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Preparation of 3,5-Disubstituted Pyrazoles and Isoxazoles from Terminal Alkynes, Aldehydes, Hydrazines, and Hydroxylamine

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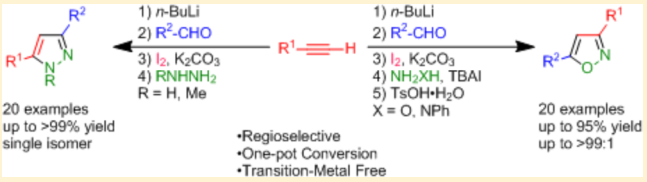
Supporting Information

ABSTRACT: The reaction of terminal alkynes with *n*-BuLi, and then with aldehydes, followed by the treatment with molecular iodine, and subsequently hydrazines or hydroxylamine provided the corresponding 3,5-disubstituted pyrazoles or isoxazoles in good yields with high regioselectivity, through the formations of propargyl secondary alkoxides and α-alkynyl ketones. The present reactions are one-pot preparation of 3,5-disubstituted pyrazoles from terminal alkynes, aldehydes, molecular iodine, and hydrazines, and 3,5-disubstituted isoxazoles from terminal alkynes, aldehydes, molecular iodine, and hydroxylamine.



INTRODUCTION

Pyrazoles and isoxazoles are extensively used as heterocyclic units of medicines and agrochemicals.[1] Pyrazoles, in particular, have been studied for more than a century as an important class of heterocyclic compounds[2] and have continued to attract considerable attention due to the broad range of biological activities, including analgesic,[3] antibacterial,[4] antidepressant,[5] anti-inflammatory,[6,7] antimicrobial,[6,8] antiobesity,[9] antiviral,[10] appetite suppressant,[11] cholesterol-lowering,[12] hypoglycemic,[13] antihypertensive,[14] and anticancer[15] activities. Pyrazoles serve as building blocks for pharmaceutical and agricultural research, and Celebrex,[7] Viagra,[16] Zometapine,[17] Cyenopyrafen,[18] Fenpyroximate,[19] and Tebufenpyrad[20] are well-known compounds bearing a pyrazole unit. Pyrazoles are generally synthesized by (i) the reaction of 1,3-dicarbonyl compounds with hydrazines,[21] (ii) the reaction of α,β-unsaturated or doubly unsaturated aldehydes or ketones with hydrazines,[22] and (iii) the 1,3-dipolar cycloaddition reaction of diazoalkanes or nitrilimines with alkenes or alkynes[23] and are occasionally prepared by (iv) the functionalization of unsubstituted or less substituted pyrazoles.[24] Although the major route to pyrazoles involves the 1,3-dipolar cycloaddition of diazomethanes to alkynes,[23] other methods with metals, Lewis acids, or bases were also recently reported.[25−35] More recently, the TsOH-catalyzed Mannich-type-cyclization-oxidation of arylhydrazines, aromatic aldehydes, and terminal arylalkynes to form 1,3,5-triarylpyrazoles was reported.[36] However, that report should be questioned, as we performed the same reaction carefully but were unable to obtain pyrazoles at all using the described procedures and conditions.[36] Namely, treatment of benzaldehyde (1.0 equiv), phenylhydrazine (1.0 equiv), phenylacetylene (1.2 equiv), and *p*-toluenesulfonic acid in dichloroethane (0.5 M) at room temperature for 24 h did not give the corresponding pyrazole at all.

Isoxazoles possess important biological activities, such as anti-inflammatory,[37] antimicrobial,[38] anticancer,[39] and antinociceptive[40] activities. Although the major route to isoxazoles is the 1,3-dipolar cycloaddition of nitrile oxides to alkynes,[23] other methods were also reported recently.[41−44] On the other hand, terminal alkynes and aldehydes are easily available, and therefore, the preparation of pyrazoles and isoxazoles with those compomds is a very attractive option. However, to the best of our knowledge, the one-pot preparation of pyrazoles and isoxazoles using terminal alkynes and aldehydes with hydrazine and hydroxylamine is little studied. Here, as part of our investigation of the synthetic use of molecular iodine in organic synthesis,[45] we would like to report the one-pot preparation of pyrazoles by reacting a terminal alkyne with *n*-BuLi and then aldehydes, followed by the treatment with molecular iodine and K_2CO_3 and the subsequent reaction with hydrazines, and the preparation of isoxazoles by reacting a terminal alkyne with *n*-BuLi and then aldehydes, followed by the treatment with molecular iodine and K_2CO_3 and the subsequent reaction with hydroxylamine.

RESULTS AND DISCUSSION

Treatment of phenylacetylene **1a** with *n*-BuLi in THF at 0 °C, followed by the addition of 4-methoxybenzaldehyde **2a** at 0 °C generated the adduct, propargyl secondary alkoxide (**I**). Further treatment of the propargyl secondary alkoxide solution with molecular iodine in the presence of K_2CO_3 under refluxing conditions, followed by the treatment with hydrazine provided 3-(4′-methoxyphenyl)-5-phenylpyrazole **3a** in 20−30% yields. The reason for the low yield of 3-(4′-methoxyphenyl)-5-phenylpyrazole **3a** was that the oxidation of propargyl secondary alkoxide (**I**) with molecular iodine did not proceed efficiently in THF solution. Therefore, after the formation of the propargyl secondary alkoxide (**I**), THF was removed by evaporation, and *t*-BuOH was added to promote the oxidation

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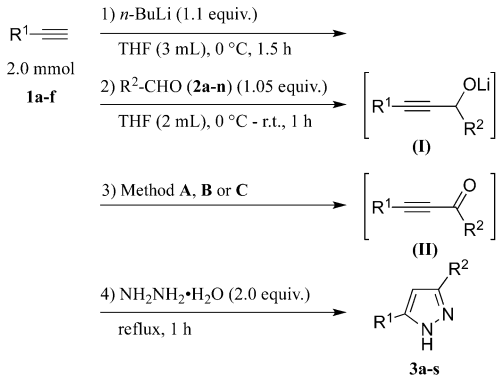
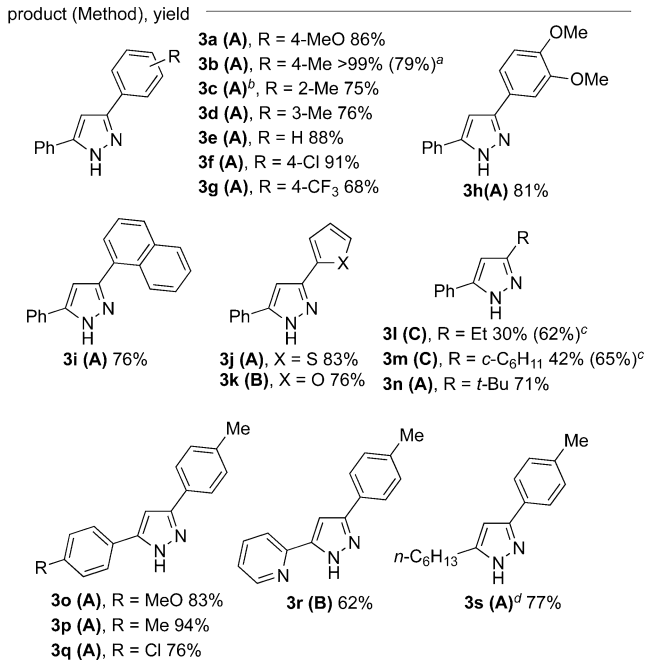
to the α-alkynyl ketone (**II**). Once the α-alkynyl ketone (**II**) was formed, the reaction with hydrazine occurred smoothly to give 3-(4′-methoxyphenyl)-5-phenylpyrazole **3a** in 86% yield in one pot, as shown in Table 1. The fourth step for the formation

Table 1. Preparation of 3,5-Disubstituted 1*H*-Pyrazoles 3



Method **A**: evaporation; I_2 (1.6 equiv.), K_2CO_3 (3.0 equiv.), *t*-BuOH (3 mL), reflux, 2 h
Method **B**: evaporation; TEMPO (10 mol%), DIB (1.2 equiv.), DCE (3 mL), r.t., 4 h.
Method **C**: Toluene was used instead of THF at 1st step.
conc. HCl *aq.*, $Fe(NO_3)_3$•$9H_2O$ (10mol%), TEMPO (10 mol%), r.t., 24 h.
Solvent was evaporated before 4th step, and *t*-BuOH (3 mL) was added.



[a] *t*-BuOH (3 mL) was added without removal of THF. [b] Reaction time was 4 h at third step. [c] Overall yield from isolated ketone (**II**), and the mixture was treated with NH_2NH_2·H_2O (1.1 equiv) in *t*-BuOH (3 mL) at refluxing temperature for 1 h. [d] Reaction time was 18 h at third step.

of pyrazole proceeded at room temperature. However, refluxing conditions gave pyrazole **3a** in a much higher yield than that achieved at room temperature. Thus, treatment of phenylacetylene **1a** with *n*-BuLi in THF at 0 °C, followed by the addition of aromatic aldehydes, such as 4-methoxybenzaldehyde **2a**, 4-methylbenzaldehyde **2b**, 2-methylbenzaldehyde **2c**, 3-methylbenzaldehyde **2d**, benzaldehyde **2e**, 4-chlorobenzaldehyde **2f**, 4-(trifluoromethyl)benzaldehyde **2g**, 3,4-(dimethoxy)-benzaldehyde **2h**, 1-naphthaldehyde **2i**, 2-thiophenecarboxaldehyde **2j**, and furfural **2k**, and the subsequent treatment with molecular iodine and K_2CO_3 in *t*-BuOH and then hydrazine under refluxing conditions (Method A) generated the corresponding 3-aryl-5-phenylpyrazoles **3a**−**3k** in good yields under the same procedure and conditions, as shown in Table 1. When *t*-BuOH was added to the THF solution without removal of THF at the third step, the yields of pyrazoles were decreased to 70−79%. Moreover, in the third step involving the oxidation of propargyl secondary alkoxide (**I**) derived from furfural **2k**, a TEMPO-catalyzed (diacetoxyiodo)benzene (DIB) oxidation system[46] (Method B) instead of a molecular iodine with K_2CO_3 oxidation system was used to promote the clean oxidation to α-alkynyl ketone (**II**).

The same treatment of 4-methoxyphenylacetylene **1b**, 4-methylphenylacetylene **1c**, 4-chlorophenylacetylene **1d**, 2-pyridylacetylene **1e**, and 1-octyne **1f** with *n*-BuLi in THF at 0 °C, followed by the addition of 4-methylbenzaldehyde **2b**, and the subsequent treatment with molecular iodine and K_2CO_3 in *t*-BuOH (Method A) and then hydrazine under refluxing conditions generated the corresponding 5-aryl-3-(4′-methylphenyl)pyrazoles **3o**−**3r** and 5-hexyl-3-(4′-methylphenyl)pyrazole **3s** in good yields. In the third step for the oxidation of propargyl secondary alkoxide (**I**) derived from 2-pyridylacetylene, a TEMPO-catalyzed DIB oxidation system (Method B) instead of a molecular iodine with K_2CO_3 oxidation system was used to promote the clean oxidation to α-alkynyl ketone (**II**). The same treatment of phenylacetylene **1a** with *n*-BuLi in THF at 0 °C, followed by the addition of aliphatic aldehydes, such as propionaldehyde **2l** and cyclohexanecarboxaldehyde **2m**, and the subsequent treatment with molecular iodine and K_2CO_3 in *t*-BuOH (Method A), or TEMPO with DIB in 1,2-dichloroethane (Method B), did not generate α-alkynyl ketones (**II**), because the oxidation of adducts (**I**) did not occur at all. However, it was found that the oxidation of adducts (**I**) with $Fe(NO_3)_3$ in the presence of TEMPO[47] in toluene (Method C) proceeded smoothly to generate α-alkynyl ketones (**II**), and further treatment of isolated α-alkynyl ketones (**II**) bearing ethyl and cyclohexyl groups with hydrazine generated 3-ethyl-5-phenylpyrazole **3l** and 3-cyclohexyl-5-phenylpyrazole **3m** in 62 and 65% yields, respectively. In contrast, the same treatment of phenylacetylene **1a** with *n*-BuLi in THF at 0 °C, followed by the addition of pivalaldehyde **2n**, and the subsequent treatment with molecular iodine and K_2CO_3 in *t*-BuOH (Method A) generated α-alkynyl ketone (**II**) smoothly, and the further treatment with hydrazine provided 3-*t*-butyl-5-phenylpyrazole **3n** in 71% yield in one pot. This may be due to the higher electron density of the oxygen atom of adduct alkoxide (**I**) than those of adducts (**I**) formed from the reaction of lithium phenylacetylide with propionaldehyde and cyclohexanecarboxaldehyde (electron-donating ability increases as follows: Et < *c*-C_6H_{11} < *t*-Bu). Here, when the direct in situ oxidation of adducts (**I**) derived from the reaction of lithium phenylacetylide with propionaldehyde **2l** and cyclohexanecarboxaldehyde **2m** was carried out with $Fe(NO_3)_3$ in the presence of TEMPO, the yields of 3-ethyl-5-phenylpyrazole **3l** and 3-cyclohexyl-5-phenylpyrazole **3m** were low. The low yields obtained when the reaction was carried out in one pot using $Fe(NO_3)_3$ in the presence of TEMPO, might have been due to the oxidation of hydrazine with oxidizing species, i.e., $Fe(NO_3)_3$, which was used in the third step. Therefore, after the isolation of the α-propargyl alcohols from adducts (**I**) derived from propionaldehyde **2l** and cyclohexanecarboxaldehyde **2m**, and the oxidation of α-propargyl alcohols with $Fe(NO_3)_3$ in the presence of TEMPO in toluene

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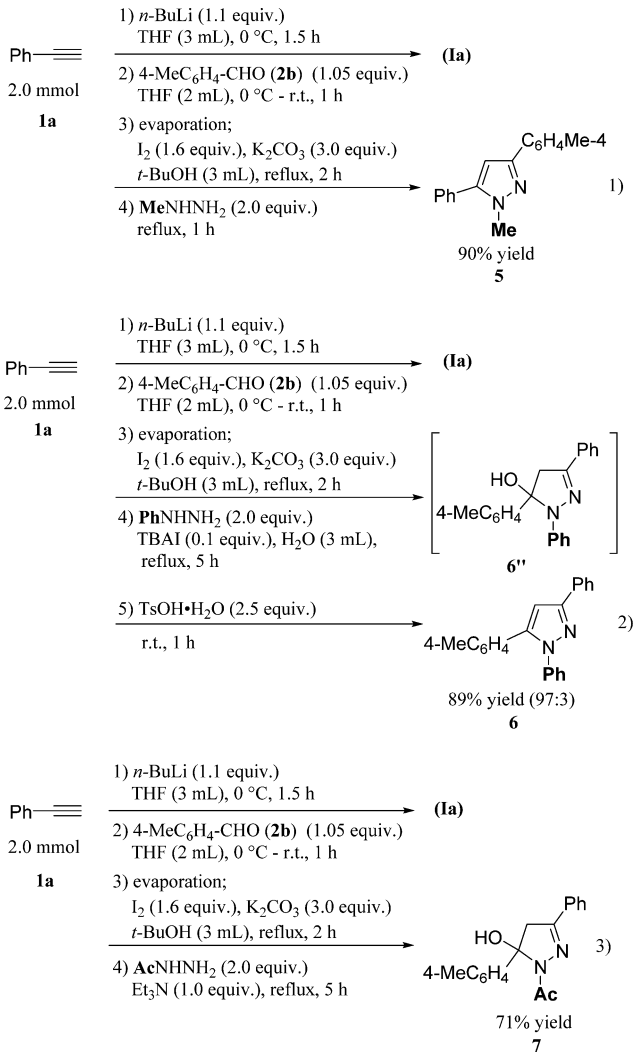
(Method C) gave α-alkynyl ketones (**II**) in higher than 80% yield. When isolated α-alkynyl ketones (**II**) were treated with hydrazine, 3-ethyl-5-phenylpyrazole **3l** and 3-cyclohexyl-5-phenylpyrazole **3m** were obtained in good yields. When methylhydrazine instead of hydrazine was used, after the reaction of phenylacetylene **1a** with *n*-BuLi and then 4-methylbenzaldehyde **2b**, followed by the oxidation with molecular iodine and K_2CO_3 in *t*-BuOH (Method A) under the same procedure and conditions, 1-methyl-3-(4′-methylphenyl)-5-phenylpyrazole **5** was obtained in 90% yield as a single isomer, as shown in Scheme 1 (eq 1). On the other hand,

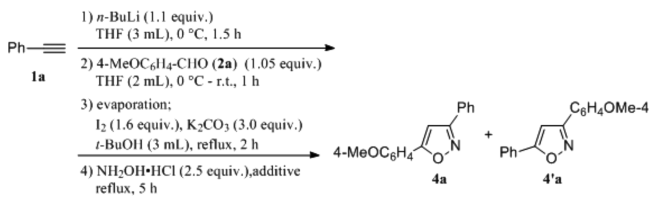
Scheme 1. Preparation of 1,3,5-Trisubstituted 1*H*-Pyrazoles 5−7



when phenylhydrazine instead of hydrazine was used under the same procedure and conditions, dehydration to the pyrazole skeleton did not proceed smoothly, and therefore, *p*-TsOH was added for the dehydration at the fifth step at room temperature to give 1-phenyl-5-(4′-methylphenyl)-3-phenylpyrazole **6** in 89% yield with high regioselectivity, including a trace amount of 1-phenyl-3-(4′-methylphenyl)-5-phenylpyrazole (eq 2). These results indicate that the methylamino group of methylhydrazine reacts at the β-position of alkynyl ketone (**II**), whereas the amino group of phenylhydrazine reacts at the β-position of alkynyl ketone (**II**). The structures of pyrazoles **5** and **6** were supported by X-ray analysis. When acylhydrazine instead of hydrazine was used, after the reaction of phenylacetylene **1a** with *n*-BuLi and then 4-methylbenzaldehyde **2b**, followed by the oxidation with molecular iodine and K_2CO_3 in *t*-BuOH (Method A) under the same procedure and conditions, 5-hydroxypyrazoline intermediate **7**, which was not dehydrated, was obtained in 71% yield (eq 3). In this case, the aromatization to 1-acetylpyrazole through the dehydration of intermediate **7** is precluded by the *N*-acetyl group, an electron-withdrawing group.

Then, the one-pot preparation of isoxazoles using hydroxylamine instead of hydrazine was conducted under the same procedure and conditions. Treatment of phenylacetylene **1a** with *n*-BuLi in THF at 0 °C, followed by the addition of 4-methoxybenzaldehyde **2a**, and the subsequent treatment with molecular iodine and K_2CO_3 in *t*-BuOH (Method A) and then hydroxylamine·HCl under refluxing conditions generated a mixture of 5-(4′-methoxyphenyl)-3-phenylisoxazole **4a** and 3-(4′-methoxyphenyl)-5-phenylisoxazole **4a**′ in 91% yield (8:1), as shown in Table 2 (entry 1). To improve the regioselective

Table 2. Optimal Conditions for Regioselective Preparation of 3,5-Disubstituted Isoxazole 4a



entry	additive	4a/4a′	yield (%)
1	none	8:1	91
2	TsOH·H_2O (1.0 equiv)	2:1	82
3	TfOH (1.0 equiv)	1:1.2	80
4	Et_3N (1.0 equiv)	20:1	88
5	*i*-Pr_2NEt (1.0 equiv)	30:1	86
6	DBU (1.0 equiv)	49:1	79
7	TBAI (0.1 equiv)	8:1	92
8[a]	H_2O (3 mL)	>99:1	85
9[a]	TBAI (0.1 equiv), H_2O (3 mL)	>99:1	88
10[a]	Et_3N (1.0 equiv), H_2O (3 mL)	>99:1	81
11[a]	*i*-Pr_2NEt (1.0 equiv), H_2O (3 mL)	>99:1	78
12[a]	DBU (1.0 equiv), H_2O (3 mL)	>99:1	76

[a]After fourth step reaction, TsOH·H_2O (2.5 equiv) was added, and the mixture was stirred for 1 h at rt.

formation of 5-(4′-methoxyphenyl)-3-phenylisoxazole **4a**, various acids and bases as an additive were used at the fourth step, and it was found that the addition of water (3 mL), water (3 mL) with tetrabutylammonium iodide (TBAI), or water (3 mL) with tertiary amines, such as Et_3N, *i*-Pr_2NEt, and DBU, gave 5-(4′-methoxyphenyl)-3-phenylisoxazole **4a** in high yields with high regioselectivity (>99:1) (entries 8−12). Especially, addition of water (3 mL) with TBAI gave 5-(4′-methoxyphenyl)-3-phenylisoxazole **4a** in the best yield with high regioselectivity (entry 9).

On the basis of these optimum conditions, treatment of phenylacetylene **1a** with *n*-BuLi in THF at 0 °C, followed by the addition of aromatic aldehydes, such as 4-methoxybenzaldehyde **2a**, 4-methylbenzaldehyde **2b**, 2-methylbenzaldehyde **2c**, 3-methylbenzaldehyde **2d**, benzaldehyde **2e**, 4-chlorobenzaldehyde **2f**, 4-(trifluoromethyl)benzaldehyde **2g**, 3,4-

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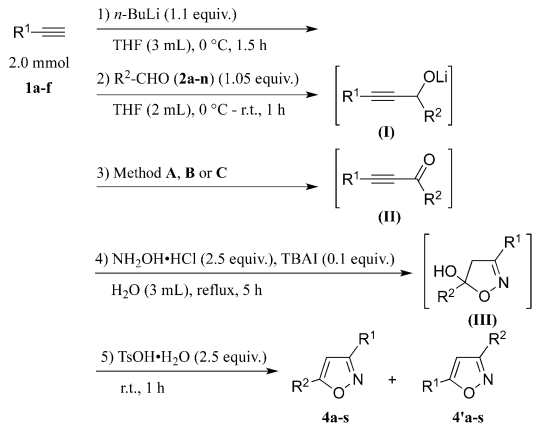
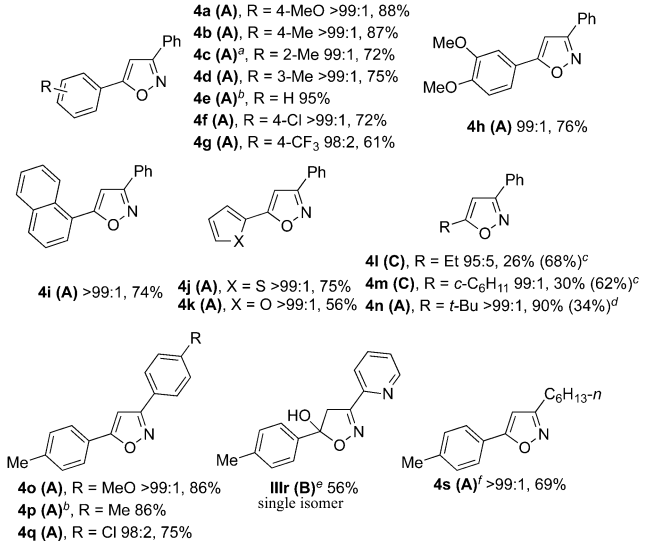
(dimethoxy)benzaldehyde **2h**, 1-naphthaldehyde **2i**, 2-thiophenecarboxaldehyde **2j**, and furfural **2k**, and the subsequent treatment with molecular iodine and K_2CO_3 in *t*-BuOH (Method A) and then hydroxylamine·HCl generated the corresponding 3-phenyl-5-arylisoxazoles **4a**−**4k** in good yields with high regioselectivity, as shown in Table 3. It was found

Table 3. Preparation of 3,5-Disubstituted Isoxazoles 4



Method **A**: evaporation; I_2 (1.6 equiv.), K_2CO_3 (3.0 equiv.), *t*-BuOH (3 mL), reflux, 2 h
Method **B**: evaporation; TEMPO (10 mol%), DIB (1.2 equiv.), DCE (3 mL), r.t., 4 h.
Method **C**: Toluene was used instead of THF at 1st step.
conc. HCl *aq.*, $Fe(NO_3)_3$•$9H_2O$ (10mol%), TEMPO (10 mol%), r.t., 24 h.
Solvent was evaporated before 4th step, and *t*-BuOH (3 mL) was added.

product (Method), **4**:**4'**, yield



[a]Reaction time was 4 h at third step. [b]TBAI, H_2O, and TsOH·H_2O were not added. [c]Overall yield is from isolated ketone (**II**), and the mixture was treated with NH_2OH·HCl (1.1 equiv), K_2CO_3 (0.6 equiv), and TBAI (0.1 equiv) in *t*-BuOH (3 mL) at refluxing conditions for 5 h. Then, TsOH·H_2O (1.0 equiv) was added, and the mixture was stirred at rt for 1 h. [d]THF was not removed. [e]TsOH·H_2O was not added. [f]Reaction time was 18 h at third step.

that intermediates (**III**) were not efficiently dehydrated smoothly and the addition of *p*-TsOH to the reaction mixture at the fifth step at room temperature increased the yields of 3,5-disubstituted isoxazoles. The same treatment of phenylacetylene **1a** with *n*-BuLi in THF at 0 °C, followed by the addition of pivalaldehyde **2n**, and the subsequent treatment I_2 and K_2CO_3 in *t*-BuOH (Method A), and then with hydroxylamine·HCl under refluxing conditions, and finally the treatment with *p*-TsOH at room temperature generated the corresponding 5-*t*-butyl-3-phenylisoxazole **4n** in 90% yield in one pot. On the other hand, the same treatment of phenylacetylene **1a** with *n*-BuLi in THF at 0 °C, followed by the addition of propionaldehyde **2l** and cyclohexanecarboxaldehyde **2m**, and the subsequent treatment with $Fe(NO_3)_3$ in the presence of TEMPO in toluene (Method C) gave *α*-alkynyl ketones (**II**) bearing ethyl and cyclohexyl groups in good yields. Treatment of the isolated alkynyl ketones (**II**) bearing ethyl and cyclohexyl groups with hydroxylamine·HCl under refluxing conditions, followed by treatment with *p*-TsOH at room temperature provided 5-ethyl-3-phenylisoxazole **4l** and 5-cyclohexy-3-phenylisoxazole **4m** in 68 and 62% yields, respectively. In contrast, the one-pot preparation of 5-ethyl-3-phenylisoxazole **4l** and 5-cyclohexy-3-phenylisoxazole **4m** through the oxidation of alkoxide (**I**) to alkynyl ketone (**II**) by $Fe(NO_3)_3$ in the presence of TEMPO (Method C), and the subsequent treatment with hydroxylamine·HCl under refluxing conditions was not effective again, and the yields were 26 and 30%, respectively. The same treatment of 4-methoxyphenylacetylene **1b**, 4-methylphenylacetylene **1c**, 4-chlorophenylacetylene **1d**, 2-pyridylacetylene **1e**, and 1-octyne **1f** with *n*-BuLi in THF at 0 °C, followed by the addition of 4-methylbenzaldehyde **2b**, and the subsequent treatment with molecular iodine and K_2CO_3 in *t*-BuOH (Method A) and then hydroxylamine·HCl under refluxing conditions generated the corresponding 3-aryl-5-(4′-methylphenyl)isoxazoles **4o**−**4q** and 3-hexyl-5-(4′-methylphenyl)isoxazole **4s** in good yields with high regioselectivity. However, 5-(4′-methylphenyl)-3-(2′-pyridyl)isoxazole **4r** was not obtained, and precursor **IIIr** containing a hydroxy group at 5-position, using Method B for oxidation, was obtained in 56% yield. It is known that the aromatic resonance energy of isoxazoles is lower than that of pyrazoles,[48] and therefore, we believe that the formation of isoxazoles through the dehydration of intermediates (**III**) is not efficient. Therefore, the addition of *p*-TsOH to cyclization intermediates (**III**) promoted the dehydration to give isoxazoles smoothly, as shown in Table 3. The structure of 5-(4′-chlorophenyl)-3-phenylisoxazole **4f** was supported by X-ray analysis.

A plausible reaction mechanism for the formation of pyrazoles and isoxazoles is shown in Scheme 2. The formed lithium acetylide reacts with aldehyde to form propargyl secondary alkoxide (**I**), which is further oxidized to *α*-alkynyl ketone (**II**) by molecular iodine in the presence of K_2CO_3 (Method A) mainly, and in some cases, DIB in the presence of TEMPO (Method B) or $Fe(NO_3)_3$ in the presence of TEMPO (Method C). Once *α*-alkynyl ketone (**II**) is formed, it smoothly reacts with hydrazine to provide pyrazole, mainly through the Michael-type addition of hydrazine to *α*-alkynyl ketone (**II**), the 5-*exo*-*trig* cyclization onto the ketone group, and the subsequent dehydration. As a related reaction, treatment of 4-methylphenyl phenylethynyl ketone, *α*-alkynyl ketone, with benzylamine (1.2 equiv) as amine nucleophile, in 1,2-dichloroethane for 11 h at 80 °C gave 2-benzylamino-2-phenylethenyl 4′-methylphenyl ketone, *β*-aminovinyl ketone, in 93% yield. For isoxazoles, *α*-alkynyl ketone (**II**) smoothly reacts with hydroxylamine through the Michael-type addition by hydroxylamine to form *β*-(*N*-hydroxyamino)vinyl ketone (**IV**). Then, the 5-*exo*-*trig* cyclization onto the ketone group and subsequent dehydration occur. The addition of *p*-TsOH at the fifth step promotes the dehydration to form 3,5-disubstituted isoxazoles.

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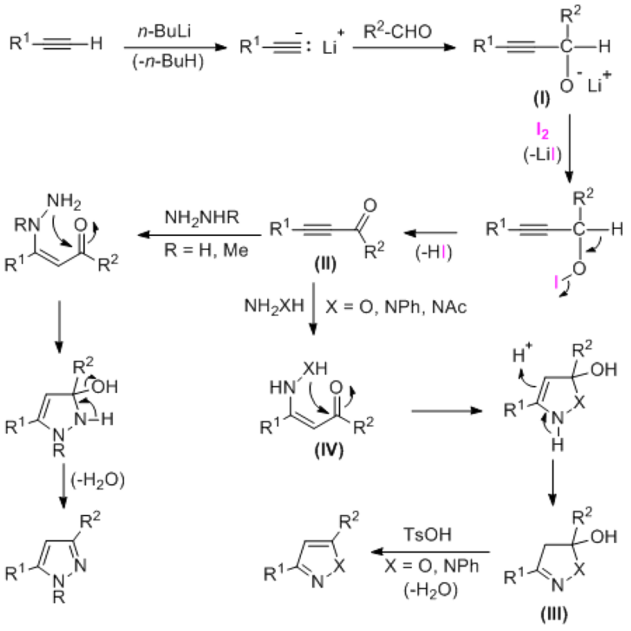
Scheme 2. Plausible Reaction Mechanism



CONCLUSION

3,5-Disubstituted pyrazoles and isoxazoles were prepared in good yields with high regioselectivity in one pot by the treatment of terminal alkynes with aromatic aldehydes, molecular iodine (in some cases, DIB or $Fe(NO_3)_3$ in the presence of TEMPO), and hydrazines, and of terminal alkynes with aromatic aldehydes, molecular iodine (in some cases, DIB or $Fe(NO_3)_3$ in the presence of TEMPO), and hydroxylamine, respectively. The present reaction is a simple and practical method for the preparation of various 1,3-disubstituted pyrazoles and isoxazoles from easily available compounds.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectra were measured on 500 and 400 MHz spectrometers. Chemical shifts were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on 125 and 100 MHz spectrometers. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm). High-resolution mass spectra (HRMS) were measured on orbitrap mass spectrometers. Characteristic peaks in the infrared (IR) spectra were recorded in wave numbers, cm^{-1}. Melting points were uncorrected. Thin-layer chromatography (TLC) was performed using 0.25 mm silica gel plates (60F-254). The products were purified by short column chromatography on silica gel 60 (63−200 mesh).

General Procedure for the Preparation of 3,5-Disubstituted 1*H*-Pyrazoles 3a−3j, 3l−3q, 3s, 3t (with Method A). A solution of *n*-BuLi (1.58 M in hexane, 1.39 mL, 2.2 mmol) was added dropwise to phenylacetylene **1a** (206 mg 2.0 mmol) in THF (3 mL) at 0 °C, and then the mixture was stirred at room temperature for 1.5 h. A solution of 4-methoxybenzaldehyde **2a** (286 mg, 2.1 mmol) in THF (2 mL) was added to the mixture at 0 °C, and the obtained mixture was stirred at room temperature for 2 h. Then, the solvent was removed, and I_2 (812 mg, 3.2 mmol), K_2CO_3 (830 mg, 6.0 mmol), and *t*-BuOH (3 mL) were added to the residue, and the obtained mixture was stirred for 2 h under refluxing conditions. Then, hydrazine monohydrate (194 μL, 4.0 mmol) was added, and the obtained mixture was stirred for 1 h under refluxing conditions. The reaction mixture was quenched with sat. aq. NH_4Cl and was extracted with $CHCl_3$ (3 × 20 mL). The organic layer was washed with brine and dried over Na_2SO_4. Purification by short column chromatography on silica gel (hexane/AcOEt = 2:1) yielded 3-(4′-methoxyphenyl)-5-phenyl-1*H*-pyrazole **3a** (434 mg, 86%).

General Procedure for the Preparation of 3,5-Disubstituted 1*H*-Pyrazoles 3k, 3r (with Method B). A solution of *n*-BuLi (1.58 M in hexane, 1.39 mL, 2.2 mmol) was added dropwise to phenylacetylene **1a** (205 mg 2.0 mmol) in THF (3 mL) at 0 °C, and then the mixture was stirred at room temperature for 1.5 h. A solution of furfural **2k** (202 mg, 2.1 mmol) in THF (2 mL) was added to the mixture at 0 °C, and the obtained mixture was stirred at room temperature for 2 h. Then, the solvent was removed, and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 31 mg, 0.2 mmol), (diacetoxyiodo)benzene (2.4 mmol, 773 mg), and 1,2-dichloroethane (3 mL) were added, and the obtained mixture was stirred for 2 h under refluxing conditions. Then, hydrazine monohydrate (194 μL, 4.0 mmol) was added, and the obtained mixture was stirred for 1 h under refluxing conditions. The reaction mixture was quenched with sat. aq. NH_4Cl and was extracted with $CHCl_3$ (3 × 20 mL). The organic layer was washed with brine and dried over Na_2SO_4. Purification by short column chromatography on silica gel (hexane/AcOEt = 2:1) yielded 3-(2′-furyl)-5-phenyl-1*H*-pyrazole **3k** (320 mg, 76%).

General Procedure for the Praparation of Substituted 1*H*-Pyrazoles 3l, 3m (with Method C). A solution of *n*-BuLi (1.58 M in hexane, 1.39 mL, 2.2 mmol) was added dropwise to phenylacetylene **1a** (204 mg 2.0 mmol) in toluene (3 mL) at 0 °C, and then the mixture was stirred at room temperature for 1.5 h. Propionaldehyde **2l** (151 μL, 2.1 mmol) was added to the mixture at 0 °C, and the obtained mixture was stirred at room temperature for 1 h. Then, conc. HCl aq. was added until the solution became acidic, and then $Fe(NO_3)_3{\cdot}9H_2O$ (81 mg, 0.2 mmol) and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 31 mg, 0.2 mmol) were added, and the obtained mixture was stirred for 24 h at room temperature. Then, the solvent was removed, and then hydrazine monohydrate (194 μL, 4.0 mmol) and *t*-BuOH (3 mL) were added, and the obtained mixture was stirred for 1 h under refluxing conditions. The reaction mixture was quenched with 4 M HCl aq. and was extracted with $CHCl_3$ (3 × 20 mL). The organic layer was washed with brine and dried over Na_2SO_4. Purification by short column chromatography on silica gel (hexane/AcOEt = 2:1) yielded 3-ethyl-5-phenyl-1*H*-pyrazole **3l** (104 mg, 30%).

3-(4′-Methoxyphenyl)-5-phenyl-1*H*-pyrazole (3a). White solid (434 mg, 86% yield): mp 165−166 °C (lit.,[49] mp 156−158 °C); IR (ATR) 3135, 2914, 1619, 1508, 1460, 1297, 1253, 1187 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.81 (s, 3H), 6.73 (s, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 7.37 (t, J = 7.2 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.71 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 55.3, 99.4, 114.2, 123.9, 125.6, 126.9, 128.1, 128.8, 131.5, 159.6; HRMS (ESI) Calcd for $C_{16}H_{15}ON_2$ $(M + H)^+$ 251.1179, found 251.1172.

3-(4′-Methylphenyl)-5-phenyl-1*H*-pyrazole (3b). White solid (469 mg, >99% yield): mp 177−178 °C (lit.,[49] mp 170−172 °C); IR (ATR) 3134, 2908, 1605, 1508, 1457, 1307, 1268, 1175 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.39 (s, 3H), 6.82 (s, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.2 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.3, 99.9, 125.5, 125.6 128.2, 128.8, 129.6, 138.3; HRMS (ESI) Calcd for $C_{16}H_{15}N_2$ $(M + H)^+$ 235.1230, found 235.1225.

3-(2′-Methylphenyl)-5-phenyl-1*H*-pyrazole (3c). White solid (350 mg, 75% yield): mp 104−105 °C; IR (ATR) 3206, 3019, 1572, 1492, 1457, 1308, 1259, 1176 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.44 (s, 3H), 6.69 (s, 1H), 7.17−7.23 (m, 1H), 7.24−7.28 (m, 2H), 7.31 (t, J = 7.2 Hz, 1H), 7.37 (t, J = 7.2 Hz, 2H), 7.43 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.8, 103.0, 125.6, 126.0, 128.0, 128.5, 128.7, 128.9, 130.9, 136.0; HRMS (ESI) Calcd for $C_{16}H_{15}N_2$ $(M + H)^+$ 235.1230, found 235.1228.

3-(3′-Methylphenyl)-5-phenyl-1*H*-pyrazole (3d). White solid (356 mg, 76% yield): mp 141−142 °C(lit.,[50] mp 120−124 °C); IR (ATR) 3204, 3030, 1566, 1457, 1293, 1268, 1162 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.38 (s, 3H), 6.84 (s, 1H), 7.16 (d, J = 7.7 Hz, 1H), 7.27−7.36 (m, 2H), 7.39−7.44 (m, 2H), 7.52 (d, J = 7.7 Hz,

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1H), 7.55 (s, 1H), 7.75 (d, J = 7.7 Hz, 2H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.3, 99.7, 122.7, 125.5, 126.2, 127.7, 128.5, 128.6, 131.0, 131.3, 138.2, 148.6; HRMS (ESI) Calcd for $C_{16}H_{15}N_2$ $(M + H)^+$ 235.1230, found 235.1227.

3,5-Diphenyl-1*H*-pyrazole (3e, Commercially Available). White solid (388 mg, 88% yield): mp 196−197 °C (lit.,[49] mp 197−199 °C).

3-(4′-Chlorophenyl)-5-phenyl-1*H*-pyrazole (3f). White solid (466 mg, 91% yield): mp 203−204 °C (lit.,[49] mp 214−215 °C); IR (ATR) 3141, 2923, 1733, 1567, 1456, 1308, 1270, 1184 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.81 (s, 1H), 7.35−7.39 (m, 3H), 7.43 (t, J = 7.5 Hz, 2H), 7.66−7.70 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 101.0, 126.0, 127.8, 129.1, 129.4, 129.9, 130.1, 133.4, 147.1, 147.2; HRMS (ESI) Calcd for $C_{15}H_{12}N_2Cl$ $(M + H)^+$ 255.0684, found 255.0678.

3-(4′-Trifluoromethylphenyl)-5-phenyl-1*H*-pyrazole (3g). White solid (395 mg, 68% yield): mp 225−226 °C (lit.,[51] mp 226 °C).

3-(3′,4′-Dimethoxyphenyl)-5-phenyl-1*H*-pyrazole (3h). White solid (456 mg, 81% yield): mp 143−144 °C; IR (ATR) 3251, 2972, 1590, 1466, 1253, 1237, 1140 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.71 (s, 3H), 3.87 (s, 3H), 6.68 (s, 1H), 6.78 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 8.2 Hz, 1H), 7.22 (s, 1H), 7.25−7.32 (m, 3H), 7.64 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 55.2, 55.7, 98.8, 108.4, 111.0, 118.0, 125.3, 127.7, 128.5, 131.1, 148.7, 148.8; HRMS (ESI) Calcd for $C_{17}H_{17}O_2N_2$ $(M + H)^+$ 281.1285, found 281.1279.

3-(1′-Naphthyl)-5-phenyl-1*H*-pyrazole (3i). White solid (411 mg, 76% yield): mp 145−146 °C(lit.,[49] mp 140−142 °C).

5-Phenyl-3-(2′-thienyl)-1*H*-pyrazole (3j). White solid (377 mg, 83% yield): mp 184−185 °C (lit.,[49] mp 187−188 °C).

3-(2′-Furyl)-5-phenyl-1*H*-pyrazole (3k). White solid (320 mg, 76% yield): mp 173−174 °C (lit.,[49] mp 170−172 °C).

3-Ethyl-5-phenyl-1*H*-pyrazole (3l). White solid (104 mg, 30% yield): mp 80−81 °C (lit.,[52] mp 82.5 °C).

3-Cyclohexyl-5-phenyl-1*H*-pyrazole (3m). White solid (192 mg, 42% yield): mp 138 °C (lit.,[49] mp 135−137 °C).

3-(*tert*-Butyl)-5-phenyl-1*H*-pyrazole (3n). White solid (286 mg, 71% yield): mp 118−119 °C (lit.,[53] mp 119−120 °C).

5-(4′-Methoxyphenyl)-3-(4″-methylphenyl)-1*H*-pyrazole (3o). White solid (443 mg, 83% yield): mp 167−168 °C (lit.,[54] mp 170 °C).

3,5-Di(4′-methylphenyl)-1*H*-pyrazole (3p). White solid (469 mg, 94% yield): mp 220−221 °C (lit.,[55] mp 221−223 °C).

5-(4′-Chlorophenyl)-3-(4″-methylphenyl)-1*H*-pyrazole (3q). White solid (412 mg, 76% yield): mp 223−224 °C (lit.,[51] mp 209 °C); IR (ATR) 3111, 2855, 1491, 1385, 1304, 1721, 1172 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.40 (s, 3H), 6.79 (s, 1H), 7.26 (d, J = 7.8 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 7.8 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 20.8, 99.5, 125.0, 126.7, 128.6, 129.5; HRMS (ESI) Calcd for $C_{16}H_{14}N_2Cl$ $(M + H)^+$ 269.0840, found 269.0840.

3-(4′-Methylphenyl)-5-(2″-pyridyl)-1*H*-pyrazole (3r). White solid (320 mg, 68% yield): mp 169 °C; IR (ATR) 3217, 3042, 1597, 1565, 1454, 1313, 1296, 1177 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.39 (s, 3H), 7.04 (s, 1H), 7.22−7.26 (m, 3H), 7.74−7.77 (m, 4H), 8.69 (td, J = 4.9, 1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.3, 100.2, 120.1, 122.9, 125.5, 129.4, 137.0, 137.8, 149.4; HRMS (ESI) Calcd for $C_{15}H_{14}N_3$ $(M + H)^+$ 236.1182, found 236.1179.

5-Hexyl-3-(4′-methylphenyl)-1*H*-pyrazole (3s). White solid (377 mg, 77% yield): mp 81−82 °C; IR (ATR) 3239, 2926, 2854, 1566, 1530, 1446, 1377, 1263, 1110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.87 (t, J = 7.0 Hz, 3H), 1.22−1.36 (m, 6H), 1.61 (quin, J = 7.7 Hz, 2H), 2.35 (s, 3H), 2.58 (t, J = 7.7 Hz, 2H), 6.30 (s, 1H), 7.16 (d, J = 7.9 Hz, 2H), 7.60 (d, J = 7.9 Hz, 2H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.0, 21.2, 22.5, 26.5, 29.0, 29.2, 31.6, 100,6, 125.6, 129.3, 137.4; HRMS (ESI) Calcd for $C_{16}H_{23}N_2$ $(M + H)^+$ 243.1856, found 243.1854.

General Procedure for the Prepration of 3,5-Disubstituted 1-Methylpyrazole 5 (with Method A). A solution of *n*-BuLi (1.58 M in hexane, 1.39 mL, 2.2 mmol) was added dropwise to phenylacetylene **1a** (206 mg 2.0 mmol) in THF (3 mL) at 0 °C, and then the mixture was stirred at room temperature for 1.5 h. A solution of 4-methylbenzaldehyde **2b** (252 mg, 2.1 mmol) in THF (2 mL) was added to the mixture at 0 °C, and the obtained mixture was stirred at room temperature for 2 h. Then, the solvent was removed, and I_2 (812 mg, 3.2 mmol), K_2CO_3 (830 mg, 6.0 mmol), and *t*-BuOH (3 mL) were added, and the obtained mixture was stirred for 2 h under refluxing conditions. Then, methylhydrazine (209 μL, 4.0 mmol) was added, and the obtained mixture was stirred for 1 h under refluxing conditions. The reaction mixture was quenched with sat. aq. NH_4Cl and was extracted with $CHCl_3$ (3 × 20 mL). The organic layer was washed with brine and dried over Na_2SO_4. Purification by short column chromatography on silica gel (hexane/$CHCl_3$ = 1:1) yielded 1-methyl-3-(4′-methylphenyl)-5-phenyl-1*H*-pyrazole **5** (449 mg, 90%).

1-Methyl-3-(4′-methylphenyl)-5-phenyl-1*H*-pyrazole (5).[56] White solid (449 mg, 90% yield): mp 131−132 °C; IR (ATR) 3335, 2973, 2915, 1526, 1484, 1437, 1089, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.37 (s, 3H), 3.91 (s, 3H), 6.57 (s, 1H), 7.21 (d, J = 7.9 Hz, 2H), 7.39−7.48 (m, 5H), 7.72 (d, J = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.2, 37.5, 103.0, 125.4, 128.5, 128.6, 128.7, 129.3, 130.7, 137.3, 144.9, 150.5; HRMS (ESI) Calcd for $C_{17}H_{17}N_2$ $(M + H)^+$ 249.1386, found 249.1385.

General Procedure for the Preparation of 3,5-Disubstituted 1-Phenylpyrazole 6 (with Method A). A solution of *n*-BuLi (1.58 M in hexane, 1.39 mL, 2.2 mmol) was added dropwise to phenylacetylene **1a** (205 mg 2.0 mmol) in THF (3 mL) at 0 °C, and then the mixture was stirred at room temperature for 1.5 h. A solution of 4-methylbenzaldehyde **2b** (252 mg, 2.1 mmol) in THF (2 mL) was added to the mixture at 0 °C, and the obtained mixture was stirred at room temperature for 2 h. Then, the solvent was removed, and I_2 (812 mg, 3.2 mmol), K_2CO_3 (830 mg, 6.0 mmol), and *t*-BuOH (3 mL) were added, and the obtained mixture was stirred for 2 h under refluxing conditions. Then, phenylhydrazine (394 μL, 4.0 mmol), tetrabutylammonium iodide (74 mg, 0.2 mmol), and H_2O (3 mL) were added, and the obtained mixture was stirred for 5 h under refluxing conditions. Then, *p*-toluenesulfonic acid monohydrate (951 mg, 5.0 mmol) was added, and the obtained mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with sat. aq. Na_2SO_3 and was extracted with $CHCl_3$ (3 × 20 mL). The organic layer was washed with brine and dried over Na_2SO_4. Purification by short column chromatography on silica gel (hexane/$CHCl_3$ = 1:1) yielded 5-(4′-methylphenyl)-1,3-diphenyl-1*H*-pyrazole **6** (558 mg, 89%).

5-(4′-Methylphenyl)-1,3-diphenyl-1*H*-pyrazole (6). White solid (558 mg, 89% yield): mp 110−111 °C (lit.,[57] mp 174 °C); IR (ATR) 3377, 3057, 2973, 1593, 1493, 1456, 1359, 1175 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.34 (s, 3H), 6.78 (s, 1H), 7.11 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.2 Hz, 4H), 7.26−7.44 (m, 8H), 7.92 (d, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.2, 104.9, 125.3, 125.8, 127.3, 127.6, 127.9, 128.5, 128.6, 128.8, 129.1, 133.1, 138.2, 140.2, 144.4, 151.8; HRMS (ESI) Calcd for $C_{22}H_{19}N_2$ $(M + H)^+$ 311.1543, found 311.1541.

General Procedure for the Preparation of 3,5-Disubstituted 1-Acetylpyrazoline 7 (with Method A). A solution of *n*-BuLi (1.58 M in hexane, 1.39 mL, 2.2 mmol) was added dropwise to phenylacetylene **1a** (206 mg 2.0 mmol) in THF (3 mL) at 0 °C, and then the mixture was stirred at room temperature for 1.5 h. A solution of 4-methylbenzaldehyde **2b** (252 mg, 2.1 mmol) in THF (2 mL) was added to the mixture at 0 °C, and the obtained mixture was stirred at room temperature for 2 h. Then, the solvent was removed, and I_2 (812 mg, 3.2 mmol), K_2CO_3 (830 mg, 6.0 mmol), and *t*-BuOH (3 mL) were added, and the obtained mixture was stirred for 2 h under refluxing conditions. Then, acethydrazide (296 mg, 4.0 mmol) and Et_3N (279 μL, 4.0 mmol) were added, and the obtained mixture was stirred for 5 h at refluxing conditions. The reaction mixture was quenched with sat. aq. Na_2SO_3 and was extracted with $CHCl_3$ (3 × 20 mL). The organic layer was washed with brine and dried over Na_2SO_4. Purification by short column chromatography on silica gel (hexane/$CHCl_3$ = 1:3) yielded 1-acetyl-5-hydroxy-5-(4′-methylphenyl)-3-phenyl-1*H*-pyrazoline **7** (423 mg, 71%).

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1-Acetyl-5-hydroxy-5-(4′-methylphenyl)-3-phenyl-1*H*-pyrazoline (7). White solid (423 mg, 71% yield): mp 133−134 °C; IR (ATR) 3374, 2974, 1650, 1600, 1434, 1360, 1329, 1243, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.33 (s, 3H), 2.43 (s, 3H), 3.35 (d, J = 18.3 Hz, 1H), 3.69 (d, J = 18.3 Hz, 1H), 5.07 (s, 1H), 7.17 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 7.38−7.43 (m, 3H), 7.68−7.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ =21.0, 22.3, 50.5, 93.8, 123.7, 126.5, 128.7, 129.4, 130.4, 131.1, 137.8, 140.9, 152.6, 170.8; HRMS (ESI) Calcd for $C_{18}H_{19}O_2N_2$ $(M + H)^+$ 295.1441, found 295.1441.

General Procedure for the Preparation of 3,5-Disubstituted Isoxazoles 4a−4q, 4s, 4t (with Method A). A solution of *n*-BuLi (1.58 M in hexane, 1.39 mL, 2.2 mmol) was added dropwise to phenylacetylene **1a** (204 mg 2.0 mmol) in THF (3 mL) at 0 °C, and then the mixture was stirred at room temperature for 1.5 h. A solution of 4-methoxybenzaldehyde **2a** (286 mg, 2.1 mmol) in THF (2 mL) was added to the mixture at 0 °C, and the obtained mixture was stirred at room temperature for 2 h. Then, the solvent was removed, and I_2 (812 mg, 3.2 mmol), K_2CO_3 (830 mg, 6.0 mmol), and *t*-BuOH (3 mL) were added, and the obtained mixture was stirred for 2 h under refluxing conditions. Then, hydroxylamine hydrochloride (348 mg, 5.0 mmol), tetrabutylammonium iodide (74 mg, 0.2 mmol), and H_2O (3 mL) were added, and the obtained mixture was stirred for 5 h under refluxing conditions. Then, *p*-toluenesulfonic acid monohydrate (951 mg, 5.0 mmol) was added, and the obtained mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with sat. aq. Na_2SO_3 and was extracted with $CHCl_3$ (3 × 20 mL). The organic layer was washed with brine and dried over Na_2SO_4. Purification by short column chromatography on silica gel (hexane/$CHCl_3$ = 1:1) yielded 5-(4′-methoxyphenyl)-3-phenylisoxazole **4a** (441 mg, 88%).

General Procedure for the Preparation of 3,5-Disubstituted Isoxazoline IIIr (with Method B). A solution of *n*-BuLi (1.58 M in hexane, 1.39 mL, 2.2 mmol) was added dropwise to 2-pyridylacetylene **1e** (207 mg 2.0 mmol) in THF (3 mL) at 0 °C, and then the mixture was stirred at room temperature for 1.5 h. A solution of 4-methylbenzaldehyde **2b** (252 mg, 2.1 mmol) in THF (2 mL) was added to the mixture at 0 °C, and the obtained mixture was stirred at room temperature for 2 h. Then, the solvent was removed, and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 31 mg, 0.2 mmol), (diacetoxyiodo)benzene (2.4 mmol, 773 mg), and 1,2-dichloroethane (3 mL) were added, and the obtained mixture was stirred for 2 h under refluxing conditions. Then, hydroxylamine hydrochloride (348 mg, 5.0 mmol), tetrabutylammonium iodide (74 mg, 0.2 mmol), and H_2O (3 mL) were added, and the obtained mixture was stirred for 5 h under refluxing conditions. The reaction mixture was quenched with sat. aq. Na_2SO_3 and was extracted with $CHCl_3$ (3 × 20 mL). The organic layer was washed with brine and dried over Na_2SO_4. Purification by short column chromatography on silica gel (hexane/EtOAc = 4:1) yielded 5-hydroxy-5-(4′-methylphenyl)-3-(2′-pyridyl)-1*H*-pyrazole **IIIr** (285 mg, 56%).

General Procedure for the Synthesis of Substituted Isoxazoles 4l, 4m (with Method C). A solution of *n*-BuLi (1.58 M in hexane, 1.39 mL, 2.2 mmol) was added dropwise to phenylacetylene **1a** (204 mg 2.0 mmol) in toluene (3 mL) at 0 °C, and then the mixture was stirred at room temperature for 1.5 h. Propionaldehyde **2l** (151 μL, 2.1 mmol) was added to the mixture at 0 °C, and the obtained mixture was stirred at room temperature for 1 h. Then, conc. HCl aq. was added until the solution became acidic, and then $Fe(NO_3)_3{\cdot}9H_2O$ (81 mg, 0.2 mmol) and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 31 mg, 0.2 mmol) were added, and the obtained mixture was stirred for 24 h at room temperature. Then, the solvent was removed. Hydroxylamine hydrochloride (348 mg, 5.0 mmol), tetrabutylammonium iodide (74 mg, 0.2 mmol), *t*-BuOH (3 mL), and H_2O (3 mL) were added, and the obtained mixture was stirred for 5 h under refluxing conditions. Then, *p*-toluenesulfonic acid monohydrate (951 mg, 5.0 mmol) was added, and the obtained mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with 4 M HCl aq. and was extracted with $CHCl_3$ (3 × 20 mL). The organic layer was washed with brine and dried over Na_2SO_4. Purification by short column chromatography on silica gel (hexane/$CHCl_3$ = 1:1) yielded 5-ethyl-3-phenylisoxazole **4l** (91 mg, 26%).

5-(4′-Methoxyphenyl)-3-phenylisoxazole (4a). White solid (410 mg, 87% yield): mp 124 °C (lit.,[58] mp 126−127 °C)

5-(4′-Methylphenyl)-3-phenylisoxazole (4b). White solid (441 mg, 88% yield): mp 135 °C (lit.,[58] mp 135−136 °C).

5-(2′-Methylphenyl)-3-phenylisoxazole (4c). White solid (342 mg, 72% yield): mp 38−39 °C; IR (ATR) 3053, 1566, 1490, 1399, 1232 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 2.54 (s, 3H), 6.70 (s, 1H), 7.28−7.36 (m, 3H), 7.42−7.48 (m, 3H), 7.74 (d, J = 7.5 Hz, 1H), 7.87 (d, J = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.4, 100.5, 126.2, 126.8, 127.0, 128.4, 128.9, 129.1, 129.9, 130.0, 131.3, 136.2, 162.6, 170.5; HRMS (ESI) Calcd for $C_{16}H_{14}ON$ $(M + H)^+$ 236.1070, found 236.1068.

5-(3′-Methylphenyl)-3-phenylisoxazole (4d). White solid (354 mg, 75% yield): mp 111−112 °C; IR (ATR) 3109, 1587, 1490, 1462, 1397, 1084 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 2.43 (s, 3H), 6.81 (s, 1H), 7.26 (d, J = 7.7 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.44−7.50 (m, 3H), 7.64 (d, J = 7.7 Hz, 1H), 7.66 (s, 1H), 7.85−7.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.4, 97.3, 123.0, 126.4, 126.8, 127.3, 128.9 (2C), 129.2, 130.0, 131.0, 138.8, 162.9, 170.6; HRMS (ESI) Calcd for $C_{16}H_{14}ON$ $(M + H)^+$ 236.1070, found 236.1069.

3,5-Diphenylisoxazole (4e, Commercially Available). White solid (420 mg, 95% yield): mp 138−139 °C (lit.,[58] mp 140−141 °C).

5-(4′-Chlorophenyl)-3-phenylisoxazole (4f). White solid (369 mg, 72% yield): mp 175−177 °C (lit.,[58] mp 177−179 °C).

5-(4′-Trifluoromethylphenyl)-3-phenylisoxazole (4g). White solid (356 mg, 61% yield): mp 184−185 °C; IR (ATR) 3110, 1600, 1465, 1394, 1320, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 6.94 (s, 1H), 7.47−7.52 (m, 3H), 7.76 (d, J = 8.3 Hz, 2H), 7.85−7.89 (m, 2H), 7.96 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 79.0, 123.8 (q. J_{C-F} = 272.3 Hz), 126.1, 126.2, 126.8, 128.9, 129.0, 130.2, 130.7, 132.1 (q, J_{C-F} = 33.6 Hz), 163.2, 168.9; HRMS (ESI) Calcd for $C_{16}H_{11}ONF_3$ $(M + H)^+$ 290.0787, found 290.0795.

5-(3′,4′-Dimethoxyphenyl)-3-phenylisoxazole (4h). White solid (428 mg, 76% yield): mp 106−107 °C (lit.,[59] mp 90 °C); IR (ATR) 3126, 1605, 1505, 1468, 1399, 1251 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 3.94 (s, 3H), 3.97 (s, 3H), 6.73 (s, 1H), 6.95 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.42 (dd, J = 8.3, 2.0 Hz, 1H), 7.45−7.50 (m, 3H), 7.85−7.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 55.9, 56.0, 96.4, 108.6, 111.2, 119.1, 120.4, 126.8, 128.9, 129.2, 129.4, 149.2, 150.7, 163.0, 170.3; HRMS (ESI) Calcd for $C_{17}H_{16}O_3N$ $(M + H)^+$ 282.1125, found 282.1124.

5-(1′-Naphthyl)-3-phenylisoxazole (4i). White solid (405 mg, 74% yield): mp 161−162 °C (lit.,[60] mp 76 °C); IR (ATR) 3107, 1563, 1509, 1457, 1402, 1272 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 6.94 (s, 1H), 7.46−7.52 (m, 3H), 7.55 (dt, J = 9.5, 3.2 Hz, 2H), 7.86−7.95 (m, 6H), 8.36 (d, J = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 97.8, 122.9, 124.7, 125.6, 126.8, 126.9, 127.3, 127.8, 128.7, 128.8, 128.9, 129.1, 130.0, 133.0, 133.9, 163.1, 170.4; HRMS (ESI) Calcd for $C_{19}H_{14}ON$ $(M + H)^+$ 272.1070, found 272.1068.

3-Phenyl-5-(2′-thienyl)isoxazole (4j). White solid (340 mg, 75% yield): mp 93−94 °C (lit.,[61] mp 95−96 °C).

5-(2′-Furyl)-3-phenylisoxazole (4k). White solid (238 mg, 56% yield): mp 76 °C (lit.,[11] mp 76−77 °C).

5-Ethyl-3-phenylisoxazole (4l).[62] Colorless oil (91 mg, 26% yield): IR (ATR) 2978, 1601, 1578, 1471 1442, 1407, 1232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.35 (t, J = 7.4 Hz, 3H), 2.83 (t, J = 7.4 Hz, 2H), 6.29 (s, 1H), 7.41−7.48 (m, 3H), 7.76−7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.7, 20.2, 98.1, 126.7, 128.8, 129.4, 129.7, 162.3, 175.3; HRMS (ESI) Calcd for $C_{11}H_{12}ON$ $(M + H)^+$ 174.0913, found 174.0913.

5-Cyclohexyl-3-phenylisoxazole (4m). White solid (137 mg, 30% yield): mp 73−74 °C; IR (ATR) 2923, 1595, 1578, 1471, 1440, 1405, 1309 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 1.24−1.55 (m, 5H), 1.71−1.77 (m, 1H), 1.80−1.87 (m. 2H), 2.07−2.14 (m, 2H), 2.82 (tt, J = 11.2, 3.5 Hz, 1H), 6.25 (s, 1H), 7.40−7.46 (m, 3H), 7.78−7.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.7, 25.8, 31.2, 36.4, 97.0, 126.7, 128.8, 129.5, 129.7, 162.1, 178.4; HRMS (ESI) Calcd for $C_{15}H_{18}ON$ $(M + H)^+$ 228.1383, found 228.1381.

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5-(*tert*-Butyl)-3-phenylisoxazole (4n). White solid (361 mg, 90% yield): mp 49−50 °C (lit.,[63] mp 41 °C); IR (ATR) 2971, 1594, 1576, 1465, 1438, 1402, 1275 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 1.40 (s, 9H), 6.25 (s, 1H), 7.40−7.46 (m, 3H), 7.78−7.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 28.9, 32.8, 96.4, 126.7, 128.8, 129.5, 129.7, 162.1, 181.7; HRMS (ESI) Calcd for $C_{13}H_{16}ON$ $(M + H)^+$ 202.1226, found 202.1226.

3-(4′-Methoxyphenyl)-5-(4″-methylphenyl)isoxazole (4o). White solid (456 mg, 86% yield): mp 149 °C (lit.,[64] mp 150−150.5 °C).

3,5-Di(4′-methylphenyl)isoxazole (4p). White solid (431 mg, 86% yield): mp 149−150 °C (lit., mp 152−152.5 °C).

3-(4′-Chlorophenyl)-5-(4″-methylphenyl)isoxazole (4q). White solid (407 mg, 75% yield): mp 193−194 °C (lit., mp 199.5−200 °C); IR (ATR) 3111, 1601, 1497, 1428, 1379, 1262, 1093 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 2.42 (s, 3H), 6.74 (s, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.5, 96.7, 124.6, 125.8, 127.7, 128.0, 129.2, 129.7, 135.9, 140.7, 161.9, 170.9; HRMS (ESI) Calcd for $C_{16}H_{13}ONCl$ $(M + H)^+$ 270.0680, found 270.0681.

5-Hydroxy-5-(4′-methylphenyl)-3-(2″-pyridyl)isoxazoline (IIIr). White solid (285 mg, 56% yield): mp 123−124 °C; IR (ATR) 3198, 1573, 1476, 1443, 1286, 1179 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.36 (s, 3H), 3.56 (d, J = 18.3 Hz, 1H), 3.85 (d, J = 18.3 Hz, 1H), 4.21 (s, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.28 (ddd, J = 7.8, 5.0, 1.1 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.72 (td, J = 7.8, 1.8 Hz, 1H), 8.03 (dt, J = 7.8, 1.1 Hz, 1H), 8.55 (dd, J = 5.0, 1.8 Hz, 1H), ; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.1, 48.2, 108.6, 121.7, 124.4, 125.5, 129.1, 136.5, 137.7, 138.6, 149.0, 149.2, 159.0; HRMS (ESI) Calcd for $C_{15}H_{15}O_2N_2$ $(M + H)^+$ 255.1128, found 255.1127.

3-Hexyl-5-(4′-methylphenyl)isoxazole (4s). White solid (335 mg, 69% yield): mp 38 °C; IR (ATR) 2927, 1602, 1516, 1468, 1421, 1421, 1264 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 0.89 (t, J = 7.0 Hz, 3H), 1.29−1.35 (m, 4H), 1.36−1.42 (m, 2H), 1.70 (quin, J = 7.7 Hz, 2H), 2.38 (s, 3H), 2.69 (t, J = 7.7 Hz, 2H), 6.31 (s, 1H), 7.24 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H),; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.0, 21.4, 22.5, 26.1, 28.3, 28.9, 31.5, 98.5, 125.0, 125.6, 129.5, 140.1, 164.7, 169.6; HRMS (ESI) Calcd for $C_{16}H_{22}ON$ $(M + H)^+$ 244.1696, found 244.1695.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H NMR and ^{13}C NMR spectra of all pyrazoles and isoxazoles, and X-ray analysis data of pyrazoles **6** and **7**, and isoxazole **4f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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