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Graphical Abstract

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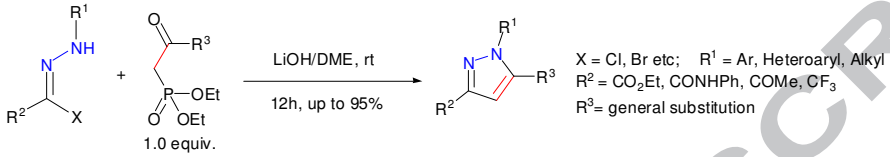

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A new efficient synthesis of pyrazoles from hydrazonoyl halides and β-oxophosphonates

Aixue Sun [a], Jia-Hai Ye [a,*], Haitao Yu [b], Wenchao Zhang [a], Xiaolong Wang [b,*]

[a] School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China
[b] College of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, 210046, China

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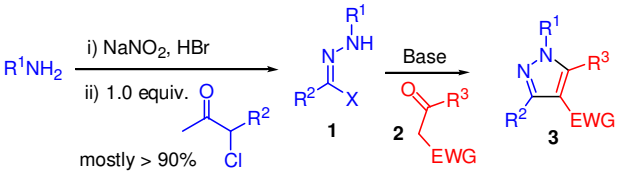
ABSTRACT

A new practical and efficient synthesis of 1,3,5-trisubstituted pyrazoles has been developed by reacting of hydrazonoyl halides with β-oxophophonates under mild conditions in good yields with excellent regioselectivity. This process employs an addition-elimination sequence. Wide scope, functional group compatibility has been established.

Pyrazoles are often found as key elements in structures of biologically active substances among both marketed pharmaceuticals and experimental medicines.[1] The anti-inflammatory drug Celecoxib, an inhibitor of cyclooxygenase-2, is perhaps the best known example. Condensation between a mono-substituted hydrazine and a 1,3-dicarbonyl compound is commonly used in the synthesis of N-substituted pyrazoles.[2a-c] Alternatively, alkylation of N-H pyrazoles, electrophilic cyclization and 1,3-dipolar cycloaddition of diazo compounds to alkenes or alkynes can also be utilized.[2,3] In addition, The Huisgen 1,3-dipolar cycloaddition between alkynes and nitrile imines, which were generated by base treatment from hydrazonoyl halides, offers another convenient alternative.[3] Even though nitrile imines are sufficiently reactive and their cycloaddition with olefins is regioselective,[4,5] only alkynes bearing electron-withdrawing groups participate in reactions with nitrile imines in good yield. Furthermore, elevated temperature is usually required and, again, isomeric products are produced.[3,5] While the previous methods exhibit broad scope and good reliability, lack of regioselectivity is often observed as a main issue. Substrate-specific reaction conditions have to be developed to achieve selectivity.[6] Chromatography often has to be employed to separate isomers during pharmaceutical research and development. As hydrazines are strong nucelophiles, electron-deficient functional groups, such as ketone and reactive halides, can not be introduced to the pyrazole products directly. Hydrazines are mutagenic and carcinogenic, which restricts their broader utilization in drug manufacture. Very recently, Ma et al. reported silver-mediated cycloaddition to give the di-substituted 3-trifluoromethylpyrazoles but not the trisubstituted products.[7] For these reasons, developing new regioselective and environment-friendly trisubstituted pyrazole synthesis would be highly appealing.



R^1 = Aryl; R^2 = CO_2Et, Ar; X = Cl, Br

Scheme 1. From anilines to pyrazoles

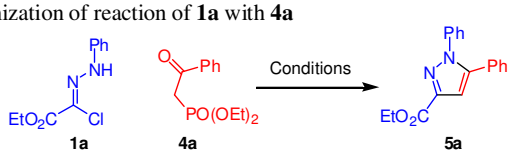
The N-arylhydrazonoyl chlorides **1** (R^1 = Ar, R^2 = carbonyl groups) employed in pyrazole synthesis were readily prepared from aryl diazonium salts and 2-chloro-1,3-dicarbonyl compounds under aqueous conditions (Scheme 1).[8] N-aryl hydrazonoyl chlorides were often isolated by simple filtration in high yield. Incidentally, since N-aryl hydrazines required for

* Corresponding author. Tel.: +86-25-84303116; fax: +86-25-8431- 5857; e-mail: yejiahai@njust.edu.cn (J.-H. Ye)

pyrazole synthesis are prepared by reduction of aryl diazonium salts, the hydrazonoyl chloride pathway, albeit of different 'connectivity', represents a more direct incorporation of the "ArN_2" fragment into the pyrazole ring than conventional hydrazine routes.

Reactions between hydrazonoyl halides and ketones **2** bearing an electron-withdrawing group at alpha position have been reported in the literature to give tetra-substituted pyrazoles (Scheme 1).[9] However, the reaction has to be performed under anhydrous conditions. The yield and product scope of the reaction were also limited, since an electron-withdrawing group has to be present at 4-position in pyrazoles **5**. Here we report our new pyrazole synthesis to address these limitations.

Table 1
Optimization of reaction of **1a** with **4a**

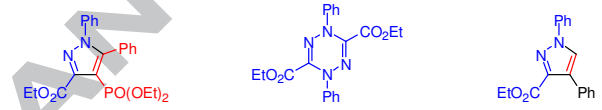


1a **4a** **5a**

Entry	Reaction conditions	Conv. (%)	**5a** Yield (%)[a]
1	Toluene, 2 eq. Et_3N, 100 ℃, 4h	100	0
2	MeCN, 2 eq. Et_3N, r.t., 4h	100	0
3	MeCN/H_2O (1:1, v:v), 2 eq. Et_3N, r.t., 4h	100	0
4	MeCN/H_2O (1:1, v:v), 2 eq. KOAc, r.t., 4h	100	0
5	MeCN/H_2O (1:1, v:v), 2 eq. NaOAc, r.t., 4h	100	0
6	EtOH, 2 eq. NaOEt, r.t., 4h	100	40
7	EtOH /H_2O (1:1, v:v), 2 eq. NaOH, r.t., 10h	100	56
8	MeCN/H_2O (1:1, v:v), 2 eq. NaOH, r.t., 10h	100	92
9	MeCN/H_2O (1:1, v:v), 2 eq. LiOH, r.t., 10h	100	93
10	**DME, 2 eq. LiOH, r.t., 10h**	**100**	**95**

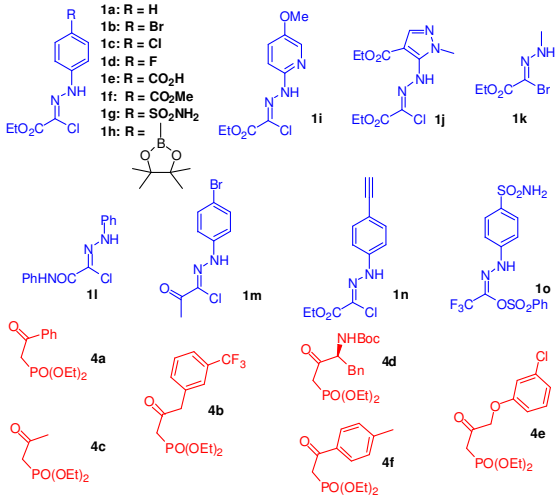
[a] Isolated Yield.

Although many pyrazoles **3** were prepared through different methods in the literature such as the reaction of hydrazonoyl halides **1** with alkynes,[3] to the best of our knowledge, the reaction between β-oxophosphonates **4** and hydrazonoyl halides **1** to give 4-phosphonated pyrazole **3** has never been reported. For the initial attempt, the reaction of commercially available hydrazonoyl chloride **1a** with β-oxophosphonate **4a** was performed using the standard conditions for the formation of **3** in literature (Table 1).[9] The heterocyclization to give the target product pyrazol **5a** did not occur but only the dimerization product **7a** (Scheme 2) was observed (Table 1, entry 1). Similarly, pyrazol **5a** was not obtained when dry acetonitrile was used as solvent (Table 1, entry 2). The challenge for us was to find a suitable reaction system (base/solvent/temperature) to fine-tune for reactivity and selectivity (of the desired pathway). It was known that water has been shown to accelerate substitution reactions of acyl halides in similar Schotten-Baumann reactions. With this in mind, water was introduced into this reaction as co-solvent. This reaction was then carried out in MeCN/H_2O solution in the presence of different bases respectively (Table 1, entries 3-9). The reaction yield increased under this aqueous condition greatly. Furthermore, The use of the lithium base in ether solvent was considered previously in Horner-Wadsworth-Emmons reactions.[10] The improved reactivity/selectivity is probably attributed to the chelating effect of Li cation by the two oxygen atoms in DME (1,2-dimethoxyethane) to form an intermediate five-membered ring.[11] A combination of solvent, base, and reaction temperature was screened to probe the best conditions. It was found that two equivalents of LiOH in dry DME appeared to be the optimal combination. This condition drives the reaction to completion at room temperature for most of the substrates bearing electron-withdrawing groups. LiOH is only partially soluble in DME, so as the reaction proceeds, all LiOH eventually goes into the solution when the reaction reaches completion. The LiOH/DME combination appears to work as a slow release for LiOH,[12] thus avoiding the inconvenience of adding base in small portions. The risk of hydrolyzing of the starting material (hydrazonoyl halides) is greatly mitigated at the beginning of the reaction, when two equivalents of base, required by the reaction, were added all at once. We were very excited to find out that the product **5a** was obtained in the highest yield (95%) when 2 equiv. lithium hydroxide was used as base in dry DME solution (Table 1, entry 10). More interesting, in all cases, as we expected, the side products, such as phosphonated pyrazole **6a** and regioisomer **8a** (scheme 2), were never observed from the reaction mixture.[3d,e,13]



6a **7a** **8a**

Scheme 2 Side products



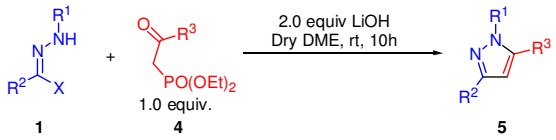
Scheme 3. The structures of Hydraozoyl halides **1** and β-Oxophosphonates **4**

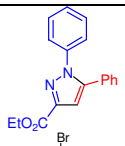
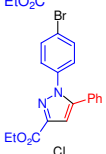
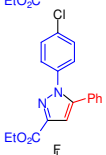
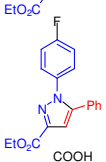
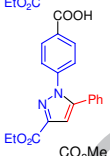
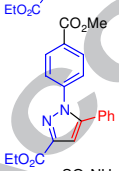
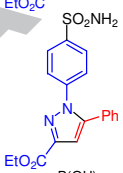
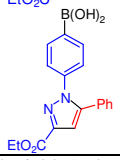
With optimized reactions in hand, we then set out to explore the scope of the substrates. The scope of a wide range of hydrazonoyl halides **1** and β-oxophosphonates **4** were investigated and they have shown good reactivity in the new pyrazole formation reactions (Scheme 3, Table 2). Pyrazoles **5b-h**, bearing different electronic-deficient substituenst in the aryl unit of hydrazonoyl halides, can be prepared all in high yield. An acid functionality in **5e** can be used directly without protection. Boronic acid **5h** can also be incorporated into the product. We were very excited to demonstrate that heterocyclic pyrazoles **5i**

and **5j** can be prepared through the hetero-aromatic amine-diazonium-hydrzonoyl chloride pathway. To the best of our knowledge, hydrazonoyl chlorides **1i**, **1j** and pyrazole products **5i**, **5j** are the first examples of their type. In pyrazole **5m**, N-methyl pyrazole was prepared through corresponding N-methyl hydrazonoyl bromide **1k**, demonstrating the possibility of preparing N-alkyl pyrazoles using this regioselective methodology. Different electron-withdrawing groups: ester, amide, ketone, CF_3, can be introduced at the 3-position. An alkyne functionality can also be incorporated as present in **5p**. Celecoxib **5q** was also prepared in moderate yield when the hydrazonoyl halide analogue **1o** was used as one of the starting materials.

Table 2

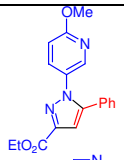
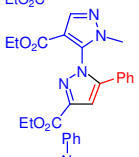
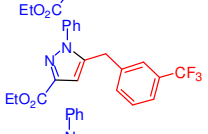
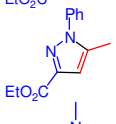
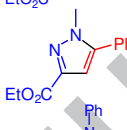
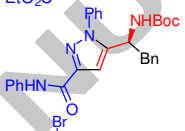
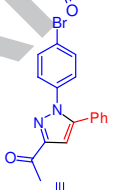
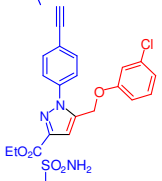
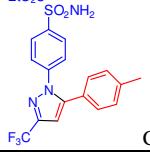
Synthesis of pyrazoles **5** from **1** and **4**



Entry	Pyrazoles **5**	Yield (%)[a]
1		**5a** (95)
2		**5b** (95)
3		**5c** (87)
4		**5d** (85)
5		**5e** (82)
6		**5f** (87)
7		**5g** (83)
8		**5h** (70)

[a] Isolated Yield. (to be continued)

(continued)

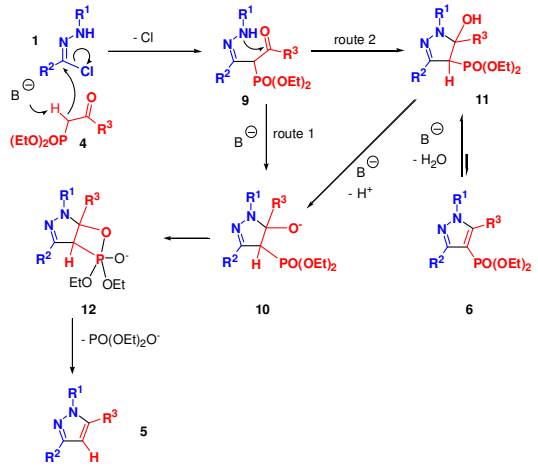
Entry	Pyrazoles **5**	Yield (%)[a]
9		**5i** (92)
10		**5j**(85)
11		**5k**(83)
12		**5l** (95)
13		**5m** (80)
14		**5n** (88)
15		**5o** (82)
16		**5p**(94)
17	 Celecoxib	**5q**(55)

[a] Isolated Yield.

The mechanism of the reaction is proposed as shown in scheme **4**. We proposed that the reaction follows a stepwise process in contrast to the cycloaddition pathway proposed for the formation of **3** (Scheme 1),[9e] where eletron-withdrawing group (EWG) is not phosphonate. The phosphonate **4** is deprotonated by the first equivalent of base. The resulting anion then replaces halide in **1** to form the intermediate **9**. The secondary hydrazine nitrogen in intermediate **9** most likely turns to be intermediate **10** after the using of the second equivalent of base (Scheme 4, route 1), followed by reaction pathway similar to Wittig reaction through the intermediate **12**, which can also be produced from **11** in the presence of base, to give the target product **5**. In contrast, the side product **6** can be formed from the known reaction mechanism through the intermediate **11**. Because LiOH is a weak inorganic base, it can not abstract the proton on the carbon center near phosphonate unit efficiently. The subsequent result is that he side product **6** was not obtained (Scheme 4, route 2).[3d]

In conclusion, we have developed an efficient and practical synthetic method of 1,3,5-trisubstituted pyrazoles utilizing easily

prepared hydrazonoyl halides or their analogue and β-oxophosphonates with wide scope and functional group compatibility. This new reaction pathway was carried out smoothly at room temperature in good yields with excellent regioselectivity which should provide better access to pyrazole molecules for the pharmaceutical industry and general synthetic interest. The plausible reaction mechanism was also proposed.



Scheme 4. Plausible reaction mechanism

Acknowledgments

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Supplementary data

Supplementary material associated with this article can be found, in the online version, at doi:

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Highlights

1. 1,3,5-trisubstituted pyrazoles were synthesized efficiently with excellent regioselectivity.
2. Reaction was carried out at mild condition: room temperature.
3. Reaction was tolerated for many substrates with a wide scope of functional groups.
4. Reaction was carried out in good yield: the yields of most products were higher than 80%.
5. A plausible reaction mechanism was proposed.