An effective and general method for the highly regioselective synthesis of 1-phenylpyrazoles from β-enaminoketoesters, tandem Blaise–acylation adducts†

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An effective and general route for the regioselective synthesis of 1-phenylpyrazoles has been developed from β-enaminoketoesters prepared by tandem Blaise–acylation. This method is applicable to a very broad range of substrates, generating a diverse set of 3-aryl-5-alkyl, 3-alkyl-5-aryl, 3,5-diaryl, and 3,5-dialkyl substituted pyrazoles regioselectively. The dichotomous regioselective synthesis of isotopically discriminated 3-CD_3-5-CH_3 and 3-CH_3-5-CD_3 substituted pyrazoles showcases the power of this protocol.

Introduction

Pyrazole is embedded as a prominent sub-structure in numerous bioactive compounds exhibiting various activities[1] such as anti-inflammatory,[1a–c] analgesic,[1d] anti-bacterial,[1e] and anti-cancer.[1f,g] Moreover, recent blockbuster drugs verify pyrazole's importance as a pharmacophore.[2] Accordingly, the pharmaceutical industry has a longstanding interest in its synthesis. Starting with the classical Knorr condensation[3] of 1,3-dicarbonyl compounds with hydrazine, where regiocontrol becomes poor with monosubstituted hydrazines, various native synthetic methods have been developed with the aim of enhancing regioselectivity in the synthesis of 1,3,5-tri and 1,3,4,5-tetrasubstituted pyrazoles.[4] Michael-type additions of monosubstituted hydrazines to alkynyl or olefinic ketones followed by intramolecular condensation[5] and regiospecific 1,3-dipolar cycloaddition of the hydrazones with nitroolefin[6] provides better control of the regioselectivity than that of the original Knorr procedure. The cross-coupling of 5-bromopyrazole derivatives with various nucleophiles[7] or the sequential Suzuki coupling of pyrazole boronate derivatives generated by lithiation using a metal directing group[8] also provide an alternative choice for enhanced regioselectivity. However, most of these methods have limited substrate-scope because either the synthetic method lacks precursors or is incompatible with reaction conditions. Particularly, regioselective synthesis of 1-aryl-3, 5-dialkyl pyrazoles having similar alkyl groups could not be accomplished using the aforementioned methods as shown in a recent report on the synthesis of *N*-arylation of 3,5-dialkyl pyrazoles.[9] In this case, simple arylation of 3,5-dialkyl pyrazoles with 4-fluoronitrobenzene resulted in poor regioselectivity, a problem that was solved by the introduction of a chelating hydroxyalkyl group at the 3-position. However, this method required extra steps such as protection, deprotection, and removal of the chelating hydroxy group. Thus, the development of a general route for regiocontrolled synthesis of pyrazoles with broad substrate-scope is quite desirable.

Our own interest in the regioselective synthesis of pyrazoles stems from our recent finding on an efficient and general synthetic route to β-enaminoketoesters **1**, which could be used as efficient surrogates of ynones and 1,3-dicarbonyl compounds in pyrazole synthesis. Although not fully recognized by synthetic chemists, an earlier work by Veronese *et al.* indicated that reactions of monosubstituted hydrazines with a β-enaminoketoester **1** (R^1 = Bn, R^2 = CH_3) afforded the corresponding pyrazoles **2** in a regioselective manner.[10] Unfortunately, this protocol has not been extended further due to the limited availability of the β-enaminoketoesters **1**, which are prepared from Knoevenagel condensation of β-ketoesters, commonly prepared by Blaise reaction with nitrile by using a stoichiometric amount of toxic tin(IV) chloride. In a similar work, Nielsen and Persson reported recently that monosubstituted hydrazine reacted with *N*-methoxy-*N*-methyl-β-enaminoketoesters, prepared by the reaction of ethyl-propynoate with Weinreb amides, to afford the 3-carboxylated pyrazoles regioselectively.[11] During our ongoing study of the Blaise reaction,[12] we developed a new general route for the synthesis of β-enaminoketoesters **1** removing this limitation completely. Quite recently we reported that the Blaise reaction intermediate, zinc bromide complexes of β-enaminoesters, could be activated *in situ* by the addition of a stoichiometric or catalytic amount of *n*-BuLi to allow chemoselective C2-acylation, which provides various β-enaminoketoesters **1**.[13] Although limited β-enaminoketoesters have been studied for the construction of the pyrazole ring moiety,[10,13] the full potential of β-enaminoketoesters **1** for the regioselective synthesis of pyrazoles **2** remained to be verified. In this work, we attempted to extend our tandem Blaise–acylation protocol to the regioselective synthesis of a variety 1-phenylpyrazoles **2**,

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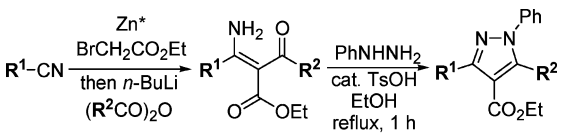
where R^1 and R^2 are aryl/alkyl, alkyl/aryl, aryl/aryl, alkyl/alkyl groups including isotopically discriminated 3-CD_3-5-CH_3 and 3-CH_3-5-CD_3 substituted pyrazoles. A mechanism for the regioselective formation of pyrazole **2** has also been proposed.

Results and discussion

In our previous study, the β-phenyl-β-enaminoketoester **1a** was synthesized in 82% yield, which reacted with phenyl hydrazine in the presence of a catalytic amount of *p*-toluenesulfonic acid to afford the corresponding 1,3-diphenyl-5-methyl pyrazole **2a** regioselectively in 91% yield (entry 1, Table 1).[13] To determine whether the opposite regioselectivity could be obtained with the β-enaminoketoesters **1b** in 81% yield with tandem Blaise–benzoylation, the nitrile and anhydride partners were switched to acetonitrile and benzoic anhydride (entry 2, Table 1). In contrast to **1a** forming a single isomer, an inseparable E/Z mixture of **1b** was formed in 1:1 ratio. Reaction of the E/Z mixture of **1b** with phenyl hydrazine provided 1,5-diphenyl-3-methyl-pyrazole **2b** in 88% yield. There was no sign of the formation of its regioisomer **2a**. In the ^{1}H NMR spectra, the methyl proton resonance peak for **2a** (δ = 2.59 ppm, s, 3H) appeared slightly up-field compared with that for **2b** (δ = 2.60 ppm, s, 3H) indicating that the methyl group in **2a** is located in the shielding region of the *N*-phenyl group. Later, their structures were determined unambiguously by X-ray crystallographic analysis (Fig. 1). In the same manner, dichotomous regioselectivity was obtained in the reaction of phenyl hydrazine with β-enaminoketoesters **1c** (entry 3, Table 1) and **1d** (entry 4, Table 1), having a sterically bulky *sec*-butyl alkyl group. **1c** and **1d** were prepared in high yields by Blaise–acylation of benzonitrile/isovaleric anhydride and isovaleronitrile/benzoic anhydride partners. Reactions of **1c** and **1d** with phenyl hydrazine afforded the corresponding 1,3-diphenyl-5-*sec*-butyl pyrazole **2c** (87%) and 1,5-diphenyl-3-*sec*-butyl pyrazole **2d** (85%) without any sign of the formation of other regioisomers. As in **2a**, the methyl group of **2c** (δ = 0.78 ppm, d, J = 6.7 Hz, 6H) was observed in the shielding region of the *N*-phenyl group, and 0.25 ppm up-field shifted compared with that in **2d** (δ = 1.03 ppm, d, J = 6.7 Hz, 6H). We next investigated the regioselective synthesis of a set of 3,5-diaryl substituted pyrazoles **2e** and **2f** with sterically similar but electronically different phenyl and 4-trifluoromethylphenyl substituents to obtain information on the effects of substituent electronic properties on regioselectivity. The tandem Blaise–benzoylations of benzonitrile with 4-trifluoromethylbenzoic anhydride provided **1e** in 84% yield with a 1.2:1 ratio of E and Z isomers (entry 5, Table 1). Switching the Blaise–acylation partners to 4-trifluoromethylbenzonitrile and benzoic anhydride afforded **1f** in 89% with E and Z in a 2:1 ratio (entry 6, Table 1). Reactions of the E/Z mixtures of β-enaminoketoesters **1e** and **1f** with phenyl hydrazine showed perfect regioselectivity providing the corresponding 1,3,5-triaryl substituted pyrazoles **2e** and **2f** in respective yields of 83% and 88%. The structures of **2e** and **2f** were determined unambiguously by X-ray analysis (Fig. 1). Finally, this β-enaminoketoester-based approach was applied to the regioselective synthesis of unsymmetrical 3,5-dialkyl substituted pyrazoles **2g** (entry 7, Table 1) and **2h** (entry 8, Table 1), having sterically and electronically less discernible methyl and ethyl groups at the 3- and 5-positions. The tandem Blaise–acylation with acetonitrile/propionic anhydride and propionitrile/acetic anhydride partners provided the corresponding β-enaminoketoesters **1g** and **1h** in respective yields of 82% and 86%. Careful ^{1}H NMR analysis indicated that an E/Z (1:1) mixture of **1h** was formed, whereas **1g** was formed as a single isomer. To our delight, reactions of **1g** and **1h** with phenyl hydrazine afforded the corresponding pyrazoles **2g** (91%) and **2h** (90%) regioselectively in extremely high yield. ^{1}H NMR analysis indicated that as observed in **2c** and **2d**, the methyl protons (δ = 1.17 ppm, t, J = 7.4 Hz, 3H) in the ethyl group of **2g** were 0.14 ppm up-field shifted compared to those of **2h** (δ = 1.31 ppm, t, J = 7.5 Hz, 3H).

Based on these results, it would be reasonable to assume that the Michael-type addition of the unsubstituted nitrogen of phenyl hydrazine occurred at the *β*-carbon bearing an electronegative free amine group followed by intramolecular condensation. To elucidate the proposed reaction mechanism, we attempted to isolate the reaction intermediate, the conjugated addition adduct, without any success. However, the reaction of benzylamine with **1a** provided Michael addition product **3** in 64% yield, thus indirectly supporting the Michael addition–condensation mechanism (path a) (Scheme 1). The other possible pathway

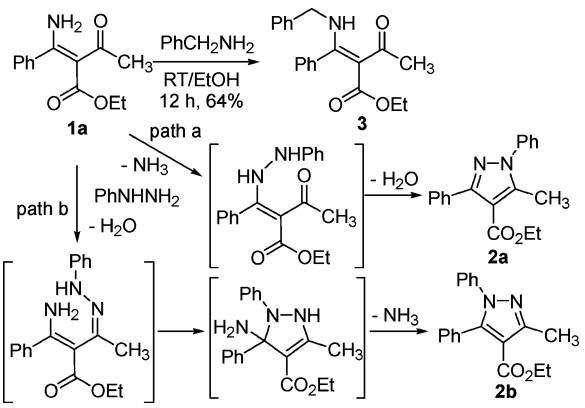
Table 1 Tandem Blaise–acylation and regioselective synthesis of 1-phenylpyrazoles **2a–2h**



1 **2**

Entry	R^1	R^2	**1** (yield, %)[a]	**2** (yield, %)[a]
1	Ph	CH_3	**1a** (82)[b]	**2a** (91)[b]
2	CH_3	Ph	**1b** (81)[c]	**2b** (88)
3	Ph	*sec*-Bu	**1c** (94)[b]	**2c** (87)
4	*sec*-Bu	Ph	**1d** (90)[c]	**2d** (85)
5	Ph	4-$CF_3C_6H_4$	**1e** (84)[d]	**2e** (83)
6	4-$CF_4C_6H_4$	Ph	**1f** (89)[e]	**2f** (88)
7	CH_3	CH_3CH_2	**1g** (82)	**2g** (91)
8	CH_3CH_2	CH_3	**1h** (86)[c]	**2h** (90)

[a] Yield after silica column chromatography. [b] Data from reference 13. [c] Mixture of E/Z = *ca.* 1:1 determined by ^{1}H NMR. [d] Mixture of E/Z = *ca.* 1.2:1 determined by ^{1}H NMR. [e] Mixture of E/Z = *ca.* 2:1 determined by ^{1}H NMR.



Scheme 1 Aminolysis of **1a** and proposed pathway for regioselective pyrazole ring formation.

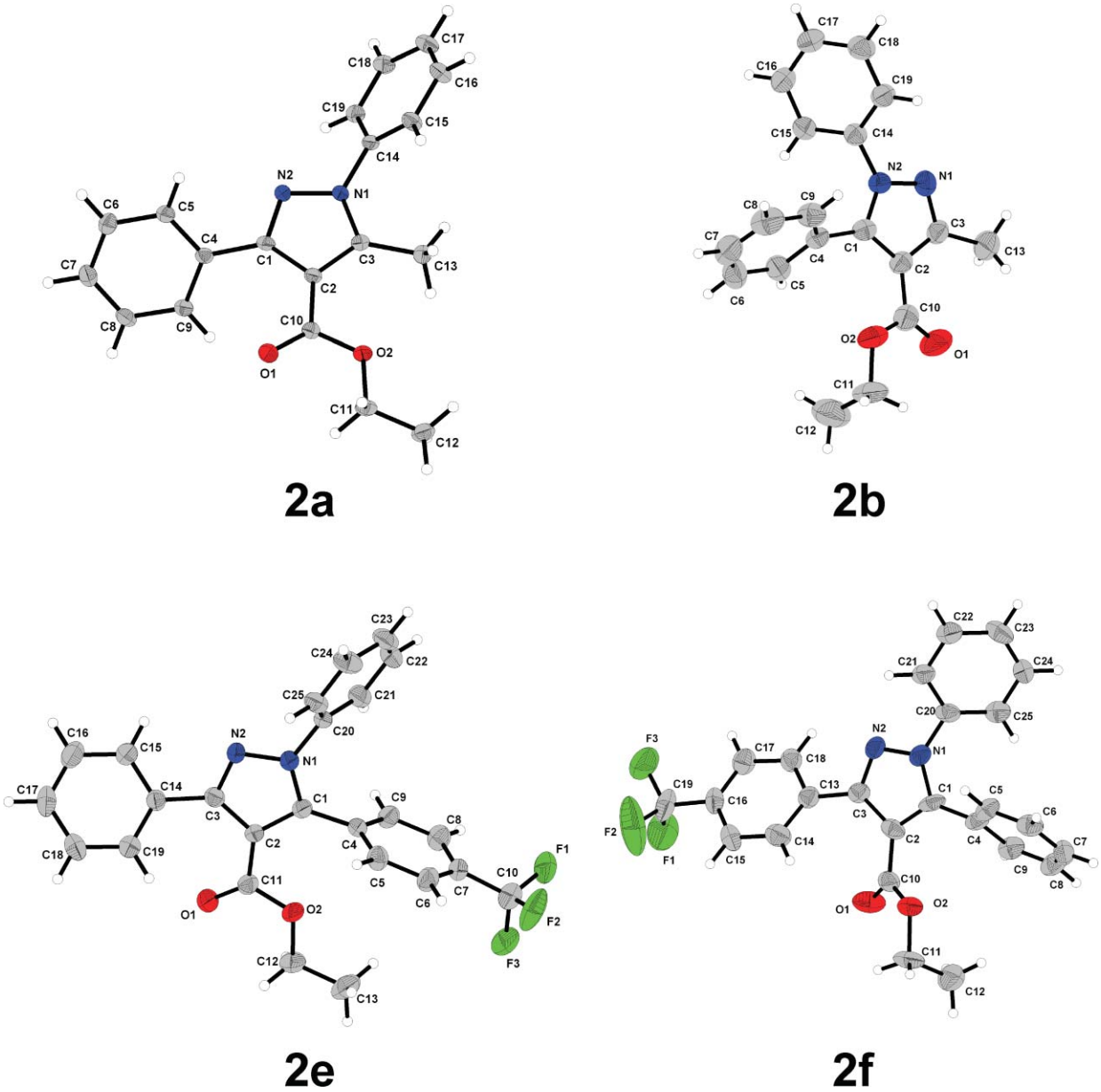
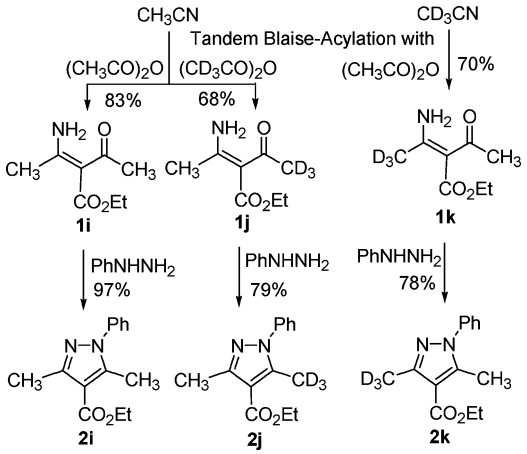


Fig. 1 X-ray structures of 1-phenylpyrazoles **2a**, **2e**, **2e**, and **2f**.‡

(path b), *i.e.* imine formation between the carbonyl group and hydrazine followed by ring-closure *via* a 5-endo-trig cyclization, would appear to be unfavorable since only one regioisomer was formed.

The highlight of our methodology is the regioselective synthesis of isotopically labelled pyrazoles **2j** and **2k**, which could only be accomplished through the discrimination of sterically and electronically indiscernible CH_3 and CD_3 groups (Scheme 2). To determine whether the two methyl groups can be differentiated in ^{1}H NMR, the 3,5-dimethyl pyrazole **2i** was synthesized first in 80% overall yield. We found that the two methyl protons resonated with slightly different chemical shifts ($\delta = 2.50$ and 2.52 ppm) (Fig. 2). For the synthesis of isotopically labelled β-enaminoketoesters **1j** and **1k**, a set of the tandem Blaise–acylations was carried out with deuterated acetonitrile (CD_3CN)/acetic anhydride and acetonitrile/deuterated $(CD_3CO)_2O$ combinations. Compared with the Blaise–acylation of acetonitrile with acetic anhydride for **1i** (83%), acylation with deuterated acetic anhydride $(CD_3CO)_2O$ providing **1j** decreased the yield to 68%. The yield was more dramatically decreased in the Blaise–acylation of CD_3CN with acetic anhydride, providing 20% of **1k** in 3 h, which could be ascribed to the secondary kinetic isotope effect. Fortunately, the yield was increased to 70% as the reaction time was prolonged to 12 h. Reactions of **1i**, **1j** and **1k** with phenyl hydrazine afforded the corresponding 3,5-dimethylated pyrazoles **2i** (97%), **2j** (79%), and **2k** (78%). We observed only one singlet resonance peak for methyl in the ^{1}H NMR spectrum of **2j**, at $\delta = 2.50$ ppm (s, 3H). In contrast, the methyl proton peak for **2k** was observed at $\delta = 2.52$ ppm

‡ CCDC numbers: **2a**:708928; **2b**:708929; **2e**:708930; **2f**:708931.†



Scheme 2 Regioselective synthesis of isotopically discriminated 3,5-dimethyl-1-phenylpyrazoles **2i**, **2j**, and **2k**.

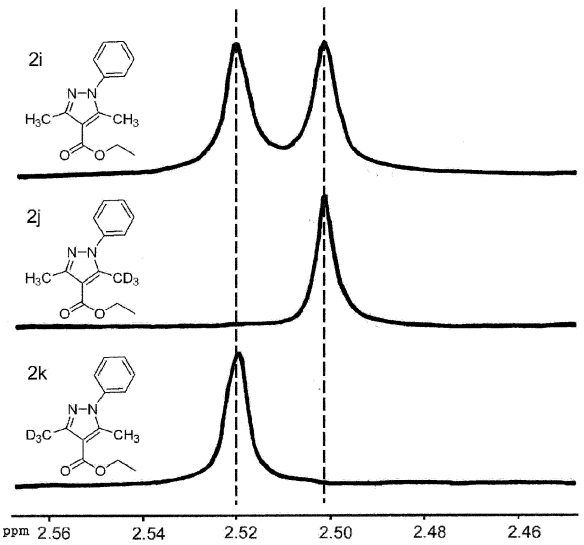


Fig. 2 ^{1}H NMR spectra of the CH_3 region in **2i**, **2j**, and **2k**.

(s, 3H), indicating that the isotopically labelled pyrazoles **2j** and **2k** were formed in high regioselectivity (Fig. 2). These results clearly demonstrated that the β-enaminoketoesters **1**, which can easily be prepared by the chemoselective tandem Blaise–acylation with broad substrate-scope, are the highly useful reagent of choice for the regioselective synthesis of pyrzoles **2**.

Conclusion

We developed an effective route for the synthesis of pyrazoles regioselectively from tandem Blaise–acylation adducts, β-enaminoketoesters. This method is very broad in substrate scope, generating a diverse set of 3,5-aryl/alkyl, 3,5-alkyl/aryl, 3,5-diaryl, and 3,5-dialkyl substituted pyrazoles regioselectively. Moreover, the indiscernible CH_3 and CD_3 groups could be discriminated using our method leading to 3-CD_3-5-CH_3 and 3-CH_3-5-CD_3 substituted pyrazoles in a completely regiocontrolled manner. Isolation of the aminolysis adduct **3** suggested that the reaction of phenyl hydrazine with the β-enaminoketoesters proceeds regioselectively *via* Michael-type addition followed by dehydrative cyclization. The readily available diverse starting materials for the tandem Blaise–acylation combined with the highly regioselective synthesis of pyrazoles provide high potential for diversity-oriented synthesis.

Experimental

General procedure for the synthesis of pyrazoles 2

To a solution of β-enaminoketoesters **1** (0.5 mmol) in absolute ethanol (1 mL) was added phenyl hydrazine (2.5 mmol) and *p*-toluenesulfonic acid (5 mg, 5 mol%) followed by stirring at room temperature for 1 h. The reaction mixture was refluxed for 1 h, and cooled to room temperature. After evaporation of solvent, the residue was dissolved in ethyl acetate, and the organic layer was washed subsequently with saturated aqueous $NaHCO_3$, 1 N HCl, and brine, and then dried with anhydrous $MgSO_4$. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel to afford the product **2** with the yield in Table 1.

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