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Facile One-Pot Synthesis of 1,3,5-Trisubstituted Pyrazoles from α,β-Enones

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A practical and efficient one-pot synthesis of 1,3,5-trisubstituted pyrazoles from α,β-enones and arylhydrazine hydrochlorides has been developed. The pyrazoles were formed *via* a tandem formation of the corresponding pyrazolines and an acid-catalyzed aerobic oxidation process.

Key Words : Pyrazoles, One-pot synthesis, Aerobic oxidation, α,β-Enones

Introduction

1,3,5-Trisubstituted pyrazolines are important heterocyclic compounds which can be prepared from substituted hydrazines and α,β-enones. The oxidation of these pyrazolines provides the corresponding pyrazoles, which are known to possess diverse biological activities.[1] Thus various oxidation methods have been reported including the use of MnO_2,[2a-c] *p*-chloranil,[2d] $Pb(OAc)_4$,[2e] $Zr(NO_3)_4$,[2f] claycop,[2g] $PhI(OAc)_2$,[2h-j] I_2,[2k] HIO_3/I_2O_5,[2l] HNO_2/AcOH,[2m] TBPA cation radical,[2n] and 1,3-dibromo-5,5-dimethylhydantoin.[2o] Hayashi and co-workers reported an effective conversion of pyrazoline to pyrazole in acetic acid with or without Pd/C catalyst.[3] An aerobic oxidation of pyrazoline to pyrazole has also been reported by using activated carbon,[4a] cobalt salts,[4b,c] or $HAuCl_4$.[4d] Very recently, Balakrishna and co-workers have reported $FeCl_3$-catalyzed aerobic oxidation of 1,3,5-trisubstituted pyrazolines to the corresponding pyrazoles.[5] A direct synthesis of 1,3,5-trisubstituted pyrazoles from α,β-enones has also been reported; however, most of them suffer from low yield and/or harsh reaction conditions.[6] Thus, an efficient and practical one-pot synthetic procedure of 1,3,5-trisubstituted pyrazoles is highly required until now.

Results and Discussion

During our recent studies on the synthesis of pyrazole and related compounds,[7] we observed that an aerobic oxidation of pyrazoline proceeded readily to afford the pyrazole in good yield in the presence of an acid catalyst. As an example, 1,3,5-triphenylpyrazoline (**2a**) was converted quantitatively to 1,3,5-triphenylpyrazole (**3a**) in the presence of phenylhydrazine hydrochloride as an acid catalyst in 1,2-dichlorobenzene (ODCB, 130 °C) in short time (40 min, *vide infra*). In these contexts, we decided to develop an efficient one-pot procedure of 1,3,5-trisubstituted pyrazoles from arylhydrazines and α,β-enones.

Initially, we examined an aerobic oxidation of **2a** under various conditions as summarized in Table 1. The oxidation in acetic acid at 80 °C under O_2 balloon atmosphere (entry 1) gave **3a** in moderate yield (72%) even in the absence of Pd/C, as already reported by Hayashi.[3] The yield of **3a** increased in AcOH at refluxing temperature (81%, entry 2). The reaction in ODCB (90-110 °C) did not afford an appreciable amount of **3a** (entries 3 and 4). The result stated that an aerobic oxidation of **2a** is effective in an acidic medium. It is interesting to note that the reaction in ODCB at elevated temperature gave **3a** in moderate to good yields (entries 5 and 6). The use of *p*-xylene instead of ODCB was less effective (entry 7) although the reaction temperature was similar.[4a] The reactions at low temperature (90-110 °C) in ODCB were not effective even in the presence of NH_4Cl (entries 8 and 9). However, the use of NH_4Cl (entries 10-12) was certainly helpful for the oxidation when we compare the results of (i) entry 5/entry 10, (ii) entry 6/entry 11, and (iii) entry 7/entry 12. When we use phenylhydrazine hydrochloride as an acid catalyst (entry 13), **3a** was obtained in high yield (91%). The reaction under N_2 balloon atmosphere (entry 14) was ineffective, and the result stated that the reaction must be an aerobic oxidation. The use of hydroxylamine hydrochloride (entry 15), *p*-TsOH (entry 16), acetic acid (entry 17), silica gel (entry 18) or $FeCl_3$ (entry 19)[5] was less effective than the use of phenylhydrazine hydrochloride. In addition, a base-mediated aerobic oxidation (entries 20 and 21) was less effective than an acid-catalyzed one.

Based on the results, we examined a one-pot synthesis of **3a** from chalcone (**1a**) and phenylhydrazine hydrochloride (1.2 equiv) in ODCB (130 °C) under O_2 balloon atmosphere. To our delight, **3a** was obtained in good yield (87%) in a one-pot reaction in short time (5 h).[8] Encouraged by the results, we prepared various pyrazoles **3b-p** from the corresponding α,β-enones **1a-n** and arylhydrazine hydrochlorides, and the results are summarized in Table 2. The reactions of chalcone (**1a**) with *p*-chlorophenylhydrazine hydrochloride and *p*-methoxyphenylhydrazine hydrochloride afforded **3b** and **3c** in good yields (80-88%). The reactions of various chalcone derivatives **1b-n** and phenylhydrazine hydrochloride provided the corresponding pyrazoles **3d-p** in good to moderate yields (74-88%) in a one-pot reaction. It is interesting to note that the yields of 4-substituted pyrazoles **3m-o** were somewhat lower (74-78%) than those of other 4-unsubstituted pyrazoles. During the preparation of **3m** and

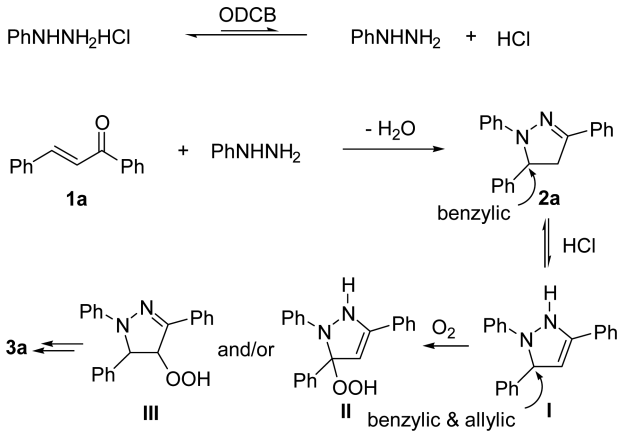
Table 1. Aerobic oxidation of **2a** to **3a**

Entry	Conditions[a]	**3a** (%)[b]
1	AcOH, 80 °C, 2 h	72
2	AcOH, reflux, 2 h	81
3	ODCB, 90 °C, 4 h	0
4	ODCB, 110 °C, 4 h	< 5
5	ODCB, 120 °C, 4 h	52
6	ODCB, 130 °C, 1 h	80
7	*p*-xylene, reflux, 30 h	46
8	ODCB, NH_4Cl (1.0 equiv), 90 °C, 4 h	0
9	ODCB, NH_4Cl (1.0 equiv), 110 °C, 4 h	< 5
10	ODCB, NH_4Cl (1.0 equiv), 120 °C, 2 h	79
11	ODCB, NH_4Cl (1.0 equiv), 130 °C, 40 min	85
12	*p*-xylene, NH_4Cl (1.0 equiv), reflux, 20 h	68
13	**ODCB, $PhNHNH_2HCl$ (1.0 equiv), 130 °C, 40 min**	**91**
14[c]	ODCB, $PhNHNH_2HCl$ (1.0 equiv), 130 °C, 1 h	< 5
15	ODCB, NH_2OHHCl (1.0 equiv), 130 °C, 1 h	84
16	ODCB, *p*-TsOH (0.2 equiv), 130 °C, 1 h	64[d]
17	ODCB, AcOH (3.0 equiv), 130 °C, 1 h	81
18	ODCB, silica gel, 130 °C, 4 h	66
19	ODCB, $FeCl_3$ (0.1 equiv), 130 °C, 2 h	72
20	DMF, DBU (0.3 equiv), 80 °C, 48 h	76
21	DMF, K_2CO_3 (2.0 equiv), 80 °C, 48 h	47

[a]Pyrazoline **2a** (0.3 mmol), O_2 balloon atmosphere. [b]Isolated yield. [c]Under N_2 balloon atmosphere. [d]Some unidentified side products were formed.

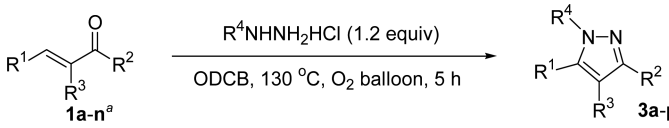
3n, the starting materials **1k** and **1l** were remained even after 4 days whereas the corresponding pyrazolines were not observed on TLC. The results stated that moderate yields of **3m** and **3n** are due to the sluggish reactivity of **1k** and **1l** for the formation of the corresponding pyrazolines.[2a] However, the reaction of α-benzyl-α,β-enone **1m** was faster than **1k** and **1l** presumably due to the presence of a small methyl group around the ketone as compared to the large phenyl group of **1k** and **1l**.

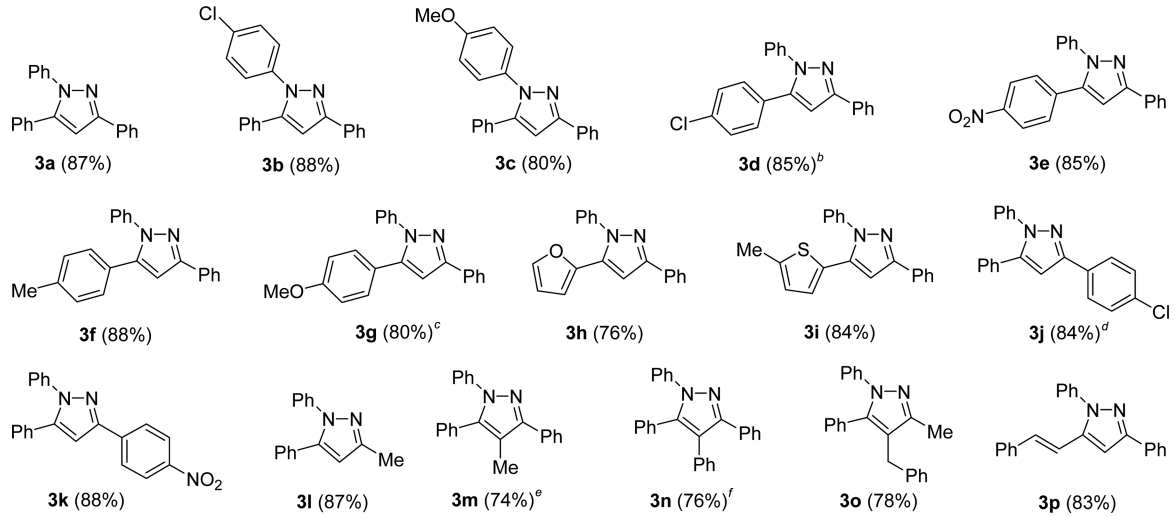
Both the formation of pyrazoline **2a** and a subsequent aerobic oxidation of **2a** to **3a** have to occur effectively in order to produce **3a** efficiently. Thus a plausible reaction mechanism is proposed in Scheme 1. Phenylhydrazine could be generated slowly by the loss of HCl under the non-polar ODCB solvent at high temperature. The liberated phenylhydrazine reacted with chalcone (**1a**) to form the pyrazoline **2a**, and a subsequent aerobic oxidation of **2a** to **3a** proceed-



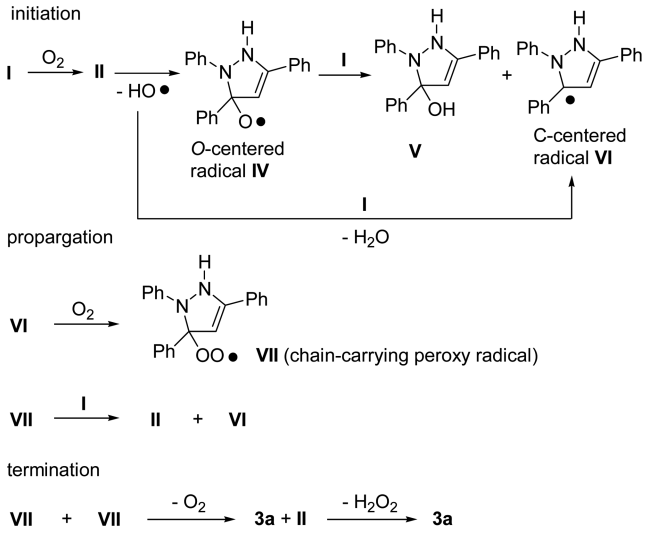
Scheme 1

Table 2. One-pot synthesis of 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazoles





[a]**1a** (R^1=Ph, R^2=Ph, R^3=H); **1b** (R^1=4-ClPh, R^2=Ph, R^3=H); **1c** (R^1=4-NO_2Ph, R^2=Ph, R^3=H); **1d** (R^1=4-MePh, R^2=Ph, R^3=H); **1e** (R^1=4-MeOPh, R^2=Ph, R^3=H); **1f** (R^1=2-furyl, R^2=Ph, R^3=H); **1g** (R^1=5-Me-2-thienyl, R^2=Ph, R^3=H); **1h** (R^1=Ph, R^2=4-ClPh, R^3=H); **1i** (R^1=Ph, R^2=4-NO_2Ph, R^3=H); **1j** (R^1=Ph, R^2=Me, R^3=H); **1k** (R^1=Ph, R^2=Ph, R^3=Me); **1l** (R^1=Ph, R^2=Ph, R^3=Ph); **1m** (R^1=Ph, R^2=Me, R^3=benzyl); **1n** (R^1=cinnamyl, R^2=Ph, R^3=H). [b]**3j** was isolated in 7%. [c]1,5-diphenyl-3-(4-methoxyphenyl)pyrazole (**3g'**) was isolated in 9%. [d]**3d** was isolated in 8%. [e]Reaction time is 6 days. [f]Reaction time is 4 days.

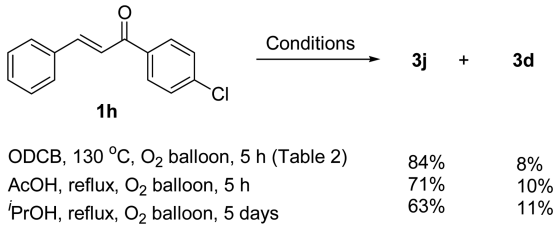


Scheme 2

ed. The role of an acid catalyst (liberated HCl) is not fully clear at this stage; however, an acid-catalyzed isomerization of imine-form **2a** to an electron-rich enamine-form **I** (imine-enamine tautomerization) could facilitate the aerobic oxidation process.[9] Aerobic oxidation at the benzylic/allylic position of **I** could generate 5-hydroperoxide **II**; however, we could not rule out the possibility for the formation of 4-hydroperoxide **III** from the electron-rich enamine-form **I**.[10] In addition, the liberated HCl in the reaction mixture might be helpful for the effective dehydration (*vide infra*).

The mechanism of aerobic oxidation might follow the generally known one,[11] as shown in Scheme 2. The hydroperoxide **II**, formed from **I** and oxygen, can be dissociated to *O*-centered radical **IV** and a hydroxide radical. This step is slow due to high activation energy barrier.[11b] The reaction of **IV** and **I** produced a C-centered radical **VI** and 5-hydroxypyrazoline **V**, which could be converted to the product **3a** by acid-catalyzed dehydration. In the propagation step, radical **VI** and O_2 produced a chain-carrying peroxy radical **VII**. The reaction of **VII** and **I** produced **II** and **VI**.[11b,12] In a termination stage, two molecules of **VII** might be converted to **3a** and **II**, which was converted eventually to **3a**.[11d-g]

A trace amount of regioisomeric pyrazole was formed together in most of the reactions. As an example, the reaction of **1h** produced **3j** as a major product along with a low yield (8%) of **3d**, as shown in Scheme 3. The minor product

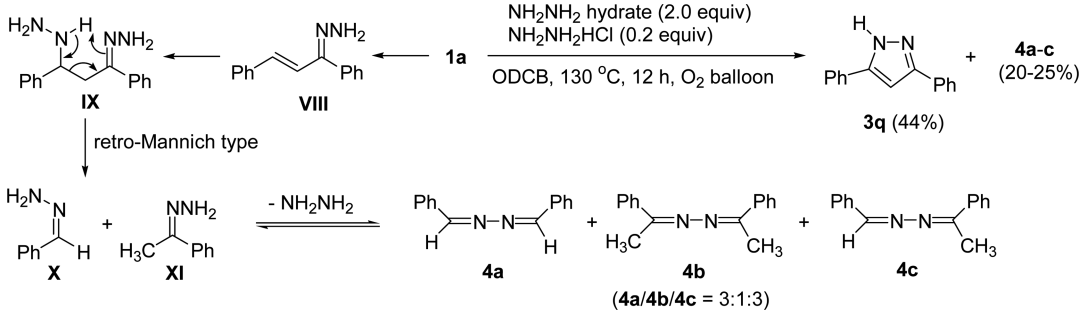


Scheme 3

3d might be produced *via* a conjugate addition of phenylhydrazine, dehydrative cyclization, and aerobic oxidation. Although the formations of regioisomeric pyrazoles were observed in most entries, albeit in a trace amount (*ca.* 5-10%), we did not separate them in every cases (see, Table 2). In order to further increase the yield of **3j**, we examined a solvent effect once again (*vide supra*). However, the ratio between **3j** and **3d** was not improved. In addition, the yield of **3j** decreased in AcOH or 2-propanol as compared to ODCB. It is interesting to note that the ratio between **3j**/**3d** is dependent on the reaction conditions including solvent polarity although the difference is minute (from 10:1 to 6:1).[13]

As a last examination, we tried the synthesis of *N*-unsubstituted pyrazole **3q**, as shown in Scheme 4. The synthesis of *N*-unsubstituted pyrazoles from α,β-enones and hydrazine afforded quite low yields of products in most cases.[6b,14] The use of an acid catalyst such as AcOH caused the formation of unwanted *N*-acetyl derivative.[14] Thus, the synthesis has been carried out with modified α,β-enones such as β-thioalkyl-α,β-enones[15a] or chalcone epoxides.[15b] When we performed the reaction of **1a** and hydrazine hydrate (2.0 equiv) in the presence of hydrazine hydrochloride (0.2 equiv) as an acid catalyst in ODCB (130 °C, 12 h) **3q** was obtained in low yield (44%), unfortunately. The major side product was confirmed as a mixture of benzaldazine (**4a**), acetophenone azine (**4b**) and a mixed azine **4c**.[16] The yield of azines was around 20-25% in a ratio of **4a**/**4b**/**4c** = 3:1:3 based on ^{1}H NMR spectrum of the mixture.[16a] The mechanism for the formation of azines might involve a conjugate addition of hydrazine to the hydrazone **VIII** to form **IX**, retro-Mannich type decomposition of **IX** to **X** and **XI** (or their corresponding carbonyl compounds), and the condensations between them.

In summary, a practical and efficient one-pot synthesis of poly-substituted pyrazoles from α,β-enones and arylhydrazine hydrochlorides has been disclosed. The mechanism is



Scheme 4

thought to be a tandem formation of pyrazoline and an acid-catalyzed aerobic oxidation. Various 1,3,5-trisubstituted and 1,3,4,5-tetrasubstituted pyrazoles could be synthesized in good to excellent yields; however, this protocol was not effective for the synthesis of *N*-unsubstituted pyrazole.

Experimental Section

Typical Procedure for the Synthesis of 3a. A mixture of chalcone (**1a**, 208 mg, 1.0 mmol) and phenylhydrazine hydrochloride (173 mg, 1.2 mmol) in ODCB (2.0 mL) was heated to 130 °C under O_2 balloon atmosphere for 5 h. After removal of ODCB and column chromatographic purification process (hexanes/ether, 12:1) pyrazole **3a** was obtained as a pale yellow solid, 258 mg (87%). Other pyrazole derivatives were synthesized similarly and identified by comparison their mp and/or ^{1}H NMR data with the reported. Known compounds are **3a**,[3] **3c**,[6d] **3d**,[4b] **3e**,[3] **3f**,[4d] **3g**,[3] **3g'**,[6c] **3h**,[4d] **3j**,[4d] **3k**,[5] **3l**,[4b] **3m**,[17a] **3n**,[2d] **3p**,[17b] **3q**,[6a,e] and the selected spectroscopic data of unknown compounds **3b, 3i** and **3o** are as follows.

Compound 3b: 88%; white solid, mp 118-120 °C; IR (KBr) 1495, 1460, 1362 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.83 (s, 3H), 7.25-7.40 (m, 10H), 7.41-7.48 (m, 2H), 7.92 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 105.55, 125.86, 126.35, 128.24, 128.60, 128.65, 128.69, 128.75, 129.06, 130.16, 132.55, 133.12, 138.41, 144.51, 152.16; ESIMS *m/z* 331 [M$^+$+H], 333 [M$^+$+H+2]. Anal. Calcd for $C_{21}H_{15}N_2$: C, 76.24; H, 4.57; N, 8.47. Found: C, 76.37; H, 4.61; N, 8.31.

Compound 3i: 84%; yellow oil; IR (film) 1596, 1499, 1457, 1363 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.45 (d, J = 1.2 Hz, 3H), 6.61 (dq, J = 3.6 and 1.2 Hz, 1H), 6.64 (d, J = 3.6 Hz, 1H), 6.82 (s, 1H), 7.22-7.51 (m, 8H), 7.90 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.17, 104.50, 125.60, 125.77, 126.21, 127.22, 127.98, 128.21, 128.59, 128.84, 128.98, 132.86, 138.49, 139.95, 141.28, 151.78; ESIMS *m/z* 317 [M$^+$+H]. Anal. Calcd for $C_{20}H_{16}N_2$: C, 75.92; H, 5.10; N, 8.85. Found: C, 75.96; H, 5.32, N, 8.79.

Compound 3o: 78%; white solid, mp 88-90 °C; IR (KBr) 1599, 1505, 1365 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22 (s, 3H), 3.82 (s, 2H), 7.09-7.33 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.27, 29.31, 117.60, 124.50, 125.85, 126.46, 128.07, 128.17, 128.36, 128.47, 128.63, 129.78, 130.67, 140.06, 140.71, 141.22, 149.05; ESIMS *m/z* 325 [M$^+$+H]. Anal. Calcd for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63. Found: C, 85.04; H, 6.15, N, 8.78.

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12. In order to further increase the yield of **3a**, we examined the reaction of **1a** and phenylhydrazine hydrochloride in ODCB (130 °C) in the presence of *N*-hydroxyphthalimide (10%) under O_2 balloon atmosphere for 5 h.[4b,12d] The yield of **3a** increased a little (89%). However, no reaction was observed at 80 °C. The reaction was also sluggish even at 100 °C and **3a** was obtained in 86% for 12 h. Although there has been reported that an aerobic oxidation of pyrazoline to pyrazole can proceed even at room temperature in the presence of NHPI,[4b] the one-pot synthesis of **3a** from **1a** required elevated temperature.
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