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One-Pot Synthesis of 4-Heteroaryl-Substituted Pyrazoles: A Gold-Catalyzed Oxidation/1,2-Heteroaryl Migration Cascade Constitutes the Key Step

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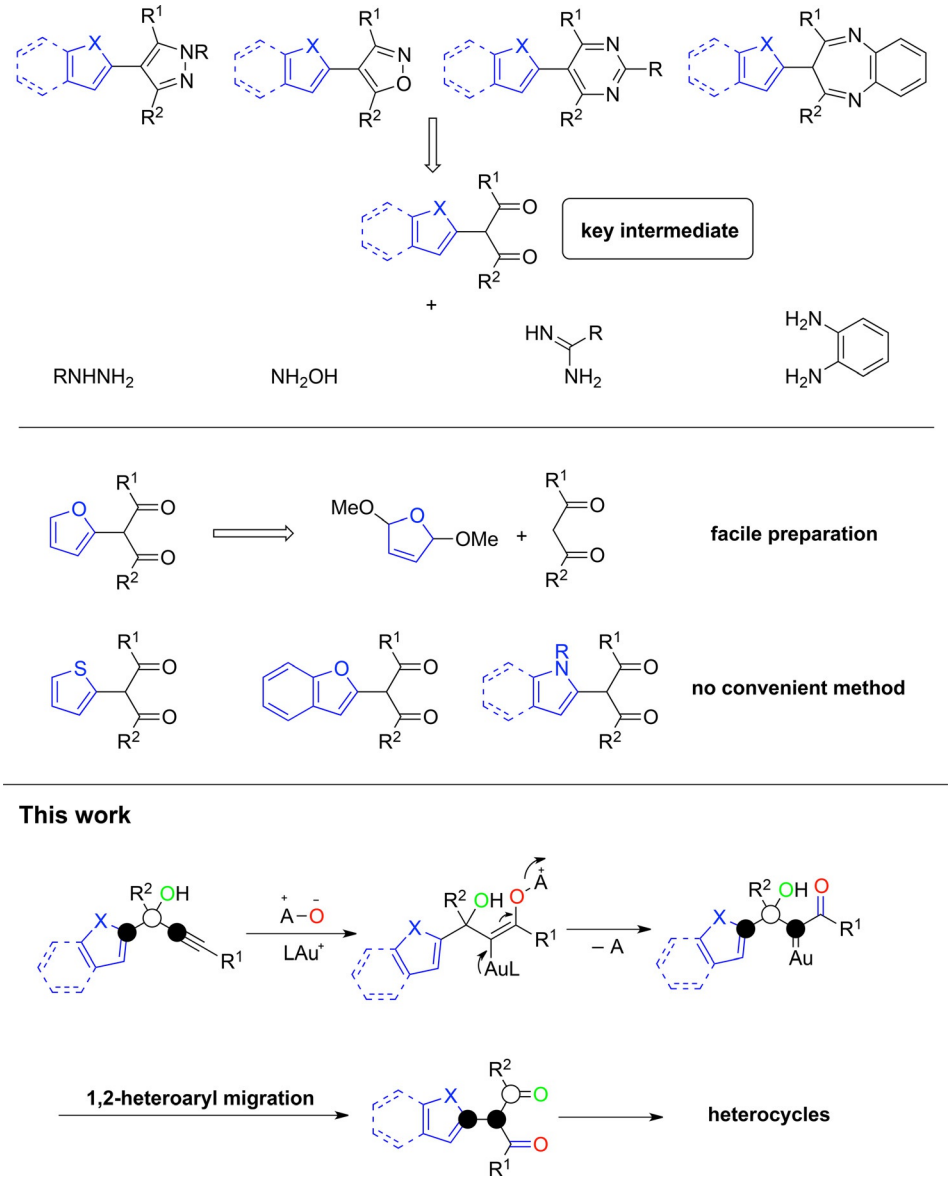
Abstract: An efficient gold-catalyzed oxidation/1,2-heteroaryl migration cascade leading to 2-heteroaryl-substituted 1,3-diketones and its further application in the one-pot synthesis of 4-heteroaryl-substituted pyrazoles and the preparation of 4-heteroaryl-substituted isoxazoles are reported. A wide variety of 4-heteroaryl-substituted pyrazoles were obtained, indicating the broad substrate scope and functional group tolerance of this method.

Keywords: 1,3-diketones; gold carbenes; gold catalysis; heterocycles; pyrazoles

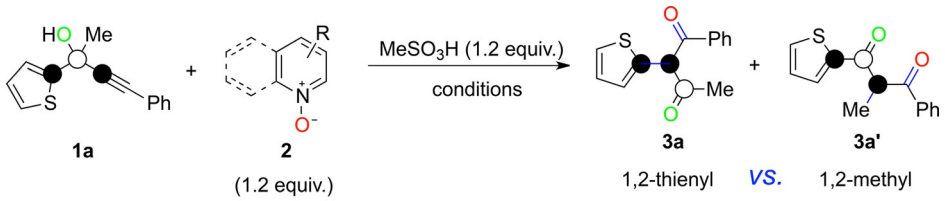
Heterocycles are widely found in bioactive natural products and pharmaceuticals,[1] for example the drugs Celebrex, Rimonabant, Sulfisoxazole and Viagra. Generally, the installation of a heteroaromatic group on a heterocyclic ring may change its biological activity dramatically. A commonly used approach for the preparation of heteroaryl-substituted heterocycles such as 4-heteroaryl-substituted pyrazoles and isoxazoles, 5-heteroaryl-substituted pyrimidines and 3-heteroaryl-substituted-3*H*-benzo[*b*][1,4]diazepines is the condensation of α-heteroaryl-substitituted 1,3-diketones with additional reagents like hydrazine, hydroxylamine, guanidine and *o*-diaminobenzene (Scheme 1, above). The α-furyl-substituted 1,3-diketone is relatively easy to obtain from a 1,3-diketone and 2,5-dihydro-2,5-dimethoxyfuran (DHDMF),[2] however no convenient method is available for the preparation of α-thienyl, α-benzofuryl and α-pyrrolyl-substituted 1,3-diketones (Scheme 1, *middle*). For example, one method for the synthesis of these compounds is the cross-coupling of heteroaryl-lead triacetate compounds with 1,3-diketones.[3] However, multi-step synthesis is required for the preparation of heteroaryl-lead triacetate compounds. In addition, the high toxicity of lead also limits the use of this method. The other choice is the conversion of 4-heteroaryl-3,5-dimethylisoxazoles to α-heteroaryl-substitituted 1,3-diketones *via* hydrogenolysis followed by acid hydrolysis.[4] However, as the starting material, 4-heteroaryl-3,5-dimethylisoxazoles have to be prepared in advance *via* multistep synthesis. The reaction of a heteroaryl ring with a carbene precursor is also a potent approach.[5] However, only the reaction of trisheteroarylmethanes with diazo compounds was successfully achieved. Fortunately, the impact of homogeneous gold catalysis on organic synthesis in the last 15 years has been significant.[6] The spectacular development of the α-oxo gold carbene chemistry[7,8] provides an opportunity for the facile synthesis of α-heteroaryl-substitituted 1,3-diketones. Since its first report by Zhang,[9] the reaction of a pyridine *N*-oxide or quinoline *N*-oxide with an alkyne in the presence of a gold catalyst has become a very useful strategy for the generation of an α-oxo gold carbene intermediate (Scheme 1, *bottom*). Based on this strategy, lots of useful transformations have been achieved. Herein, we report an efficient method for the preparation of α-heteroaryl-substituted 1,3-diketones *via* a gold-catalyzed oxidation/1,2-heteroaryl migration cascade from readily accessible propargyl alcohols and its further application in the one-pot synthesis of pyrazoles and isoxazoles (Scheme 1, *bottom*). As a key step, for the first time a highly selective 1,2-heteroaryl migration of a gold-carbene intermediate is presented, previous reports[10] only reported 1,2-migrations of aromatic groups,[11] hydride,[12] alkyl,[13] alkynyl groups[10b,c,d,14] and alkenyl groups.[15]



Scheme 1. Known routes to α-heteroaryl-substituted 1,3-diketones and the new route.

Propargyl alcohol **1a** was prepared facilely by treating phenylacetylene with *n*-butyllithium and the following one-pot addition of 1-(thiophen-2-yl)ethanone. In our initial study, **1a** was treated with 4-methylpyridine *N*-oxide (**2a**) and methanesulfonic acid in the presence of IPrAuCl/$AgNTf_2$ [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, Tf = trifluoromethylsulfonyl] at room temperature (Table 1, entry 1). According to literature,[7c] acid was added to remove the pyridine by-product so that it would not deactivate the gold catalyst. The pyridine *N*-oxide played not only the role of an oxidant, but also buffers the acidity of the reaction considering the instability of the tertiary alcohol under the acidic conditions. To our delight, a 1,2-thienyl migration product **3a** was obtained with high selectivity over the also conceivable 1,2-methyl migration product **3a′**. Encouraged by this result, we started to optimize the reaction conditions. First the *N*-oxides were varied (Table 1, entries 1–5). The electron-deficient pyridine *N*-oxide (**2b**; entry 2) as well as a pyridine *N*-oxide with large steric hindrance (**2c**; entry 3) reacted with **1a** just gave trace amount of 1,3-diketone **3a**. Fortunately, 8-methylquinoline 1-oxide (**2e**) afforded **3a** in high yield (87%) with high chemoselectivity (>20:1). The control experiment revealed that methanesulfonic acid was essential for this reaction (entry 6). In the next step, various catalysts were examined (Table 1, entries 7–11) by the use of 8-methylquinoline 1-oxide (**2e**) as oxygen-transfer reagent. Among the tested catalysts, (2,4-*t*-Bu-$C_6H_3O)_3$PAuCl together with $AgNTf_2$ gave the best result (entry 8). Besides dichloromethane, the

Table 1. Optimization of the reaction conditions for the synthesis of α-thienyl 1,3-diketone.[a]



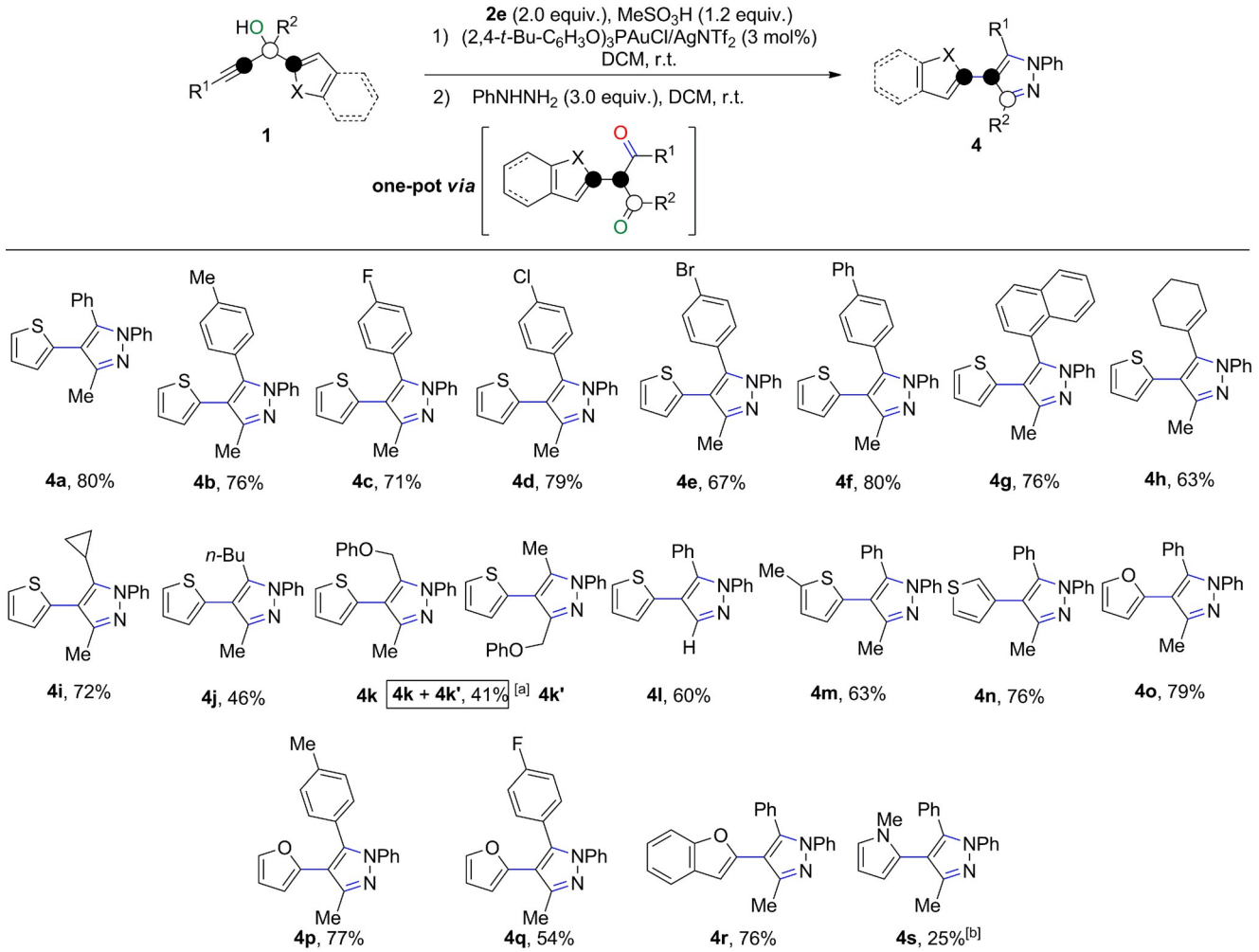
2a (R = 4-Me); **2b** (R = 3,5-Cl_2); **2c** (R = 2,6-Br_2); **2d** (R = H); **2e** (8-methylquinoline 1-oxide)

Entry	*N*-Oxide	Catalyst	Solvent/Time	Yield of **3a** [%][b]	**3a**:**3a′**
1	**2a**	IPrAuCl/$AgNTf_2$	DCM/15 min	70	13:1
2	**2b**	IPrAuCl/$AgNTf_2$	DCM/15 min	trace	–
3	**2c**	IPrAuCl/$AgNTf_2$	DCM/15 min	trace	–
4	**2d**	IPrAuCl/$AgNTf_2$	DCM/2 h	52	12:1
5	**2e**	IPrAuCl/$AgNTf_2$	DCM/15 min	87	15:1
6	**2e**	IPrAuCl/$AgNTf_2$	DCM/12 h	<10[c]	–
7	**2e**	$Ph_3PAuCl/AgNTf_2$	DCM/8 h	32	>20:1
8	**2e**	(2,4-*t*-Bu-$C_6H_3O)_3PAuCl/AgNTf_2$	DCM/2 h	88	>20:1
9	**2e**	JohnPhosAuCl/$AgNTf_2$	DCM/5 h	50	>20:1
10	**2e**	(2,4-*t*-Bu-$C_6H_3O)_3PAuCl/AgOTf$	DCM/8 h	80	>20:1
11	**2e**	(2,4-*t*-Bu-$C_6H_3O)_3PAuCl/AgSbF_6$	DCM/8 h	84	>20:1
12	**2e**	(2,4-*t*-Bu-$C_6H_3O)_3PAuCl/AgNTf_2$	THF/24 h	77	>20:1
13	**2e**	(2,4-*t*-Bu-$C_6H_3O)_3PAuCl/AgNTf_2$	DCE/8 h	57	>20:1
14	**2e**	(2,4-*t*-Bu-$C_6H_3O)_3PAuCl/AgNTf_2$	CH_3CN/24 h	trace	–
15	**2e**	(2,4-*t*-Bu-$C_6H_3O)_3PAuCl/AgNTf_2$	toluene/24 h	89	>20:1
16	**2e**	**(2,4-*t*-Bu-$C_6H_3O)_3PAuCl/AgNTf_2$ (3 mol%)**	**DCM/4 h**	**90**	**>20:1**
17	**2e**	(2,4-*t*-Bu-$C_6H_3O)_3PAuCl/AgNTf_2$ (1 mol%)	DCM/4 h	73	>20:1
18	**2e**	$Zn(OTf)_2$	DCM/12 h	ND[d]	–
19	**2e**	$Cu(OTf)_2$	DCM/12 h	ND[d]	–

[a] All reactions were carried out on a 0.2 mmol scale in 2 mL of solvent at room temperature.
[b] Yields of isolated products.
[c] Without the addition of $MeSO_3H$, the conversion of **1a** was less than 80%.
[d] No product was detected.

reaction also worked well in tetrahydrofuran (THF) and 1,2-dichlorethane (DCE). However, the use of the coordinative solvent acetonitrile resulted in deactivation of the catalyst (entry 14). On lowering of the amount of the catalyst from 5 to 3 mol%, no drop in yield was observed (entry 16). However, reducing catalyst loading to 1 mol% led to a sharp decrease of the yield (entry 17). Literature reports revealed that zinc[16] and copper[17] salts could also promote the oxygen transfer reaction from pyridine *N*-oxides to alkynes. However, neither $Zn(OTf)_2$ nor $Cu(OTf)_2$ could catalyze this reaction (entries 18 and 19).

With the optimized conditions for the preparation of 1,3-diketones in hand, we hypothesized that this reaction could be used in a one-pot synthesis of pyrazoles because the acid which was added in the first step could also promote the following condensation of hydrazine and 1,3-diketone.[18] To prove this, phenylhydrazine was added after the propargyl alcohol **1** was fully consumed. Gratifyingly, a pyrazole product was obtained in good yield as we expected. Scheme 2 shows the reaction scope of the one-pot synthesis of 4-heteroaryl-substituted pyrazoles. As summarized in Scheme 2, thiophene-derived propargyl alcohols were examined first. Propargyl alcohols with a substituted phenyl group on the alkyne terminal afforded the corresponding pyrazoles in good yield, no matter if the substituents were electron-donating groups or electron-withdrawing groups (Scheme 2, **4a**–**4f**). A 1-naphthyl group (**4g**) or a cyclohexenyl group (**4h**) was readily tolerated in the one-pot reaction. Aliphatic propargyl alcohols also worked well leading to the corresponding pyrazoles in good yields. For example, the cyclopropyl-substituted pyrazole **4i** and the *n*-butyl-substituted pyrazole **4j** were isolated in 72% and 46% yields, respectively. However, **4k** and its isomer **4k′** were obtained as a mixture in 41% total yield. This might be explained by the decreased steric bulk of the $PhOCH_2$- group, which resulted in the poor regioselectivity in the condensation step. Interestingly, in analogy to the above-mentioned results, when R^2 was an H atom instead of a methyl group, only a 1,2-thienyl migration product **4l** was isolated. A methyl group in the thiophene ring did not affect



[a] The ratio of **4k**:**4k'** = 4:1.

[b] **4s** was obtained *via* the condensation of an isolated 1,3-diketone and phenylhydrazine. The yield given is the total yield of the two-step reaction.

Scheme 2. One-pot synthesis of 4-heteroaryl-substituted pyrazoles. Yields given in this Scheme refer to isolated products.

this reaction, delivering the desired product **4m** in good yield. 3-Methyl-1,5-diphenyl-4-(thiophen-3-yl)-1*H*-pyrazole (**4n**) was also obtained in good yield. Besides thiophene, furan (**4o**, **4p** and **4q**), benzofuran (**4r**) and *N*-methylpyrrole (**4s**) derived propargyl alcohols also worked smoothly leading to 4-heteroaryl-substituted pyrazoles in good yields, respectively. The structure of **4b** was confirmed by an X-ray diffraction single crystal structure analysis (Figure 1).[19]

As a key step, the gold-catalyzed oxidation/1,2-heteroaryl group migration approach was also used for the synthesis of 4-heteroaryl-substituted isoxazoles. Scheme 3 shows some examples. Isoxazoles were obtained *via* the condensation of isolated 1,3-diketones and hydroxylamine hydrochloride. The yield given is the total yield of the two-step reaction. As depicted, thiophene (**5a**), furan (**5b**), *N*-methylpyrrole (**5c**) and benzofuran derived (**5d**) propargyl alcohols worked smoothly, delivering 4-heteroaryl-substituted isoxazoles in good yields.

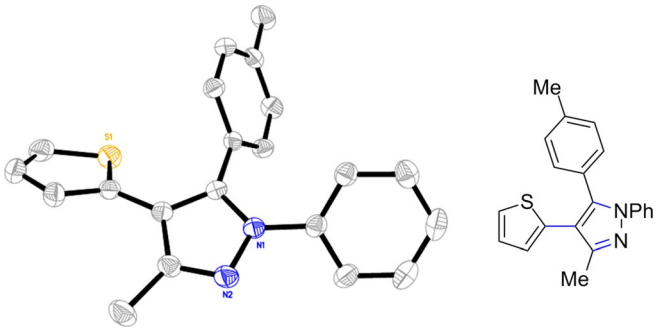
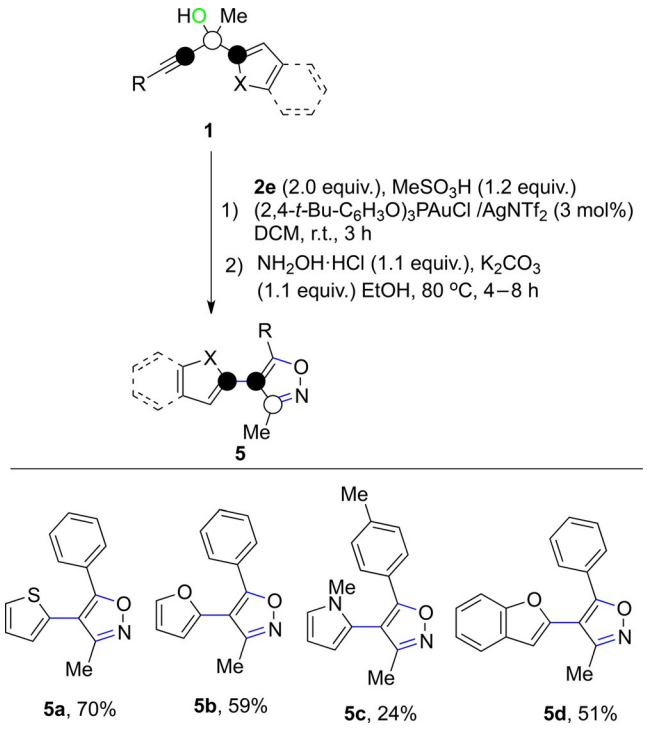


Figure 1. Solid-state molecular structure of **4b**.



Scheme 3. Synthesis of 4-heteroaryl-substituted isoxazoles.

In conclusion, we have described an efficient gold-catalyzed oxidation/1,2-heteroaryl group migration cascade leading to α-heteroaryl-substituted 1,3-diketones and its further application in the one-pot synthesis of 4-heteroaryl-substituted pyrazoles and the preparation of isoxazoles. The approach showed a broad substrate scope and functional group tolerance. Research on the biological activity of the products obtained is currently underway in our laboratory.

Experimental Section

General Procedure for the Preparation of 1,3-Diketones (Procedure A)

8-Methylquinoline 1-oxide (0.4 mmol) and $MeSO_3H$ (0.24 mmol) were added successively to a stirring suspension of $(2,4\text{-}t\text{-Bu-}C_6H_3O)_3PAuCl$ (6.0 μmol) and $AgNTf_2$ (6.0 μmol) in dichloromethane (2.0 mL) at room temperature. After that the propargyl alcohol (0.2 mmol) was added and the combined solution was then stirred at room temperature until the reaction was completed (monitored by TLC). After evaporation, the residue was purified by column chromatography on silica gel affording the desired product.

1-Phenyl-2-(thiophen-2-yl)butane-1,3-dione (3a): yield: 90%; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 17.50$ (s, 1H), 7.30 (d, 2H, $J = 7.6$ Hz), 7.20–7.15 (m, 2H), 7.12–7.06 (m, 2H), 6.86–6.83 (m, 1H), 6.70 (d, 1H, $J = 3.2$ Hz), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 197.9$, 184.3, 138.3, 136.0, 130.7, 129.9, 128.7, 127.8, 127.3, 127.2, 106.2, 25.6; IR (KBr): $\nu = 3553$, 3476, 3414, 3238, 3098, 2963, 2027, 1616, 1387, 1271, 1078, 1022, 878, 835, 789, 714, 619, 482 cm^{-1}; HR-MS (ESI): $m/z = 267.0447$, calcd. for $C_{14}H_{12}O_2SNa$ [M]+Na: 267.0456.

General Procedure for the One-Pot synthesis of Pyrazoles

According to Procedure A, after the propargyl alcohol was fully consumed (monitored by TLC), 3 equiv. of hydrazine (0.6 mmol) were added directly to the solution. The resulting mixture was allowed to stir at room temperature until the diketone was fully consumed (monitored by TLC). After that the solvent was removed and the residue was purified by column chromatography on silica gel affording the desired product.

3-Methyl-1,5-diphenyl-4-(thiophen-2-yl)-1*H*-pyrazole (4a): yield: 85%; yellow solid; mp 152–153 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.33$–7.20 (m, 8H), 7.20–7.15 (m, 3H), 6.99–6.93 (m, 1H), 6.82 (d, 1H, $J = 3.0$ Hz), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 148.2$, 140.9, 139.9, 134.6, 130.6, 130.2, 128.8, 128.7, 128.5, 127.1, 127.0, 126.3, 125.0, 124.8, 115.0, 13.2; IR (KBr): $\nu = 3061$, 2922, 2856, 2733, 1963, 1892, 1798, 1728, 1665, 1591, 1499, 1431, 1369, 1225, 1161, 1026, 966, 835, 760, 689, 455; HRMS (ESI): $m/z =$ 339.0926, calcd. for $C_{20}H_{16}N_2SNa$ [M]+Na: 339.0930.

General Procedure for the Synthesis of Isoxazoles

1,3-Diketone (0.20 mmol), hydroxylamine hydrochloride (0.22 mmol) and K_2CO_3 (0.22 mmol) were dissolved in ethanol (1.0 mL). The reaction mixture was allowed to reflux for 4–8 h. After that the solvent was removed and the residue was purified by column chromatography on silica gel affording the desired product.

3-Methyl-5-phenyl-4-(thiophen-2-yl)isoxazole (5a): yield: 70%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.62$–7.59 (m, 2H), 7.43 (d, 1H, $J = 6.8$ Hz), 7.39–7.33 (m, 3H), 7.12–7.11 (m, 1H), 7.02 (d, 1H, $J = 4.4$ Hz), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 165.6$, 160.6, 130.9, 130.2, 128.8, 128.6, 128.4, 127.9, 127.7, 127.2, 109.6, 10.8; IR (KBr): $\nu = 3520$, 3443, 3323, 3069, 2959, 2864, 1962, 1894, 1807, 1728, 1628, 1441, 1286, 1227, 1078, 1032, 926, 843, 771, 700, 592, 546, 494 cm^{-1}; HR-MS (ESI): $m/z = 264.0449$, calcd. for $C_{14}H_{11}NOSNa$ [M]+Na: 264.0459.

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[19] CCDC 1450381 (**4b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

