The substituent on the aldehydes did not significantly distinguish the yields. Furthermore, the three types of Julia reagents, containing ester, amide or ketone combined with sodium azide, reacted with the aldehydes to form the corresponding (*NH*)-1,2,3-triazoles, though the reactivity of the amide is a little weaker than the ester and ketone (Table 2, Entries 24 and 25). Hence, by varying both the Julia reagents and aldehydes, a wide variety of 4,5-disubstituted-(*NH*)-1,2,3-triazoles could be readily prepared. Furthermore, the reaction mechanism study displayed that it is difficult to drive the Knoevenagel condensation to completion in the presence of 10% mol amount of ammonium acetate. After 24 h at 30 °C, only a small amount of Julia reagent was

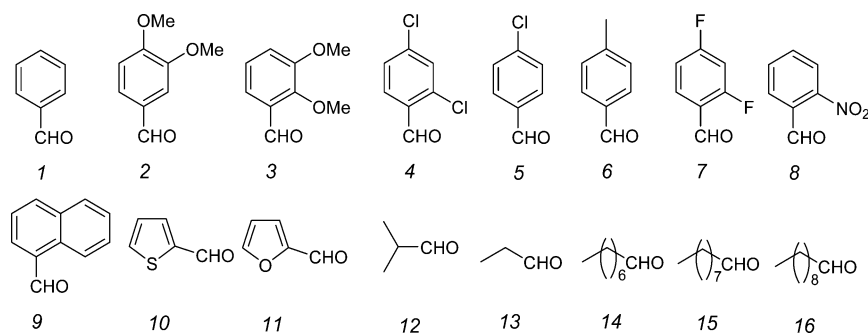


Figure 2. Diversity of aldehydes 2{1–16}.

Table 2. Scope of the Three-Component Reaction

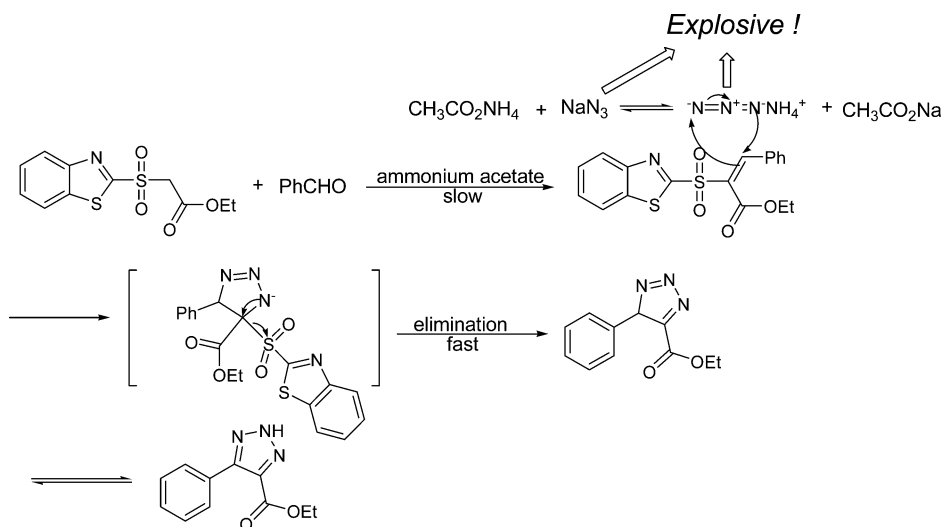
Entry	product	Yield (%) <sup>a</sup>	Entry	product	Yield (%) <sup>a</sup>
1	 4{1,1}	98	14	 4{1,14}	85
2	 4{1,2}	93	15	 4{1,15}	95
3	 4{1,3}	90	16	 4{1,16}	80
4	 4{1,4}	88	17	 4{2,1}	88
5	 4{1,5}	94	18	 4{2,3}	82
6	 4{1,6}	80	19	 4{2,3}	84
7	 4{1,7}	99	20	 4{2,4}	65
8	 4{1,8}	99	21	 4{2,5}	85
9	 4{1,9}	80	22	 4{3,1}	70
10	 4{1,10}	74	23	 4{3,1}	84
11	 4{1,11}	91	24	 4{3,3}	60
12	 4{1,12}	94	25	 4{4,1}	55
13	 4{1,13}	60		 4{4,3}	

<sup>a</sup>Reaction conditions: aldehyde (1.1 mmol), Julia reagent (1 mmol) and sodium azide (1.5 mmol), ammonium acetate (8 mg, 0.1 mmol); temperature, 30 °C; 2 mL of 95% aqueous methanol (methanol/water = 95:5, v:v) was used. The yields are for the isolated product.

transformed to the corresponding vinyl sulfone. Thus, the 1,3-dipolar cycloaddition between the vinyl sulfone and sodium

azide drove the three component reaction forward. Also, the equilibrium between ammonium acetate and sodium azide

Scheme 2. Plausible Mechanism for the Multicomponent Reaction



likely affords some ammonium azide, which is the more active nucleophile toward the vinyl sulfone. This would explain the catalytic role of ammonium acetate in this reaction. A plausible mechanism is shown in Scheme 2. (**Caution:** Ammonium azide is highly volatile at or near room temperature, and both ammonium azide and sodium azide are very shock sensitive. They have been known to spontaneously explode.)

## CONCLUSION

In summary, the ammonium catalyzed three component reaction described here provides a direct, simple, highly selective and efficient method for the synthesis of 4,5-disubstituted-(NH)-1,2,3-triazoles, in which the Knoevenagel condensation and 1,3-dipolar cycloaddition was combined in one pot without any precaution. Starting from commercial and readily available reagent, 4,5-disubstituted-(NH)-1,2,3-triazoles with several functional groups can be prepared conveniently, which is quite useful for construction of small focused library.

## EXPERIMENTAL PROCEDURES

Azides can be very explosive compounds and should be handled with care. Aldehydes were distilled before use. Ammonium acetate, ammonium chloride, ammonium nitrate, ammonium carbonate, ammonium formate, sodium azide, and methanol, as well as other starting materials were commercially available and used without further purification. Melting points were obtained with a Reichert Thermovar apparatus and are uncorrected.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on Bruker Avance 400 spectrometers (400 MHz for  $^1\text{H}$  NMR, and 125 MHz for  $^{13}\text{C}$  NMR); chemical shifts were reported in  $\delta$ (ppm) and coupling constants ( $J$ ) in hertz, relative to the internal standard of tetramethylsilane (TMS). All infrared (IR) spectra were recorded using a KBr disc or coating on a Nicolet 6700 spectrometer. Mass spectra were performed on a GCT Premier spectrometer under electron impact (EI). Thin layer chromatography (TLC) was performed on 10–40  $\mu\text{m}$  silica plates and column chromatographic purifications were performed on 300–400 mesh silica gel.

**General Procedure for the One-Pot Multicomponent Synthesis of 4,5-Disubstituted-(NH)-1,2,3-triazole.** A solution of the modified Julia reagents ethyl 2-(benzo[*d*]-thiazol-2-ylsulfonyl)acetate (286 mg, 1 mmol), benzaldehyde

(116 mg, 1.1 mmol), sodium azide (98 mg, 1.5 mmol) and ammonium acetate (8 mg, 0.1 mmol) in 2 mL methanol (containing 5% water) was stirred at 30 °C for 4 h. The reaction was detected by thin layer chromatography (TLC). After the Julia reagent was consumed out, the solvent was removed by evaporation and the residue was purified by a flash column on silica gel to afford compound 4{1,1} in 98% yield.

## ASSOCIATED CONTENT

### Supporting Information

Further details on the experimental and isolation procedures, spectral data, and copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

### Corresponding Author

\*Fax: +86-21-64250627. E-mail: [chuch@ecust.edu.cn](mailto:chuch@ecust.edu.cn).

### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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