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Efficient one-pot synthesis of substituted pyrazoles

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ABSTRACT

An efficient, one-pot synthesis of substituted pyrazoles from enones, hydrazides, and halides was developed. In comparison with the classical Knorr pyrazole synthesis, this methodology gave a different type of product ($R^3 \geq R^5$). A range of substituted pyrazoles were prepared in good to high yields with complete regioselectivity.

1. Introduction

Pyrazoles and their derivatives represent an important class of compounds that are used extensively in the pharmaceutical and agrochemical industries.[1] Compounds containing the pyrazole moiety have a wide range of biological activities, such as the HIV-1 reverse transcriptase inhibitor PNU-32945,[2] cyclooxygenase-2 (COX-2) inhibitor Celecoxib,[3] herbicide Fluazolate,[1b] and fungicide Pyraclostrobin[4] (Fig. 1).

One of the most important methods for constructing pyrazole rings[5,6] is the classical Knorr pyrazole synthesis.[7] The Knorr synthesis suffers from a regioselectivity issue,[8] which arise for pyrazoles with $R^3 \neq R^5$. When considering the sizes of the substituents, Knorr synthesis products typically have R^5 larger than R^3 (Scheme 1a), such as in PNU-32945 and Celecoxib. To prepare a product with R^3 larger than R^5, such as Fluazolate and Pyraclostrobin, this method is usually unsuitable. Therefore, a general and convenient method for synthesis of pyrazoles with $R^3 > R^5$ is required.

2. Results and discussion

In the course of our study on the synthesis of substituted allenes from enones,[9] we found that when using inorganic Brønsted bases, the reaction led to a different product, which was 1*H*-pyrazoles **A** and/or **B** (Scheme 2). This kind of transformation has been reported several times,[10] however, to the best of our knowledge, this method has not been widely used in pyrazole synthesis. It is well known that under basic conditions, tautomerism between 1*H*-pyrazoles **A** and **B** occurs easily. Therefore, we investigated sequential synthesis of 1-position substituted pyrazoles by combining several elementary steps. Here, we report a three-step, one-pot synthesis of 1-position substituted pyrazole derivatives from readily available and simple starting materials, such as enones, *p*-toluenesulfonyl hydrazide ($TsNHNH_2$) and halides (R^1–X) (Scheme 1b).

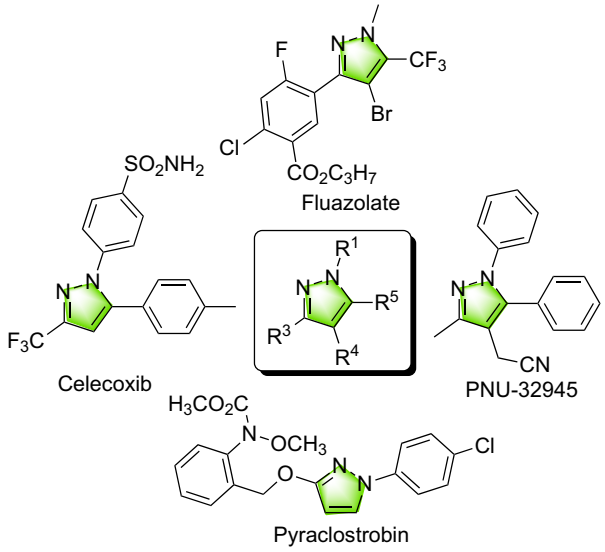

Fig. 1. Representative pyrazole derivatives.

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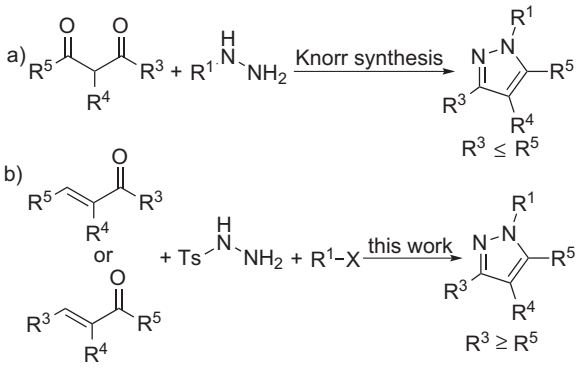
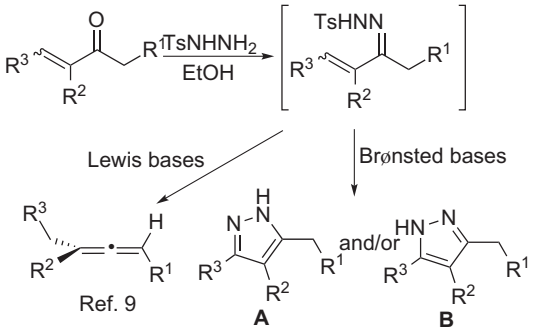


Scheme 1. Regioselectivity in the construction of pyrazole rings.

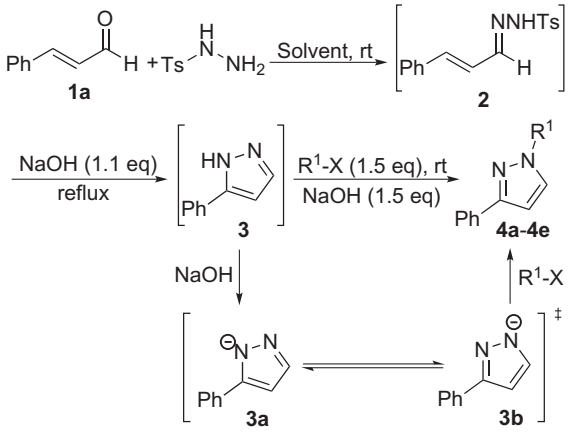


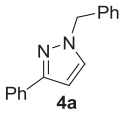
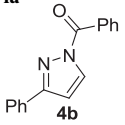
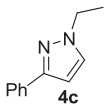
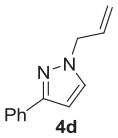
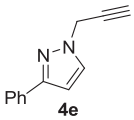
Scheme 2. α,β-Unsaturated tosylhydrazones as versatile synthetic intermediates lead to allenes or pyrazoles.

Encouraged by previous results,[9] our study was performed with cinnamaldehyde (**1a**) as a model substrate and NaOH as the base in EtOH (Table 1). First, trapping of the intermediate 5-phenyl-1*H*-pyrazole (**3**)[11] with benzyl bromide was attempted. The progress of pyrazole **3** formation was monitored by TLC, and when complete, NaOH and benzyl bromide were added. Under basic conditions, deprotonation of the NH moiety and rapid tautomerism resulted in **3a** and/or **3b**. Then **4a** was obtained by a nucleophilic substitution reaction of **3b** with benzyl bromide. The structure of **4a** was unambiguously established by NMR and single-crystal X-ray analysis (Fig. 2). However, the reaction of pyrazole **3** with benzyl bromide was quite slow, and the yield was only 44% after two days (entry 1, Table 1). Of the solvents screened, acetonitrile gave an excellent yield within 2 h (91%, entry 2, Table 1). We then investigated the scope of R^1–X, and found benzoyl chloride, iodoethane, allyl bromide, and propargyl bromide all gave the corresponding pyrazole derivatives (**4b**–**e**) in good to high yields (entries 3–6, Table 1). The reaction showed consistent, complete regioselectivity, with only single isomers obtained in all reactions. This regioselectivity could be a result of repulsion between the phenyl substituent and R^1.

Syntheses of a variety of pyrazoles were attempted to investigate the scope of the method. As shown in Table 2, different di-, tri- and tetrasubstituted pyrazole derivatives were obtained in good yields. However, the substituent R^5 apparently affected the formation of tosylhydrazone. Compared with benzalacetone (**1e**) as the substrate, tosylhydrazone production was very slow in acetonitrile with chalcone (**1d**) and **1f** as substrates (entries 9–13, 16, 17, Table 2). EtOH was used in the initial stage of the reaction, and after the pyrazole formed, it was removed under reduced pressure and acetonitrile was used to complete the procedure. When **1e** was used as the substrate, the bulk of R^1 apparently affected the regioselectivity of the reaction, benzyl bromide and benzoyl chloride could trap the intermediate 1*H*-pyrazole with complete

Table 1
One-pot synthesis of 1,3-disubstituted pyrazoles and the scope of the halides



Entry	Solvent	R^1–X	Product	Yield[a] (%)
1	EtOH		 **4a**	44[b]
2	CH_3CN		**4a**	91
3	CH_3CN		 **4b**	89
4	CH_3CN		 **4c**	87
5	CH_3CN		 **4d**	86
6	CH_3CN		 **4e**	71

[a] The yields are for the isolated product.
[b] 5-Phenyl-1*H*-pyrazole **3** was isolated in 51% yield.

regioselectivity, and only one product (**4s** or **4t**) was isolated, (entries 14, 15, Table 2) however, iodoethane gave a disappointing result, and the ratio of **4v**:**4w**[12] was 2.2:1 (Scheme 3). Moreover, substrates **1e** and **1f** led to the same product **4s** or **4t** when trapped with benzyl bromide or benzoyl chloride (entries 14–17, Table 2).

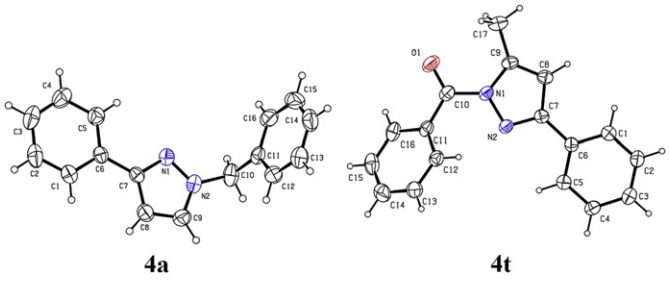


Fig. 2. X-ray structure of **4a** and **4t**.