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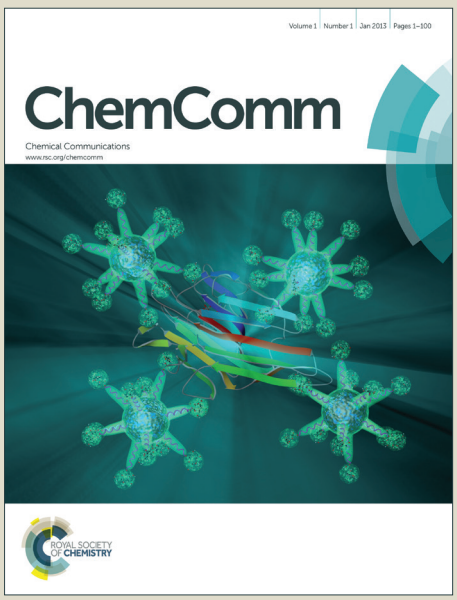

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Direct Synthesis of Pyrazoles from Esters using *tert*-Butoxide-Assisted C-(C=O) Coupling

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Bo Ram Kim,[a] Gi Hyeon Sung,[a] Ki Eun Ryu,[a] Sang-Gyeong Lee,[a] Hyo Jae Yoon,*[b] Dong-Soo Shin,[c] and Yong-Jin Yoon*[a]

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This paper describes the direct synthesis of pyrazoles from esters that comprises two sequential reactions: *tert*-butoxide-assisted C-C(=O) coupling reaction to yield *β*-ketonitrile or *α,β*-alkynone intermediates, and condensation by hydrazine addition. The method reported allows for easy control of the regioselectivity and structure of substituents at N-1, C-3, C-4 and/or C-5 positions.

Pyrazole—1,2-azole that is a five-membered heterocycle comprising adjacent two nitrogens and three carbons—is a key structural motif for pharmaceutical and pesticide compounds.[1] Pyrazole derivatives have been extensively studied in past few decades as important heterocycles and still receive great attention for biological properties[2] such as antitumor,[3] CNS disorders,[4] antimicrobial,[5] anti-inflammatory[6] and antiviral activities.[7] Pyrazole moiety is a core structure in a large variety of leading drugs and pesticides: for example, Celebrex,[8] Viagra,[9] Zometapine,[10] Cyenopyrafen,[11] Fenpyroximate,[12] and Tebufenpyrad.[13] The condensation of hydrazine with 1,3-dicarbonyl compounds,[14] *β*-ketonitriles,[15] ynones[16] or aminoalkenylnitriles[17] is commonly used to synthesize pyrazole derivatives. These methods, however, have drawbacks such as low reactivity and poor regioselectivity of C-3, C-4, C-5 positions of pyrazole, limited scope for starting compounds, use of expensive/toxic reagents, harsh reaction conditions, and/or multistep reactions with low yields.

Herein, we report a convenient and efficient protocol for *direct* conversion of esters to regioselectively substituted pyrazoles (Fig. 1). The central idea for the method reported is based on a facile, room-temperature C-C(=O) coupling reaction facilitated by *tert*-butoxide to form *β*–ketonitrile or *α,β*–alkynone intermediates. Several sets of experiments with a wide range of esters, nitriles, alkynes and hydrazines under various reaction conditions showed that the method allows one to prepare highly substituted pyrazoles in an economical way—*i.e.*, without using expensive catalysts—and under mild conditions in fairly good yields (24–86 % of overall yields).

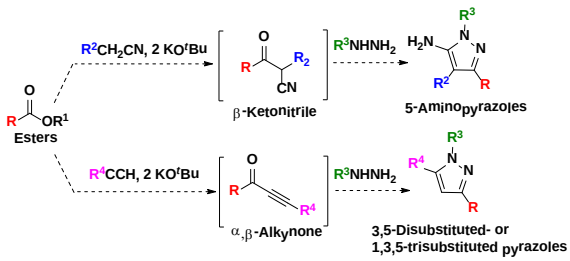


Fig. 1 Newly designed synthetic strategies for synthesis of substituted pyrazoles.

To develop a method for the synthesis of pyrazoles from esters, we utilized *tert*-butoxide-assisted C-(C=O) coupling reaction. Previously, we developed synthetic methodologies that use *tert*-butoxide for synthesis of amides, *β*-ketonitriles, *α,β*-alkynones, and biscarbinols from esters.[18] These methodologies were particularly attractive in that reactions proceed under ambient conditions in the presence of *tert*-butoxide that is easily accessible and cheap, rather than transition metal catalysts that are often prepared through tedious, multi-step reactions. The proposed mechanism of the reactions involves the radical cleavage of C-O bond in ester resulting from the reaction of ester with *tert*-butoxide in technical grade of THF in air at room temperature. Typically, two equivalents of *tert*-butoxide, relative to an ester, is used for the reaction: two equivalents of *tert*-butoxide is needed, presumably, to form superoxide anion radical and then acyl radical species, which are important intermediates for the C-(C=O) coupling reaction.[18] In this study we develop a novel strategy to transform directly esters to pyrazoles in conjunction with condensation of ketone by hydrazine (Fig. 1).

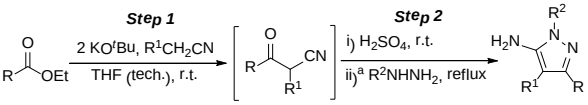
For preparing *β*-ketonitrile and *α,β*-alkynone from esters we used the literature conditions: technical grade (containing *ca*. 0.2% H_2O) of THF under ambient conditions.[18a] To optimize the

second step conditions—those for the reaction of β-ketonitrile or α,β-alkynone with hydrazine—we performed the cyclization of β-ketonitrile in different conditions (Table S1 in the ESI). We changed i) a type of hydrazine ($NH_2NH_2{\cdot}X$; X=H_2O or H_2SO_4), ii) equivalent of hydrazine (1.5 – 3.0 equiv), and iii) solvent (THF, EtOH, toluene or a mixture of THF and H_2O). When solvent was different between the first and the second reactions, the suitable solvent for the second step was used after evaporating the first-reaction solvent (THF). We monitored a reaction designed for synthesis of 5-amino-3-phenyl-1*H*-pyrazole from ethyl benzoate *via* β-ketonitrile; and found that the reaction of β-ketonitrile with hydrazine hydrate either in THF, EtOH or toluene did not proceed at all (Table S1). It was attributed to the basicity of the reaction mixture: the use of acidic hydrazine sulfate, gave the desired product in 65% overall and isolated yield (Table S1, entry 4). Once we increased the equivalent of hydrazine sulfate from 1.5 to 3.0 equiv (Table S1, entry 4-6), no significant change was observed in reaction yield. To increase the solubility of hydrazine sulfate, we tested a mixture of THF and H_2O (THF:H_2O=1:6, v/v); unfortunately, this reaction resulted in decrease in the yield (34%) (Table S1, entry 7).

The significant difference in the reaction yield between hydrazine hydrate and hydrazine sulfate implies that the basicity of the first-reaction mixture influences the second reaction (*e.g.*, the solubility of hydrazine salt, and/or enolization of β-ketonitrile). We thereby hypothesized that a better yield for the second reaction may be achieved by neutralizing the first-step prior to the addition of hydrazine sulfate. To find a suitable acid for neutralization of the first-step mixture, four protic acids (H_2SO_4, HCl, HNO_3 and H_3PO_4) of different equivalents were evaluated; Table S2 in the ESI summarizes the results. Among ten entries, the reaction with one equivalent of sulfuric acid gave the best result (Table S2, entry 1): 78% yield was achieved with one equivalent of H_2SO_4 in 0.6 h. Hydrochloric acid (Table S2, entries 5 and 6) and nitric acid (Table S2, entries 7 and 8) gave the same yield but required a longer reaction time or more equivalents than sulfuric acid. When phosphoric acid as weak acid was used, the yields were low (~60%; Table S2, entries 9 and 10). These observations allowed us to determine the final optimum conditions for the synthesis of pyrazole *via* β-ketonitrile: step 1) i) ester (1 equiv) / cyanomethylene (1 equiv) / KO^{t}Bu (2 equiv) / tech. THF / room temperature, ii) H_2SO_4 (1 equiv); step 2) $NH_2NH_2{\cdot}H_2O$ (1.5 equiv) / reflux.

We next examined the substrate scope of esters, cyanomethylenes and hydrazines. The reaction of aryl and aliphatic esters with cyanomethylenes and then with hydrated or free hydrazines under the optimum conditions gave the corresponding 5-amino-4-alkyl-3-aryl (or alkyl) pyrazoles in 37-80% (Table 1). Interestingly, this reaction offered the ability to control the substituents at N-1, C-3 and/or C-4 and to introduce primary amino group (-NH_2) on C-5 position of pyrazole. It is noteworthy that this is a one-pot synthesis without purification of the intermediate, β-ketonitrile. We observed the lowest yield (37%; entry 9 in Table 1) for *p*-nitrophenyl-substituted hydrazine; it is attributed to the decreased nucleophilicity of hydrazine for the cyclization in the step 2.

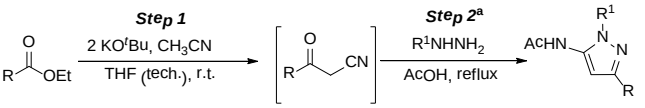
Table 1. Substrate scope for synthesis of 5-aminopyrazoles with cyanomethylenes



entry	R	R^1	R^2	time step 1 (min)	time step 2 (h)	5-amino-pyrazole yield(%)[b]
1	*p*-Cl-C_6H_5	H	H	35	0.7	77
2	*p*-Cl-C_6H_5	CH_3CH_2	H	35	1.2	53
3	C_6H_5	$C_6H_5CH_2$	H	30	1.3	61
4	C_6H_5	CH_3CH_2	H	30	0.8	55
5	$(CH_3)_2CH$	H	H	35	0.6	80
6	C_6H_5	H	H	35	0.6	78
7	C_6H_5	H	C_6H_5	35	24	58
8	C_6H_5	H	*p*-$MeOC_6H_5$	35	9	56
9	C_6H_5	H	*p*-$NO_2C_6H_5$	35	68	37
10	C_6H_5	H	CH_3	35	48	42

[a]Entries 1-6 used $R^2NHNH_2{\cdot}H_2O$; entries 7-9 used free R^2NHNH_2; entry 10 used $R^2NHNH_2{\cdot}HCl$.
[b]Isolated yield; and overall yield for the two sequential reactions in one-pot synthesis.

Table 2. Synthesis of 5-acetamidopyrazoles



entry	R	R^1	time step1 (min)	time step 2 (h)	5-acetami-dopyrazole yield (%)[a]
1	C_6H_5	H	30	15	53
2	$(CH_3)_2CH$	H	35	16	47
3	*p*-Cl-C_6H_5	H	35	18	86
4	C_6H_5	C_6H_5	35	68	82

[a]Entries 1-3 used $R^2NHNH_2{\cdot}H_2O$; entry 4 used free R^2NHNH_2.
[b]Isolated yield; and overall yield for the two sequence reactions in one-pot synthesis.

We further demonstrated the synthesis of 5-acetamido-3-substituted-pyrazoles from aryl and aliphatic esters using excess amount of AcOH (Table 2). After forming β-ketonitrile by the reaction of ester with acetonitrile in the presence of KO^{t}Bu, the resulting β-ketonitrile was reacted with hydrated or free hydrazines in acetic acid. The corresponding 5-acetamido-3-alkyl (or aryl)pyrazoles were obtained in 47-86% yields in one-pot synthesis (Table 2). In this reaction, acetic acid serves as: i) acylation reagent for the amino group, ii) acid for neutralization after the first step reaction, and iii) solvent for the second step reaction. The method described in Table 2 is useful for one-pot synthesis of 5-acetamidopyrazoles from esters *via* β-ketonitriles.

The FT-IR, NMR and HR-MS established the structure of the prepared pyrazole compounds. The IR spectrum of 5-aminopyrazoles exhibited the absorption bands at 3434 - 3148

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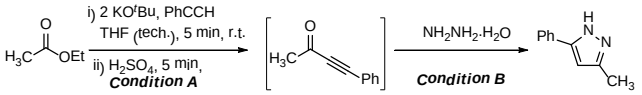
cm^{-1} (multi-peaks were observed due to tautomerism of 5-aminopyrazoles)[19] corresponding to -NH_2 and -NH functional groups. For 5-acetamidopyrazole the IR absorption bands of -NH (3248 - 3100 cm^{-1}) and C=O (1663 - 1617 cm^{-1}) were detected, indicative of the presence of amide carbonyl group. The NMR and HR-MS spectra were also consistent with the proposed structures (see the ESI for detailed analytical data).

Table 3. Optimization of reaction conditions for synthesis of 3-methyl-5-phenyl-1*H*-pyrazole

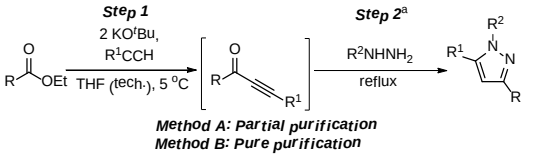


entry	equiv of H_2SO_4	condition		product yield(%)[a]
		A	B	
1	-	r.t.	r.t., 10 min	-[b]
2	1	r.t.	r.t., 10 min	11
3	1	5 °C	5 °C, 360 min	31
4	1	5 °C	25 °C, 60 min	24
5	1	5 °C	reflux, 10 min	18
6	-	H_2O/EtOAc[c]	25 °C, 720 min	54
7	-	H_2O/EtOAc[c]	reflux, 5 min	58

[a]Isolated yield; and overall yield for two sequential reactions. [b]Decomposition of *α,β*-alkynone intermediate (4-phenylbut-3-yn-2-one) was observed on TLC monitoring. [c]Partial purification method: when the first reaction was finished, it was quenched by adding water (10 mL), and then stirred for 1 min under 5 °C. The reaction mixture was further extracted with cold EtOAc (10 mL × 2), and organic layer was separated. Hydrazine hydrate was then added to the organic layer for the second reaction (see the ESI for details).

We also investigated the synthesis of pyrazoles from esters *via* *α,β*-alkynones. To search optimal conditions for the reaction (in particular for the neutralization-step and the second-step involving *α,β*-alkynones and hydrazine), ethyl acetate was reacted with phenylacetylene in the presence of KO^{t}Bu in technical THF under ambient conditions, and then with hydrazine hydrate under various conditions. Table 3 summarizes the results. The desired product, 3-methyl-5-phenyl-1*H*-pyrazole was not obtained without neutralization process (Table 3, entry 1); it was due to the decomposition of 4-phenylbut-3-yn-2-one (confirmed by TLC monitoring). Alternatively, the first-reaction mixture was neutralized by one equivalent of sulfuric acid, and then reacted with hydrazine hydrate (Table 3, entry 2); the product begun to form but the yield was low (11%). We changed the temperature in neutralization process (Condition A in Table 3), or the reaction time and/or temperature (Condition B in Table 3) for the cyclization by addition of hydrazine (Table 3, entries 3 - 5); however the yields were still low (18 - 31%). We assumed that the low reaction yields result from the low stability of *α,β*-alkynone intermediates that are decomposed by the addition of sulfuric acid. Thus, we performed the cyclization of *α,β*-alkynones without neutralization process and after partial purification—water was added to quench the first reaction at the point where *α,β*-alkynone intermediate forms maximally, and the resulting mixture was extracted with organic solvent (see the ESI for detailed procedures). The intention for the partial purification was to neutralize the reaction mixture without using strong acid. Indeed, the addition of hydrazine hydrate to the first-reaction mixture, which was partially purified by adding H_2O at 5°C following extraction with ethyl acetate, at room temperature gave 3-methyl-5-phenyl-1*H*-pyrazole in an increased yield (54%; Table 3, entry 6). Increasing reaction temperature for refluxing in the reaction gave a similar yield (58%; Table 3, entry 7) but reaction time was much shorter (5 min) than that (720 min) for the reaction at room temperature. Based on the preliminary experiments, we were able to determine the final optimum conditions for the synthesis of pyrazole *via* *α,β*-alkynone intermediate: step 1) i) ester (1 equiv) / alkyne (1 equiv) / KO^{t}Bu (2 equiv) / tech. THF / ambient temperature (17 - 19 °C), and ii) extraction of reaction mixture with H_2O and EtOAc; step 2) $NH_2NH_2{\cdot}H_2O$ (1.5 equiv) / reflux.

Table 4. Substrate scope for synthesis of 3,5-disubstitued- or 1,3,5-trisubstituted pyrazoles from esters



entry	R	R^1	R^2	Conditions			
				Method A[b]		Method B[c]	
				time (min)[c]	pyrazole yield (%)[e]	time (min)[d]	pyrazole yield (%)[e]
1	CH_3	C_6H_9[f]	H	3/80	31	3/10	72
2	$(CH_3)_2CH$	C_6H_5	H	5/60	51	5/10	59
3	$(CH_3)_2CH$	$CH_3(CH_2)_5$-C_6H_4	H	5/60	27	5/10	44
4	$C_6H_5(CH_2)_2$	C_6H_5	H	5/20	38	5/10	56
5	*c*-C_6H_{11}[g]	C_6H_5	H	5/60	28	5/5	50
6	$CH_3(CH_2)_6$	C_6H_5	H	5/30	28	5/5	47
7	3-(C_5H_4N)-CH_2CH_2	C_6H_5	H	5/25	11	5/5	8
8	CH_3	C_6H_5	C_6H_5	3/240	46	2/120	24

[a]Entries 1-7 used $R^2NHNH_2{\cdot}H_2O$; entry 8 used free R^2NHNH_2.
[b]Method A (partial purification): when the first reaction was finished, H_2O (10 mL) was added to the reaction mixture and then stirred at 1 min under 5 °C followed by extraction with cold EtOAc (10 mL × 2), organic layer was separated. Hydrazine (1.5 equiv.) was then added and refluxed. [c]Method B (pure purification): Pure *α,β*-alkynones were used for the second reaction. [d]Time: the step 1/the step 2. [e]Isolated yield; and overall yield for the two sequence reaction. [f]Cyclohex-1-en-1-yl. [g]*c*-C_6H_{11}: Cyclohexyl.

We examined the substrate scope under the optimal conditions. 3,5-Disubstituted- or 1,3,5-trisubstituted pyrazoles were obtained from various esters, alkynes and hydrazines in 27-51% overall yields (Table 4, Method A, except entry 7). We did not test aryl esters; the previous work demonstrated that the reaction of aryl esters with *tert*-butoxide affords over-addition

product, biscarbinols, and not α,β-alkynone.[18a] We further investigated whether yields of the cyclization of α,β-alkynones could be improved upon complete isolation of α,β-alkynone intermediates. Eight pyrazoles were obtained from aliphatic esters by Method B (using pure α,β-alkynones) in 24-72% overall yields. In most of reactions, the yields by the Method B were higher than those by the Method A except for the use of ethyl 3-(pyridin-3-yl)propanoate as a starting compound (Table 4, entry 7), and for the use of free hydrazine (Table 4, entry 8). The high yields by the Method B are accounted for by the low stability of α,β-alkynone intermediates in the basic and ambient conditions. We observed the lowest yield (8%) for ethyl 3-(pyridin-3-yl)propanoate (Table 4, entry 7 by Method B); it was due to the decomposition of the corresponding α,β-alkynone intermediate (confirmed by TLC monitoring).

Conclusions

In conclusion, this study demonstrates the synthesis of pyrazoles starting from esters, using *tert*-butoxide-assisted C-(C=O) coupling and hydrazine cyclization *via* β-ketonitriles or α,β-alkynones. The synthetic method reported here offers an opportunity to prepare conveniently and efficiently regioselectively functionalized pyrazoles in two sequential reactions; many of pyrazoles are prepared in one-pot synthesis (and/or under mild conditions). 5-Aminopyrazoles (ten examples), 5-acetoamidopyrazoles (four examples), and 3,5-disubstituted- or 1,3,5-trisubstituted pyrazoles (nine examples) are synthesized from esters *via* β-ketonitrile or α,β-alkynone intermediates in moderate to good yields.

The synthetic method reported has three useful features: i) it allows one to control readily the regioselectivity and structure of substituents—particularly those at N-1, C-3, C-4 and/or C-5 positions; ii) it avoids use of transition metal catalysts that are often expensive, and/or difficult to access; and iii) it starts from esters—a wide variety of ester derivatives are commercially available, or easily accessible by straightforward synthetic pathways. The reported method would be applicable in synthetic, medicinal and industrial chemistry.

Notes and references

[a]Department of Chemistry & Research Institute of Natural Science, Gyeongsang National University, Jinju 660-701, Korea
E-mail: yjyoon@gnu.ac.kr
[b]Department of Chemistry, Korea University, Seoul 136-701, Korea
E-mail: hyoon@korea.ac.kr
[c]Department of Chemistry, Changwon National University, Changwon, 660-773, Korea

† Electronic Supplementary Information (ESI) available: experimental procedures and analytical data. See DOI: 10.1039/c000000x/

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