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Brönsted acid-mediated annulations of 1-cyanocyclopropane-1-carboxylates with arylhydrazines: efficient strategy for the synthesis of 1,3,5-trisubstituted pyrazoles†

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1-Cyanocyclopropane-1-carboxylates are reacted with arylhydrazines to afford 1,3,5-trisubstituted pyrazoles under the influence of a Brönsted acid. Formally, this transformation can be regarded as an annulation of three-membered rings with α-carbonyl and hydrazines. This newly efficient method provides access to a variety of structurally diverse pyrazole derivatives. The structures of five typical products were confirmed by X-ray crystallography.

Cyclopropanes and their derivatives have been broadly used as valuable building blocks for the construction of various carbo- and heterocyclic systems due to their high π character, intrinsic ring strain and straightforward synthesis.[1] They easily underwent a variety of ring-opening reactions, and the subsequent annulations with dipoles formed five-, six-, or seven-membered ring systems.[2] Recently we reported the direct annulations of 2-aroyl-3-aryl-1-cyanocyclopropanecarboxylates with pyridine derivatives, nitromethane or β-nitrostyrenes to construct five-membered cyclic cores in a regioselective manner,[3] which stimulated research into new pathways for the construction of cyclic units *via* the ring-opening reactions of 2-aroyl-3-aryl-1-cyanocyclopropanecarboxylates. Some previous studies revealed the most importantly synthetic value of donor–acceptor cyclopropanes has been extensively demonstrated in the preparation of highly substituted cyclic products *via* the vicinal arrangement of donor and acceptor moieties of cyclopropane that is able to stabilize a 1,3-zwitterionic relationship for formal [3 + 2] cycloaddition reactions.[4]

However, the main research efforts have been devoted to use the skeleton of cyclopropane for the construction of new cyclic skeletons *via* the ring-opening reactions of the common donor–acceptor cyclopropanes such as 2-arylcyclopropane 1,1-diesters. 2-Aroyl-3-aryl-1-cyanocyclopropanecarbonates could provide various 1,3-zwitterionic intermediate through different pathways for ring-opening due to involvement in conjugate hybrid from α-carbonyl group. Based on our studies on the reactivity of 2-aroyl-3-aryl-1-cyanocyclopropanecarbonates, we envisioned that the reaction of 2-aroyl-3-aryl-1-cyanocyclopropanecarbonates with arylhydrazines may offer an efficient approach to pyrazole skeletons. Although, the reported reactions of substituted cyclopropanes with hydrazines afforded pyridazin-3(2*H*)-ones and indole derivatives, or ring-opening products.[2h,5] To the best of our knowledge, no example using the annulations of substituted cyclopropanes with arylhydrazines to afford 1,3,5-trisubstituted pyrazoles was reported. In this context, the annulation reactions of 1-cyanocyclopropane-1-carboxylates with arylhydrazines could provide an easy access to 1,3,5-trisubstituted pyrazoles under acidic conditions.

As is known to us, a pyrazole unit as a key structural motif exists in large numbers of pharmaceutically and agrochemically active compounds.[6] Pyrazoles and their derivatives exhibit antimicrobial, antioxidant, antinflammatory, analgesic, anticonvulsant, anticancer, antiHIV-1 reverse transcriptase and herbicidal activities[7] that are extensively used for the treatment of metabolic, CNS, and oncological diseases.[8] For instances, a number of compounds containing a pyrazole scaffold have been successfully commercialized, such as Celebrex, Viagra, Fipronil, Lonazolac, Rimonabant, and Acomplia (Scheme 1).[9] Additionally, pyrazole derivatives are also applied widely in supramolecular and polymer chemistry, in the food industry, and in the fine chemical industry such as fluorescent brightening agents, while some have liquid crystal properties.[10]

Pyrazole derivatives were usually synthesized through traditional approaches including the condensation of 1,3-dicarbonyl compounds with hydrazines and 1,3-dipolar cycloaddition of dipolarophiles with appropriate dipoles.[11] The importance of the pyrazole moiety has prompted the development of many practical and efficient synthetic routes to construct their derivatives. Recently, the efficient methods have been developed with the

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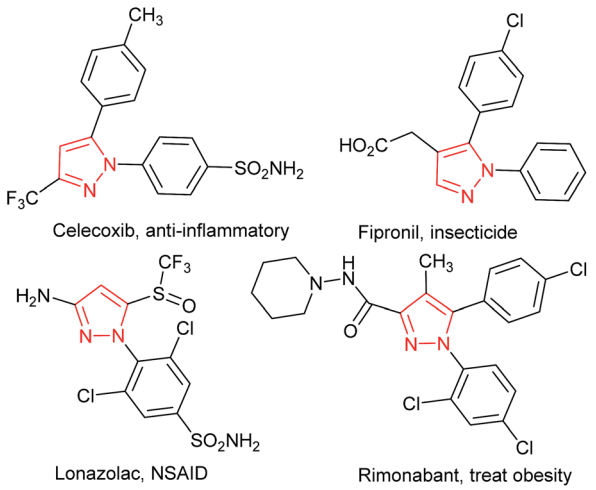
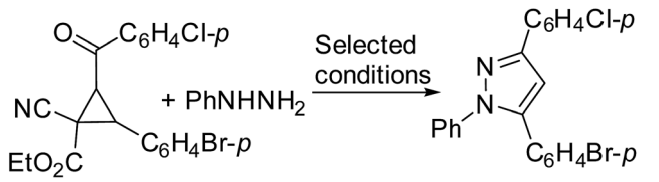


Scheme 1 Pyrazole representative biologically active analogues.

aim of increasing the regioselectivity in the diverse synthesis of substituted pyrazoles. Among them, those involving the formation of C–N and C–C bonds by multicomponent reactions have emerged as a promising alternative to conventional methodologies.[6b,10g,12] Nevertheless, the most common and efficiently synthetic method for the preparation of substituted pyrazoles still involves the cyclocondensation of an appropriate hydrazine, which acts as a double nucleophile, with a three-carbon unit featuring two electrophilic carbons in a 1,3-relationship, such as 1,3-dicarbonyl, α,β-unsaturated carbonyl compounds, and β-enaminones or related compounds. In addition, we have recently published a method for the generation of the specially 1,3-dipolar intermediate from 2-aroyl-3-aryl-1-cyanocyclopropanecarboxylates,[3,13] which could allow for the construction of the pyrazole ring *via* annulation reaction with hydrazines.

At first, we treated the 1-cyanocyclopropane-1-carboxylate **1a** with phenylhydrazine (**2a**, 2 equiv.) in AcOH as the solvent at 110 °C for 12 h (Table 1, entry 1). The desired product **3a** was formed in 52% yield. The result indicated that acidic agents should promote the reaction. Subsequently, while inorganic acid H_2SO_4 was used as a promoter, we were pleased to find out that the yield was improved to 78% (Table 1, entry 2). Then, we examined the reaction using toluene as the solvent to replace AcOH at the above reaction. After overnight, the reaction yielded the required product in 82% yield (Table 1, entry 3). The preliminary results indicated the Brönsted acid and aprotic solvent could afford better results. Recently these studies showed that simple organic acids were used as green and highly efficient catalysts in the preparation of containing-nitrogen heterocycles.[14] Thus, further many Brönsted acids such as sulfamic acid, malonic acid, benzoic acid, cinnamic acid, *p*-toluenesulfonic acid and inorganic acid phosphoric acid were screened (Table 1, entries 4–9), the desired product **3a** was obtained in yield of 75%, 70%, 68%, 65%, 76%, and 81% respectively. Of these acids, sulfamic acid and *p*-toluenesulfonic acid gave the moderate yield (*ca.* 75%), however, the reaction needed the longer reaction time while *p*-toluenesulfonic acid was used. The use of malonic acid, benzoic acid, and cinnamic acid gave

Table 1 Optimization of the reaction conditions[a]



Entry	Acid (equiv.)/solvent/T (°C)/t^a (h)	Yield[b] (%)
1	(−)/AcOH/110/12	52
2	H_2SO_4 (1.0)/AcOH/110/12	78
3	H_2SO_4 (1.0)/PhMe/110/12	82
4	Sulfamic acid (1.0)/PhMe/110/12	75
5	Malonic acid (1.0)/PhMe/110/12	70
6	Benzoic acid (1.0)/PhMe/110/12	68
7	Cinnamic acid (1.0)/PhMe/110/12	65
8	*p*-TsOH (1.0)/PhMe/110/16	76
9	H_3PO_4 (1.0)/PhMe/110/12	80
10	H_2SO_4 (1.0)/PhMe/120/12	80
11	H_2SO_4 (1.0)/PhMe/100/12	78
12	H_2SO_4 (0.8)/PhMe/110/12	84
13	H_2SO_4 (0.6)/PhMe/110/12	78
14	H_2SO_4 (0.8)/PhMe/110/8	82
15	H_2SO_4 (0.8)/PhMe/110/16	80
16[c]	H_2SO_4 (0.8)/PhMe/110/12	82
17	H_2SO_4 (0.8)/CH_3CN/reflux/12	70
18	H_2SO_4 (0.8)/1,4-dioxane/110/12	65
19	H_2SO_4 (0.8)/xylene/110/12	82
20	H_2SO_4 (0.8)/cyclohexane/reflux/12	67
21[d]	H_2SO_4 (0.8)/PE (90–120 °C)/110/12	72

[a] Unless otherwise stated, reactions of **1a** (1 mmol) and phenylhydrazine (2 mmol) were carried out in 5 mL of solvent. [b] Isolated yield. [c] **1a** (1 mmol) and phenylhydrazine (1.5 mmol) were used. [d] PE: petroleum ether.

similar results (Table 1, entries 5–7). Under the same reaction conditions, phosphoric acid promoted the title reaction as much as the reaction activity of sulfuric acid (Table 1, entry 9), which indicated the detrimental effect of strong acids on the reaction. The results showed that sulphuric acid afforded the best result (84% in yield). Further study on the effect of temperature led to the observation that the reaction at 120 °C or 100 °C resulted in a lower yield of 80% and 78%, respectively (Table 1, entries 10–11). Further study on the effect of the amount of sulphuric acid led to the observation that the reaction using 0.8 equiv. H_2SO_4 afforded the best result (Table 1, entries 12 and 13). When the reaction was carried out in shorter reaction time (Table 1, entry 14) or in longer reaction time (Table 1, entry 15), the yield of product **3a** was slightly decreased. Reducing the amount of phenylhydrazine (**2a**) to 1.5 equiv. did not afford the better result (Table 1, entry 17). Next, we studied the effect of solvent on reaction, the reaction was carried out with different solvents such as acetonitrile, 1,4-dioxane, xylene, cyclohexane and petroleum ether (90–120 °C) gave the desired product **3a** in 65–82% of yields (Table 1, entries 17–21), screening of the solvents revealed that toluene and xylene were good candidates. Thus, reconsidering easy removal

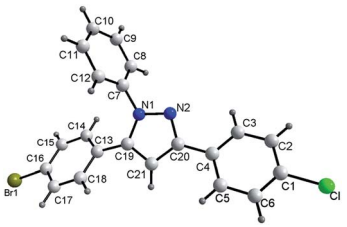
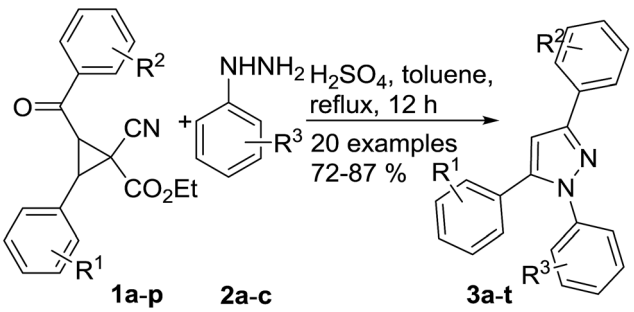


Fig. 1 Molecular structure of 1*H*-pyrazole **3a**.

of toluene in the work-up step, we defined the reaction of the 1-cyanocyclopropane-1-carboxylate **1a** with 2 equiv. phenylhydrazine (**2a**) and 0.8 equiv. sulphuric acid in toluene at 110 °C for 12 h as the standard conditions (Table 1, entry 10).

The structure of **3a** was shown in Fig. 1.[15] X-ray crystallographic analysis determined that product **3a** possess three aryls contiguous substituents at N(1), C(3) and C(5). On the basis of spectroscopic evidence the structure of compound **3a** was identified as 5-(4-bromophenyl)-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole (**3a**).

Table 2 Scope with respect to 1-cyanocyclopropane-1-carboxylates and arylhydrazines[a]



Entry	R^1	R^2	R^3	3	Yield[b] (%)
1	*p*-Br	*p*-Cl	H	**3a**	84
2	*p*-Cl	*p*-Cl	H	**3b**	87
3	*p*-Cl	*p*-CH_3O	H	**3c**	83
4	*p*-Br	H	H	**3d**	82
5	*m*-Cl	*p*-CH_3O	H	**3e**	76
6	*o*-Cl	*p*-CH_3O	H	**3f**	78
7	*o*-Cl	H	H	**3g**	79
8	*p*-Br	*p*-CH_3O	H	**3h**	80
9	*m*-CH_3	*p*-CH_3O	H	**3i**	72
10	3-F-4-PhO	*p*-Br	H	**3j**	81
11	*p*-I	*p*-Br	H	**3k**	85
12	3-F-4-PhO	H	H	**3l**	80
13	*m*-Cl	H	H	**3m**	75
14	*m*-Cl	*p*-CH_3O	*p*-Cl	**3n**	73
15	*p*-Br	*p*-Cl	*p*-Cl	**3o**	87
16	*o*-Cl	H	*p*-CH_3	**3p**	80
17	*p*-CH_3	H	H	**3q**	81
18	*p*-Br	*p*-CH_3O	*p*-Cl	**3r**	84
19	*p*-Br	*p*-Cl	*p*-CH_3	**3s**	85
20	*m*-Br	*p*-CH_3O	H	**3t**	73

[a] 1-Cyanocyclopropane-1-carboxylates **1a–p** (1 mmol), arylhydrazines **2a–c** (2 mmol) and sulphuric acid (0.8 equiv.) toluene (5 mL), 110 °C, 12 h. [b] Isolated yield.

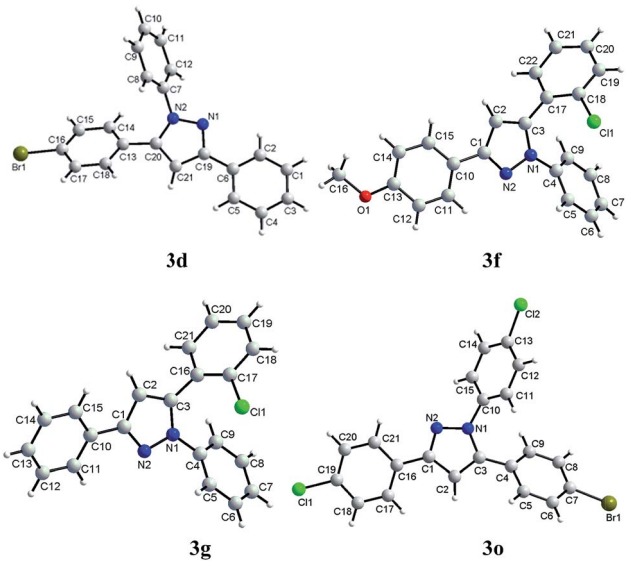
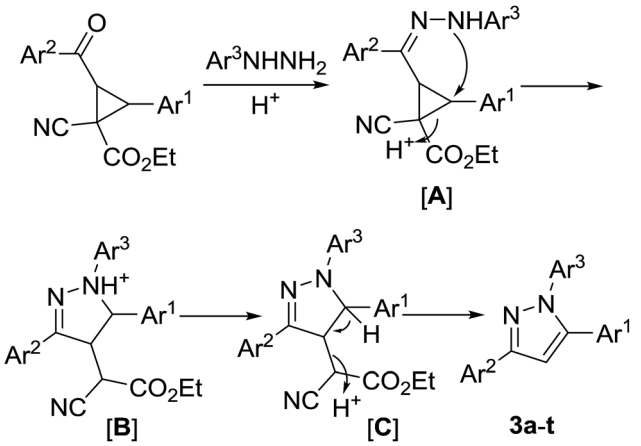


Fig. 2 Molecular structure of 1*H*-pyrazoles **3d**, **3f**, **3g**, **3o**.

The scope of this transformation was then investigated under the standard conditions using different 1-cyanocyclopropane-1-carboxylates, and substituted arylhydrazines. The results are summarized in Table 2. The reaction tolerated different substituents on the aromatic ring of the 1-cyanocyclopropane-1-carboxylates and arylhydrazines such as methyl, methoxy, chloro, iodo, and bromo at *ortho*-, *meta*- or *para*-positions of phenyl groups. Generally, substrates with *para*-position phenyl groups gave the products in higher yields than those with *ortho*-, or *meta*-position phenyl groups. The electronic properties of the substituents on the benzene ring of 1-cyanocyclopropane-1-carboxylates had a slight effect on the reaction. The introduction of an electron-withdrawing group such as Cl, Br or I speeded up the reaction and increased the yield of product, thus facilitating the synthesis of diversely substituted 1*H*-pyrazoles. Substrates with aryl and aroyl groups bearing electron-donating groups such as methyl, and methoxy afforded the corresponding pyrazoles in moderate yields (Table



Scheme 2 Tentative reaction mechanism.

2, entries 3, 5, 6, 9, 14, and 20). It is worth noting that substrates with aryl group bearing multi-substituents may also be applied (entries 10 and 12, Table 2). All corresponding substituted 1*H*-pyrazoles were analyzed by their ^{1}H NMR, ^{13}C NMR and MS. Characteristic ^{1}H chemical shift of 1*H*-pyrazoles C(4)–H at δ *ca.* 6.75(s), unequivocally indicated the exclusive chemical environment of 1*H*-pyrazole C(4) proton. Products 1*H*-pyrazoles **3d**, **3f**, **3g** and **3o** were further characterized by single X-ray crystallography (Fig. 2).[15]

On the basis of the above experimental results together with related reports, the reaction mechanism shown in Scheme 2 was proposed. In terms of pyrazole formations, the condensation of 1-cyanocyclopropane-1-carboxylates with arylhydrazine gave firstly the intermediate arylhydrazone [**A**], then donor–acceptor cyclopropane was attacked intramolecularly by α nitrogen of arylhydrazone, the following ring-opening reaction afforded dihydropyrazole salt [**B**].[5] Next, the deprotonation of the dihydropyrazole salt [**B**] afforded dihydropyrazole [**C**]. Subsequent the elimination of ethyl cyanoacetate and aromatization furnished the pyrazole products **3a–t**.

Conclusions

In conclusion, we have developed an efficiently Brönsted acid-promoted annulation reaction of 1-cyanocyclopropane-1-carboxylates with arylhydrazines to afford 1,3,5-trisubstituted pyrazoles in moderate to good yields (72–87%). This reaction involved the sequential condensation, intra-molecular addition/ring-opening reaction of 2-aroyl-3-aryl-1-cyanocyclopropanecarboxylates with arylhydrazines to give the corresponding pyrazoles. The development of this strategy offers a complementary approach to substituted pyrazole compounds with advantages that include a variety of cheap and readily available reactants and a wide range of substrates with dense or flexible substitution patterns.

Acknowledgements

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15 Crystallographic data for 1*H*-pyrazoles **3a**, **3d**, **3f**, **3g**, **3o** have been deposited with the Cambridge Crystallographic Data Centre with the deposition number CCDC 1427486, 1433734, 1465079, 1457746 and 1473251.

