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A Base-Promoted Tandem Cycloaddition/Air Oxidation Reaction of Electron-Deficient Conjugated Enynes and Hydrazines: Synthesis of Highly Substituted Pyrazoles

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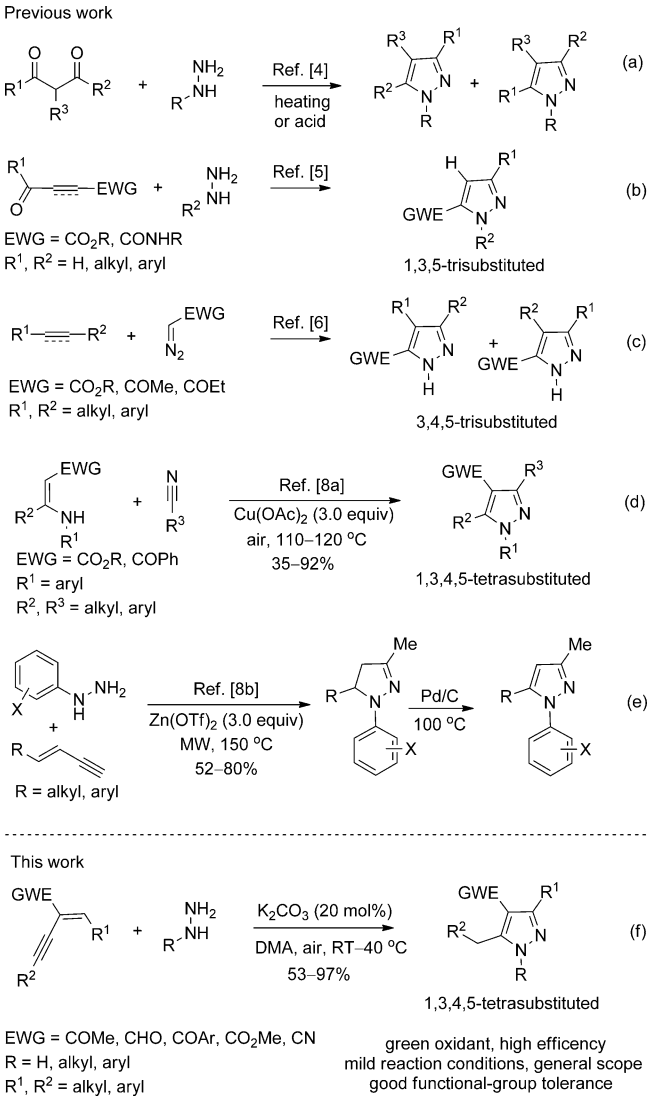
Pyrazoles are important motifs in bioactive molecules used in the pharmaceutical and agrochemical industries.[1] Moreover, pyrazoles are used in supramolecular and polymer chemistry, in the food industry, and as cosmetic colorings and UV stabilizers.[2] Substituted pyrazoles have also been used as ligands for transition metal catalyzed reactions.[3] Typical methods for the synthesis of pyrazoles include approaches based either on the condensation of hydrazines with 1,3-dicarbonyl compounds[4] and α,β-unsaturated aldehydes and ketones[5] (Scheme 1a and b) or on the intermolecular 1,3-dipolar cycloaddition of diazoalkanes and nitrile imines with alkenes and alkynes (Scheme 1c)[6] The drawbacks of these protocols, such as poor reactivity and regioselectivity, and the potential hazards associated with detonation of the substrates, limit their practical application to some extent. Although over the years, diverse methodologies have been developed,[7,8] access to a regioselective and broadly applicable method for the synthesis of pyrazoles remains challenging. In 2010, Glorius and co-workers[8a] reported a novel method for the preparation of highly substituted pyrazoles; the method involved oxidative C–C/N–N bond formation using amines, ketones, and nitriles as substrates, although a high reaction temperature and an excess of oxidant ($Cu(OAc)_2$, 3.0 equiv) were required (Scheme 1d). Patil and Singh[8b] developed a novel Lewis-acid-mediated microwave-based hydroamination reaction of terminal enynes and aryl hydrazines that gives, for example, 3-methyl-4,5-dihydro-pyrazole, which upon Pd/C-catalyzed dehydrogenative aromatization gives 3-methyl-pyrazole (Scheme 1e). However, the need for a high reaction temperature and an excess of Lewis acid (3.0 equiv), as well as the poor functional-group compatibility may limit the use of this reaction in organic synthesis. Consequently, the development of novel, generally applicable, and very efficient methods for the synthesis of highly substituted pyrazoles under mild reaction conditions is still highly desirable. Herein, we report a facile route to highly substituted functionalized pyr-



Scheme 1. Previous work and this work for the synthesis of highly substituted pyrazoles. DMA = *N*,*N*-dimethylacetamide.

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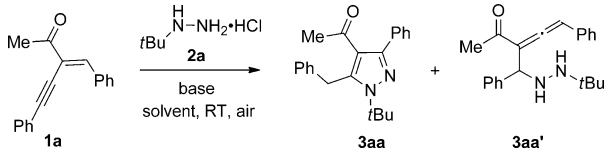
azoles through an unprecedented cycloaddition/oxidation reaction of hydrazines and electron-deficient 1,3-conjugated enynes (Scheme 1 f).

Recent studies from our research group and that of Hu have shown that electron-deficient 1,3-conjugated enynes are good Michael acceptors and can undergo tandem addition reactions with nucleophiles, thus leading to various acyclic and cyclic compounds.[9] However, previous studies have shown that the carbonyl group of α,β-unsaturated aldehydes and ketones will react with hydrazines through condensation followed by cyclization to afford pyrazoles (Scheme 1 b). However, as expected, we found that highly substituted pyrazoles that bear functional groups could be efficiently prepared from the corresponding electron-deficient 1,3-enynes and hydrazines by tandem inter- and intramolecular nucleophilic addition and air oxidation. It is notable that ketone and aldehyde carbonyl groups in the substrate do not undergo a condensation reaction with hydrazines under the reaction conditions (Scheme 1 f).

To test the feasibility of our proposed tandem reaction, we conducted a reaction using easily accessible 1,3-enyne **1a**[9,10] as a substrate, together with *tert*-butylhydrazine hydrochloride (**2a**) and Et_3N (1.7 equiv) in DMF at room temperature under air atmosphere. To our delight, following a reaction time of 7 hours, the desired 1-(5-benzyl-1-*tert*-butyl-3-phenyl-1*H*-pyrazol-4-yl)ethanone (**3aa**) was isolated in 90% yield as a single isomer (entry 1, Table 1). This result shows that the ketone moiety remains intact following transformation of the substrate, a result that is different from that of previous work (the hydrazine first reacts with the ketone moiety), and that air is sufficient to oxidize the intermediate. These results encouraged us to optimize the other reaction parameters. Various solvents such as THF, DCE, CH_2Cl_2, DMSO, and CH_3CN were tested; the results showed that the use of polar solvents benefits the reaction and when the reaction was conducted in DMA, the product could be isolated in up to 96% yield (Table 1, entries 2–10). Notably, with shorter reaction times, allene product **3aa′** was obtained when using some less polar solvents. Subsequently, a series of organic and inorganic bases such as TMEDA, DABCO, DBU, DMAP, NaOH, NaOAc, and K_2CO_3 were tested for reactions conducted in DMA. The results show that in many cases, the use of these bases lead to high yields of product, except the use of NaOH and DMAP (Table 1, entries 11–16); the use of K_2CO_3 gave the best results (Table 1, entry 17). Finally, we found that decreasing the amount of the hydrazine and base to 1.2 and 1.4 equivalents, respectively, does not adversely affect the reaction outcome (Table 1, entry 18). The structure of the product was confirmed by X-ray crystallographic analysis of **3aa** (Figure 1, top).[11]

The scope of this reaction was examined by variation of the hydrazine component (**2b–e**; Table 2). Gratifyingly, hydrazine hydrate (**2b**) is a good substrate, the product, pyrazole **3ab**, being isolated in 61% yield (Table 2, entry 1); this product should be amenable to further functionalization through reaction at the NH group. We were surprised that the reaction of tosylhydrazine (**2c**) with **1a** afforded pyrazole **3ab** in 72% yield rather than the expected 1-Ts pyrazole **3ac** (Table 2, entry 2). Phenylhydrazine and methylhydrazine reacted efficiently with **1a** to give the corresponding pyrazoles in 90% and 86% yields with levels of regioselectivity of 10:1 and 4.9:1, respectively (Table 2, entries 3 and 4).

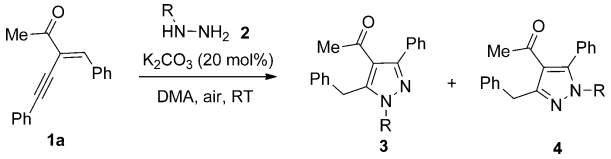
Table 1. Screening of reaction conditions for the reaction of enyne **1a** with hydrazine **2a**.[a]



Entry	Base	Solvent	Time [h]	Yield [%][b] **3aa** **3aa′**
1	Et_3N	DMF	7	90 –
2	Et_3N	THF	20	74 15
3	Et_3N	DCE	20	65 26
4	Et_3N	CH_2Cl_2	20	81 15
5	Et_3N	$CHCl_3$	20	68 31
6	Et_3N	toluene	20	23 54
7	Et_3N	1,4-dioxane	20	50 25
8	Et_3N	DMSO	9	71 –
9	Et_3N	CH_3CN	9	95 –
10	Et_3N	DMA	1.5	96 –
11	TMEDA	DMA	3.5	95 –
12	DABCO	DMA	3.3	96 –
13	DBU	DMA	3.3	87 –
14	DMAP	DMA	24	65 11
15	NaOH	DMA	24	22 39
16	NaOAc	DMA	3.3	93 –
17	K_2CO_3	DMA	1.2	97 –
18[c]	K_2CO_3	DMA	1.5	97 –

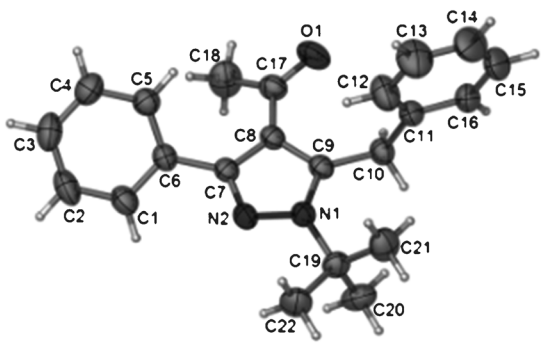
[a] All reactions were carried out using **1a** (0.2 mmol) and **2a** (0.3 mmol) in the presence of base (1.7 equiv) in solvent (2.5 mL), unless otherwise specified. [b] Yield of isolated product. [c] 1.2 equiv hydrazine and 1.4 equiv base were used. DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undecen-7-ene, DCE = dichloroethane, DMAP = 4-dimethyl-aminopyridine, DMF = *N*,*N*-dimethylformamide, TMEDA = *N*,*N*,*N*′,*N*′-tetramethyleth-ane-1,2-diamine.

Table 2. Base-promoted tandem reactions of enyne **1a** with various hydrazines **2**.[a]

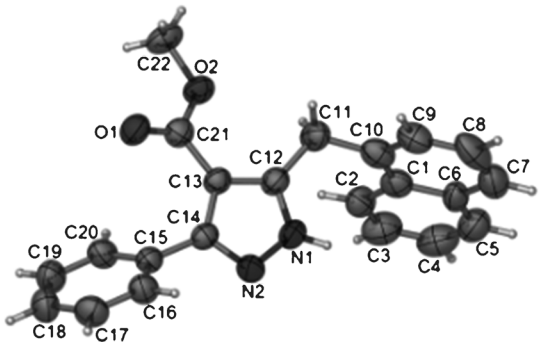


Entry	Hydrazine **2**	Time [h]	Yield [%][b] **3**/**4**
1[c]	$H_2NNH_2{\cdot}H_2O$ **2b**	13	61 **3ab**
2[d]	$TsNHNH_2$ **2c**	30	72 **3ab**
3	$PhNHNH_2$ **2d**	9	90 (**3ad**/**4ad** 10:1)
4[e]	$MeNHNH_2{\cdot}H_2O$ **2e**	3.5	86 (**3ae**/**4ae** 4.9:1)

[a] The reaction was carried out using **1a** (0.2 mmol) and hydrazine **2** (0.24 mmol) in the presence of K_2CO_3 (20 mol%) in DMA (2 mL) unless otherwise specified. [b] Yield of isolated product. [c] 85 wt.% of $NH_2NH_2{\cdot}H_2O$ was used. [d] The product is the same as that obtained from the reaction of **1a** and **2b**. [e] 40 wt.% of $MeNHNH_2{\cdot}H_2O$ was used. Ts = *p*-toluenesulfonyl.



3aa

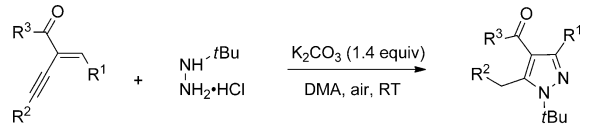


3jb

Figure 1. X-ray crystal structures of **3aa** (top) and **3jb** (bottom).

The scope of the reaction was then explored using various 2-(1-alkynyl)-2-alkene-1-ones **1b–h** in combination with *tert*-butylhydrazine hydrochloride (**2a**) (Table 3). To our delight, the use of every tested substrate gave good to excellent yields of the desired products, although substrates containing either electron-donating R^1 or electron-donating R^2 groups required a longer reaction time (Table 3, entries 1 and 4). The reaction of phenyl ketone **1h** gave the desired product **3ha** in 93% yield as a single isomer under the same reaction conditions (Table 3, entry 7). Notably, cyclic enynyl ketone **1i** gave the corresponding bicyclic pyrazole **3ia** in 75% yield as a single isomer [Eq. (1)].

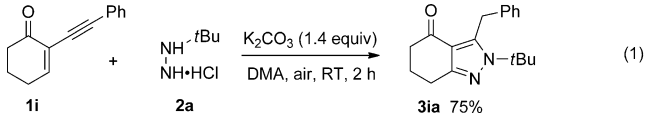
Table 3. Reaction of various enynes **1** with hydrazine **2a**.[a]



1 2a 3

Entry	$R^3/R^1/R^2$ **1**	Time [h]	Yield [%][b] **3**
1	Me/PMP/Ph **1b**	4	85 **3ba**
2	Me/4-NCC_6H_4/Ph **1c**	1	90 **3ca**
3	Me/Ph/1-naphthyl **1d**	1.8	97 **3da**
4	Me/Ph/PMP **1e**	4	88 **3ea**
5	Me/Ph/4-$NO_2C_6H_4$ **1f**	1.2	84 **3fa**
6	Me/Ph/4-FC_6H_4 **1g**	1.5	91 **3ga**
7	Ph/Ph/Ph **1h**	1.5	93 **3ha**

[a] The reaction was carried out using **1** (0.2 mmol) and hydrazine **2a** (0.24 mmol) in the presence of K_2CO_3 (1.4 equiv) in DMA (2 mL) unless otherwise specified. [b] Yield of isolated product. PMP = *para*-methoxyphenyl.

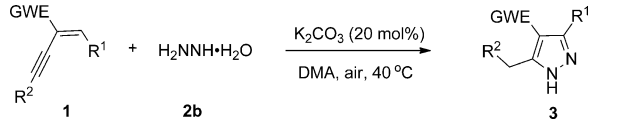


1i 2a 3ia 75% (1)

Considering that 1-nonsubstituted pyrazoles are highly important intermediates in synthesis, we carried out further screening of reaction conditions. Ultimately, we found that product **3ab** could be isolated as a single isomer in an improved 80% yield when the reaction is conducted in CH_3CN at 40 °C (Table 4, entry 1). Encouraged by this promising result, the scope of this reaction was explored further using various electron-deficient enynes. The following points are noteworthy:

(1) Either DMA or CH_3CN can be used as a solvent for the reactions of 2-(1-alkynyl)-2-alkene-1-ones (Table 4, entries 1–4, 7, 18, and 19).
(2) The presence of various electron-withdrawing groups such as ketones, esters, cyano, ketoesters, and aldehydes are well tolerated. We were surprised that the ketone,

Table 4. Reaction of various enynes **1** with hydrazine hydrate **2b**.[a]



1 2b 3

Entry	EWG/R^1/R^2 **1**	Time [h]	Yield of **3** [%][b,c]	
1	COMe/Ph/Ph **1a**	4 (5.5)	65 (80)	**3ab**
2	COMe/4-NCC_6H_4/Ph **1c**	1.8 (4)	61 (78)	**3bb**
3	COMe/styryl/Ph **1j**	3.5 (6)	49 (53)	**3cb**
4	COMe/Ph/4-$NO_2C_6H_4$ **1f**	1.5 (4)	54 (73)	**3db**
5	COMe/Ph/1-cyclohexenyl **1k**	3	76	**3eb**
6	COPh/Ph/Ph **1h**	4	78	**3fb**
7	4-ClC_6H_4CO/Ph/Ph **1l**	3.5 (6)	72 (84)	**3gb**
8	CO_2Me/Ph/Ph **1m**	22	95	**3hb**
9	CO_2Me/Ph/PMP **1n**	10	75	**3ib**
10	CO_2Me/Ph/1-naphthyl **1o**	10	94	**3jb**
11	CO_2Me/Ph/*n*-C_4H_9 **1p**	11.5	55	**3kb**
12	CO_2Me/Ph/cyclopropyl **1q**	11	78	**3lb**
13	CO_2Me/PMP/Ph **1r**	10.5	95	**3mb**
14	CO_2Me/4-FC_6H_4/Ph **1s**	10	93	**3nb**
15[d]	CO_2Me/PMP/PMP **1t**	10	58	**3ob**
16[e]	CO_2Me/PMP/1-naphthyl **1u**	8	97	**3pb**
17	CN/Ph/Ph **1v**	3.5	97	**3qb**
18	$COCO_2$Me/Ph/Ph **1w**	3.5 (4)	47 (61)	**3rb**
19	$COCO_2$Me/Ph/4-MeC_6H_4 **1x**	2 (4)	75 (45)	**3sb**
20	CHO/Ph/Ph **1y**	3.5	58	**3tb**

[a] The reaction was carried out using **1** (0.2 mmol) and **2** (0.24 mmol) in the presence of K_2CO_3 (20 mol%) in DMA (2 mL) unless otherwise specified. [b] Yield of isolated product; [c] Yields in brackets refer to reactions conducted in CH_3CN as the solvent. [d] Ratio of isomers: **3ob**/**4ob** = 1.7:1. [e] Ratio of isomers: **3pb**/**4pb** = 3:1.

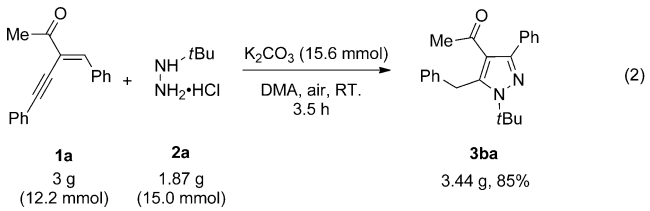
aldehyde, and ketoester groups did not participate in further condensation reactions; these pyrazoles, which contain reactive ketone, aldehyde, and ketoester groups are difficult to prepared using previously established methods.

(3) Compound **1j**, which contains a styryl group (R^1), afforded the desired pyrazole **3cb** in moderate yield; the reaction was regioselective in that no 1,6-addition product was observed (Table 4, entry 3).

(4) In most cases, the reactions give the products as single isomers, with the exception of **3ob** and **3pb**, the reactions of which had poor regioselectivity (Table 4, entries 15 and 16).

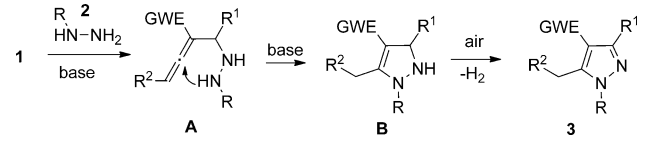
(5) The structure of the *N*-nonsubstituted pyrazoles was confirmed by X-ray crystallographic analysis of **3jb** (Figure 1).[11]

Notably, when the reaction is scaled-up (12.2 mmol), the substrates can be used in less excessive amounts without any reduction in yield [Eq. (2)]. For example, the reaction of *tert*-butylhydrazine hydrochloride (**2a**, 15 mmol) with 2-(1-alkynyl)-2-alkene-1-one (**1a**, 12.2 mmol) exposed to air in DMA was complete within 3.5 hours, thus giving 3.44 grams of **3ba** (85% yield upon isolation). Notably, the bubbling-in of air is not necessary for the reaction done on a smaller scale or on a gram scale.



(2)

One plausible mechanism that accounts for this base-promoted cycloaddition/oxidation reaction is proposed (Scheme 2). Regioselective nucleophilic conjugate addition



Scheme 2. A plausible mechanism for the tandem cycloaddition/oxidation reaction.

of $RNHNH_2$ to the electron-deficient 1,3-conjugated enyne **1**, through attack by the terminal NH_2 group, which is the less sterically hindered nitrogen atom, would generate the 1,2-allene intermediate **A**. Subsequent intramolecular nucleophilic addition would give 2,3-dihydro-1*H*-pyrazole **B**,[12] which can then undergo rapid dehydrogenative aromatization under air to generate the final products **3**.

In summary, we have developed a simple and efficient synthetic strategy for preparing pyrazoles based on an unprecedented tandem cyclization/air oxidation of hydrazines and electron-deficient 1,3-conjugated enynes under mild reaction conditions. The presence of a variety of functional groups, such as ketones, aldehydes, and ketoesters, are tolerated in this transformation; these functional groups often undergo side reactions in many known processes. The reaction is efficient and 'green'. We anticipate that this methodology will find many applications in the fields of synthetic organic chemistry and pharmaceutical science. The generation of libraries of pyrazoles and their biological evaluation is currently being investigated.

Experimental Section

Typical procedure for the synthesis of pyrazole 3aa (Table 1, entry 18): K_2CO_3 (0.28 mmol, 38.6 mg) was added in one portion to a solution of 3-benzylidene-5-phenylpent-4-yn-2-one (**1a**; 0.2 mmol, 49.2 mg) and *tert*-butylhydrazine hydrochloride (**2a**; 0.24 mmol, 29.8 mg) in 2.5 mL of DMA under air at room temperature. After 1.5 h, the enyne **1a** was consumed, as determined by TLC analysis. 3 mL of H_2O was added to quench the reaction and the mixture was extracted with diethyl ether. The combined organic layers were washed with saturated NaCl solution and dried over $MgSO_4$. After filtration and concentration, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate 10:1) to give **3aa** (64.4 mg, 97% yield) as a white solid. m.p.: 127–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.55 (d, J = 7.2 Hz, 2H), 7.45–7.37 (m, 3H), 7.26 (t, J = 7.2 Hz, 2H), 7.17 (t, J = 7.2 Hz, 1H), 7.04 (d, J = 7.2 Hz, 2H), 4.59 (s, 2H), 2.01 (s, 3H), 1.59 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 196.54, 149.96, 143.07, 138.34, 134.29, 129.28, 128.38, 128.32, 128.23, 127.59, 126.08, 121.83, 61.62, 31.84, 30.96, 30.52 ppm; MS (70 eV): m/z (%): 332 (M^+, 94.70), 261 (100). HRMS calcd for $C_{22}H_{24}NO_3$: 332.1889, found: 332.1890.

Acknowledgements

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Keywords: cycloaddition · enynes · hydrazines · oxidation · pyrazoles

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[12] This intermediate **B** appears as a new spot on the TLC plate if the reaction is run under an atmosphere of N_2, **B** rapidly undergo dehydrogenative aromatization during the work-up and the attempts to isolate this compound failed.

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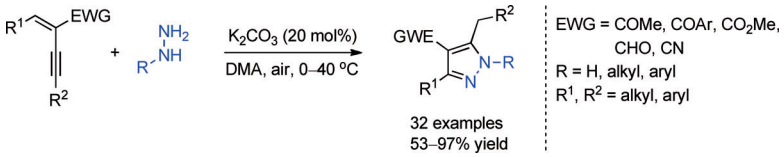
Tandem Reactions

*X. Yu, J. Zhang** ..... ▮▮▮▮–▮▮▮▮

A Base-Promoted Tandem Cycloaddition/Air Oxidation Reaction of Electron-Deficient Conjugated Enynes and Hydrazines: Synthesis of Highly Substituted Pyrazoles



Rapid access: A base-mediated cycloaddition/oxidation reaction of hydrazines and electron-deficient 1,3-conjugated enynes gives pyrazole derivatives, some of which are not easily accessible by other methods (see scheme). The reaction conditions are mild, thus enabling a variety of functional groups to be tolerated.

