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One-flask synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from nitriles and hydrazonoyl chlorides via 1,3-dipolar cycloaddition†

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Abstract

A one-flask strategy for the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles **4a**–**s** and **8a**–**b** from nitriles **5a**–**i** with *N*-arylhydrazonoyl hydrochlorides **3a**–**h** and **7a**–**b** under basic conditions was developed. The reaction provided the desired 1,2,4-triazoles in moderate to excellent yields (56–98%), and was applicable to aliphatic and aromatic nitriles as well as *N*-phenylhydrazonoyl hydrochlorides bearing ester and acetyl functionalities. A 1,3-dipolar cycloaddition between imidate and nitrilimine generated from the respective nitrile and *N*-arylhydrazonoyl chloride in one flask was proposed for the new transformation.

Introduction

Substituted 1,2,4-triazoles are considered important classes of heterocyclic compounds for they show various biological activities.[1] Among the traditional methods for their preparation,[2] the dehydrative cyclization of acylamidrazone intermediates,[3] formed from the reaction of hydrazides and the activated nitriles with amides including imidates or a thioamides at the high temperature, are frequently used.[4] However, the harsh reaction conditions including the use of corrosive $POCl_3$ or $SOCl_2$ limit their application to sensitive substrates.[5,6]

In our previous study,[7] we report the synthesis of 1,3,5-trisubstituted 1,2,4-triazole **4** by a new 1,3-dipolar cycloaddition between oxime **2** and hydrazonoyl chloride[8] **3** under basic conditions (equation 1 in Figure 1). In this reaction, compound **2** serves as the dipolarphile and **3** serves as the precursor to 1,3-dipole nitrilimine.[9] In a further study we present that 1,2,4-triazole **4** can be obtained in "one flask" by reacting aldehyde **1**, the precursor to **2**, with hydroxylamine hydrochloride following with **3**.[7c] The two reactions proceed under mild conditions and produce **4** regiospecifically in good to excellent yields. We also demonstrate that triazoles **4** inhibit the proliferation of NCI-H226, NPC-TW01, and Jurkat cancer cells at low micromolar concentrations.[7a]

Figure 1

As imidate **6** is electronically analogous to oxime **2**, we envisage that **6** could substitute oxime **2** as the dipolarphile for the synthesis of 1,3,5-trisubstituted 1,2,4-triazole **4** (see equation 2 in Figure 1). Moreover, due to the preparation of **6** can be achieved by partial alcoholysis (Pinner reaction)[10] of the precedent nitrile **5** under acidic conditions, an "one-flask" synthesis of triazole **4** can thus be achieved from nitrile **5** without the isolation of imidate **6**. The use of unstable aldehydes and toxic hydroxylamine as the starting materials can be avoided. Despite direct cycloaddition

of nitriles with hydrazonoyl chlorides is also reported to provide 1,2,4-triazoles, the substrates are limited to nitriles such as ethyl carbonocyanidate ($EtO_2C–CN$), benzyl carbonocyanidate ($BnO_2C–CN$), and 2,2,2-trichloroacetonitrile ($Cl_3C–CN$) that bear a strong electron-withdrawing group.[11] Herein, we present our investigation on the one-flask synthesis of 1,3,5-trisubstituted 1,2,4-triazoles **4** from nitriles **5** with hydrazonoyl chlorides **3** thorough imidates **6**. The reaction provided the desired products in moderate to excellent yields and was applicable to simple aliphatic and aromatic nitriles.

Results and discussion

For the nitrilimine as the 1,3-dipole is generated from hydrazonoyl chloride under basic conditions,[9] we first screened the suitable base for the new 1,3-dipolar cycloaddition by use of commercially available ethyl acetimidate hydrochloride (**6a**) with *N*-phenylhydrazonoyl chloride **3a** as the model (Table 1). Reaction of acetonitrile (**5a**) with HCl(g) and ethanol in CH_2Cl_2, then with **3a** in one flask was also studied for comparison.[12] For the reaction of imidate **6a** with hydrazonoyl chloride **3a**, we observed that the 1,3-dipolar cycloaddition did not take place without a base (entry 1 in Table 1), neither did the use of diethylamine or *N,N*-diisopropylethylamine or pyridine (entries 2–4). Use of DBU only gave **4a** in low yield (23%, entry 5). Among the bases we have tried, only the use of triethylamine displayed a satisfactory result (77% yield, entry 6). For the one-flask transformation from acetonitrile (**5a**) with hydrazonoyl chloride **3a** to 1,2,4-triazole **4a**, the reaction provided almost the identical results and the use of triethylamine also provided the best yield of **4a** (76%, see entry 6). Triethylamine was thus used as the base for all the following studies.

Table 1

In control experiment, **5a** was directly reacted with **3a** in the presence of Et_3N

without being reacted preferentially with HCl to form imidate **6a**. The desired 1,3,5-trisubstituted 1,2,4-triazoles **4a** was not obtained with the decomposition of starting materials. The result suggested the higher reactivity of imidate **6a** than nitrile **5a** as the dipolarphile to react with hydrazonoyl chloride **3a**.

We then focused on the one-flask 1,3-dipolar cycloaddition strategy for the synthesis of 1,2,4-triazole **4** (equation 2 in Figure 1). We prepared various *N*-phenylhydrazonoyl chlorides **3a**–**h**[8] bearing different substituents on the phenyl ring and allowed them to react with alkyl nitriles **5a**–**e** (see Table 2). For the reaction of acetonitrile (**5a**) with hydrazonoyl chlorides **3a**–**h** bearing *o*-CF$_3$, *m*-Br, *p*-Me, *p*-CF$_3$, *p*-OMe, *p*-F, and *p*-Cl on the phenyl group, the reaction readily gave the corresponding 1,2,4-triazoles **4b**–**h** in 56–91% yields (entries 2–8 in Table 2). The use of compound **3h** (X = *p*-Cl) gave the best result (91% yield) nevertheless **3d** (X = *p*-Me) gave a poor result (56% yield).

Table 2

The one-flask 1,3-dipolar cycloaddition strategy was also applicable to various aliphatic nitriles. Reaction of ethyl, *i*-propyl, *n*-butyl, and cyclopentyl nitriles **5b**–**e** with *p*-chloro-*N*-phenylhydrazonoyl chloride **3h** in the presence of triethylamine provided the corresponding 1,3,5-trisubstituted 1,2,4-triazoles **4i**–**l** in 57–98% yields (see entries 9–12 in Table 2). The results in Table 2 indicated that aliphatic nitriles and *N*-phenylhydrazonoyl hydrochlorides bearing different substituents on the phenyl group were tolerable in the new 1,3-dipolar cycloaddition. The structures of 1,2,4-triazoles **4a**–**l** were fully characterized by spectroscopic methods and consistent with the data in our previous studies.[7]

We turned to study the reactivity of aromatic nitriles including benzonitrile (**5f**), 2-furonitrile (**5g**), thiophene-2-carbonitrile (**5h**), and 1*H*-pyrrole-2-carbonitrile (**5i**) for the one-flask 1,3-dipolar cycloaddition (Table 3). Reaction of compounds **5f**–**i** with

N-phenylhydrazonoyl hydrochloride **3h** bearing the *p*-Cl substituent gave the corresponding 1,2,4-triazoles **4m**–**p** in 56–86% yields (entries 1–4 in Table 3). In comparison with the results from aliphatic nitriles **5a**–**e** (entries 8–12 in Table 2), use of aromatic nitriles **5f**–**i** demonstrated slightly poorer results. The lower yields of **4m**–**p** might come from the conjugation of the double bond of imidate with the π-system in the aryl group to alter the HOMO–LUMO interactions of imidate with nitrilimine,[13] or the instability of π-excessive furyl, thienyl, and pyrrolyl groups in acidic conditions.[14] Reaction of 1*H*-pyrrole-2-carbonitrile (**5i**) with *N*-phenylhydrazonoyl hydrochloride **3b**, **3i**, or **3e** bearing *ortho*-, *meta*-, or *para*-trifluoromethyl group on the phenyl group also provided the corresponding 1,2,4-triazoles **4q**–**s** in 43–75% yields. The experimental results presented in Table 2 and 3 demonstrated that the one-flask 1,3-dipolar cycloaddition was applicable to aliphatic, cyclic aliphatic, and aromatic nitriles with various *N*-phenylhydrazonoyl chlorides to synthesize 1,3,5-trisubstituted 1,2,4-triazoles in moderate to excellent yields.

Table 3

Table 4 presents the results of the one-flask 1,3-dipolar cycloaddition strategy for the synthesis of 1,2,4-triazoles bearing different C-3 substituents. The reaction of acetonitrile (**5a**) with *N*-phenylhydrazonoyl hydrochloride **7a**–**e** was studied using the optimized reaction conditions from Table 1. Not surprisingly, reaction of **5a** with **7a** bearing ethoxycarbonyl group also provide the corresponding 1,2,4-triazole **8a** in 81% yield (see entry 1 in Table 4). Reaction of *N*-phenylhydrazonoyl hydrochloride **7b** bearing acetyl group also gave the corresponding **8b** in 79% yield. However, reaction of *N*-phenylhydrazonoyl hydrochloride **7c** with amido group, **7d** with ethyl group, and **7e** with phenyl group did not give the corresponding 1,2,4-triazole **8c**–**e** (entries 3–5 in Table 4). Decomposition of the starting materials was observed. The results in

Table 4 indicated the one-flask 1,3-dipolar cycloaddition strategy was applicable to *N*-phenylhydrazonoyl hydrochlorides bearing ester and acetyl functionalities.

Table 4

We proposed a plausible mechanism for the one-flask synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from nitriles and *N*-arylhydrazonoyl chlorides through a new 1,3-dipolar cycloaddition in Scheme 1. Upon reaction with EtOH in the presence of HCl(g), nitrile **5** was converted to its corresponding imidate **6**. *N*-Arylhydrazonoyl **3** was converted to the corresponding nitrilimine **8** by Et₃N in the same flask, then the 1,3-dipolar cycloaddition between dipolarphile **6** and 1,3-dipole **8** took place to generate cyclic intermediate **9**. Aromatization of **9** by releasing EtOH generated 1,2,4-triazole **4** in one flask.

Scheme 1

Conclusions

We developed a one-flask methodology for the synthesis 1,3,5-trisubstituted 1,2,4-triazoles using nitriles and *N*-arylhydrazonoyl chlorides as the starting materials. The reaction was applicable to aliphatic and aromatic nitriles with *N*-arylhydrazonoyl chlorides bearing various substituents on the phenyl group. A plausible 1,3-dipolar cycloaddition mechanism was proposed for the reaction of imidate from nitrile with nitrilimine from hydrazonoyl chloride in one flask to generate the desired 1,2,4-triazole.

Acknowledgments

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Table 1 Screening of a suitable base (3.0 equivalents) for the one-flask synthesis of 1,3,5-trisubstituted 1,2,4-triazole **4a** via 1,3-dipolar cycloaddition

entry	base	yield (%) of **4a**	
		from **6a**	From **5a**
1	—	N.D.[a]	N.D.
2	diethylamine	N.D.	N.D.
3	*N,N*-diisopropylethylamine	N.D.	N.D.
4	pyridine	N.D.	N.D.
5	DBU	23	21
6	triethylamine	77	76

[a] N.D.: not detectable.

Table 2 One-flask synthesis of 1,2,4-triazoles **4a–l** from alkyl nitriles **5a–e** and
N-phenylhydrazonoyl chlorides **3a–h** via 1,3-dipolar cycloaddition

entry	nitrile 5a–c		hydrazone 3a–h		triazole 4a–l	reaction time (h)	yield (%)
	R	No.	X	No.			
1	Me	**5a**	H	**3a**	**4a**	3.0	76
2	Me	**5a**	o-CF$_3$	**3b**	**4b**	3.0	71
3	Me	**5a**	m-Br	**3c**	**4c**	4.0	66
4	Me	**5a**	p-Me	**3d**	**4d**	5.0	56
5	Me	**5a**	p-CF$_3$	**3e**	**4e**	3.0	81
6	Me	**5a**	p-OMe	**3f**	**4f**	2.5	90
7	Me	**5a**	p-F	**3g**	**4g**	3.5	77
8	Me	**5a**	p-Cl	**3h**	**4h**	2.0	91
9	Et	**5b**	p-Cl	**3h**	**4i**	3.5	93
10	i-Pr	**5c**	p-Cl	**3h**	**4j**	2.5	98
11	n-Bu	**5d**	p-Cl	**3h**	**4k**	4.5	76
12	cyclopentyl	**5e**	p-Cl	**3h**	**4l**	5.0	57

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Table 3 Synthesis of 1,2,4-triazoles **4m–s** from aromatic nitriles **5f–i** with substituted

N-phenylhydrazonoyl chlorides **3b**, **3e**, **3h**, and **3i**

entry	nitrile 5f–i		hydrazone 3h–e		triazole 4m–s	reaction time (h)	yield (%)
	R	No.	X	No.			
1	phenyl	**5f**	*p*-Cl	**3h**	**4m**	3.0	86
2	2-furyl	**5g**	*p*-Cl	**3h**	**4n**	3.0	61
3	2-thienyl	**5h**	*p*-Cl	**3h**	**4o**	4.0	82
4	2-pyrrolyl	**5i**	*p*-Cl	**3h**	**4p**	5.0	56
5	2-pyrrolyl	**5i**	*o*-CF$_3$	**3b**	**4q**	3.0	43
6	2-pyrrolyl	**5i**	*m*-CF$_3$	**3i**	**4r**	2.5	44
7	2-pyrrolyl	**5i**	*p*-CF$_3$	**3e**	**4s**	3.5	75

Table 4 Synthesis of 1,2,4-triazoles **8a–e** bearing various C-3 substituents

entry	hydrazone **7a–e**			triazole **8a–e**	yield (%)
	X	R	No.		
1	CF$_3$	–CO$_2$Et	**7a**	**8a**	81
2	H	–(C=O)Me	**7b**	**8b**	79
3	H	–CONMe$_2$	**7c**	**8c**	N.D.^{a}
4	H	–Et	**7d**	**8d**	N.D.
5	H	–Ph	**7e**	**8e**	N.D.

^{a} N.D.: Not detectable.
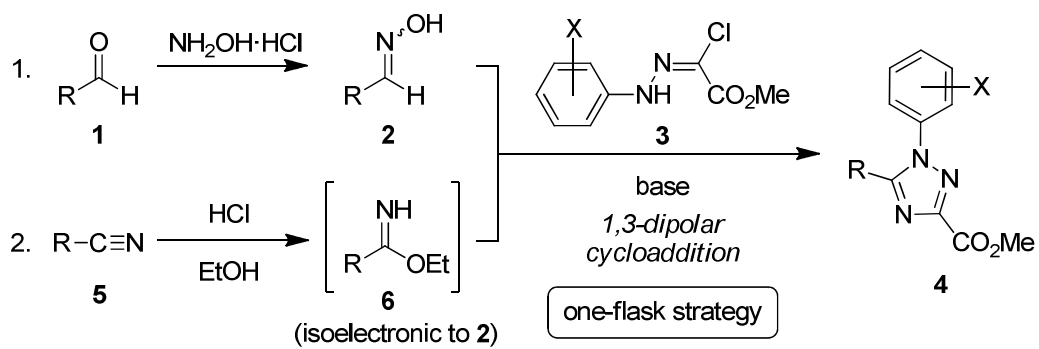
Figure 1 One-flask 1,3-dipolar cycloaddition strategies for the synthesis of 1,3,5-trisubstituted 1,2,4-triazole **4**.
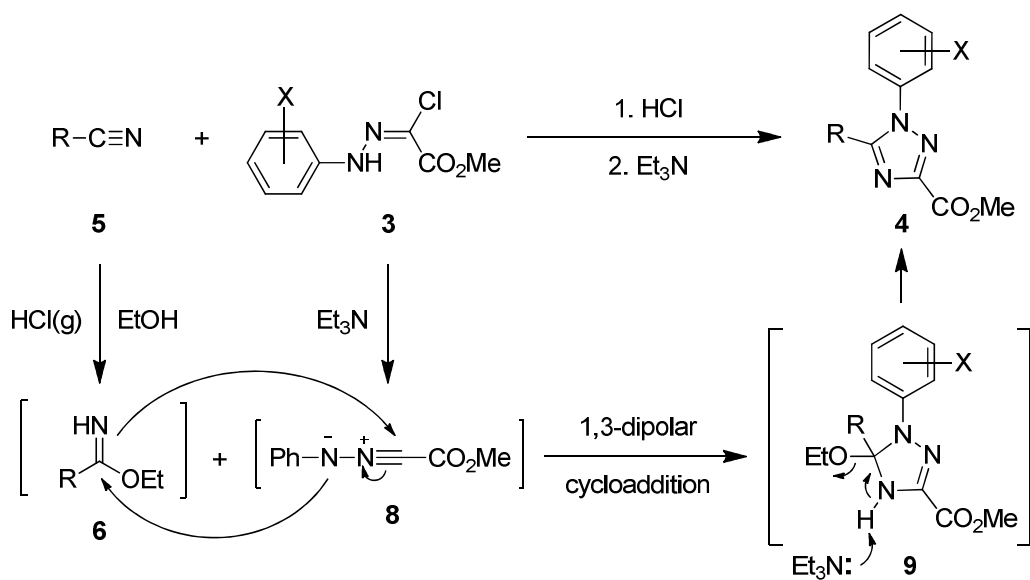
Scheme 1 Proposed mechanism of the one-flask synthesis of 1,2,4-triazole **4** from nitrile **5** and hydrazonoyl chloride **3** via 1,3-dipolar cycloaddition.

Graphical abstract

One-flask synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from nitriles and hydrazonoyl chlorides via 1,3-dipolar cycloaddition

Li-Ya Wang, Henry J. Tsai, Hui-Yi Lin, Kimiyoshi Kaneko, Fen-Ying Cheng, Hsin-Siao Shih, Fung Fuh Wong, and Jiann-Jyh Huang

One-Flask Synthesis of 1,3,5-Trisubstituted 1,2,4-Triazoles from Nitriles and Hydrazonoyl Chlorides via 1,3-Dipolar Cycloaddition