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Facile Route to Tetrasubstituted Pyrazoles Utilizing Ceric Ammonium Nitrate

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Abstract

A convenient approach for the synthesis of tetrasubstituted pyrazoles is described. The method involves the treatment of 1,3-diketones and allyltrimethylsilane with CAN followed by cerium-catalyzed addition of substituted hydrazines to construct pyrazoles in good yields.

Keywords

heterocycles; pyrazoles; ceric ammonium nitrate; allylation; hydrazines

Pyrazoles have numerous applications in both the pharmaceutical and agrochemical industries.[1] Recent work has shown the utility of pyrazole motifs as HIV-1 reverse transcriptase inhibitors,[2] antidiabetics,[3] COX-2 inhibitors, [4] A_{2A} receptor antagonists,[5] CB1 receptor antagonists, [6] transforming growth factor-β receptor type I inhibitors,[7] DNA intercalating agents,[8] and estrogen receptor ligands.[9] Due to the importance of pyrazoles, alternative synthetic routes to their production are useful.

Ceric ammonium nitrate (CAN) has long been used in organic synthesis as both an oxidant and a Lewis acid for functional-group conversion and promotion of bond-forming reactions. 10 Our group has been exploring the mechanism and use of this reagent.11 In particular, we have explored several reactions involving the oxidative coupling of β-diketones and radicophiles using Ce(IV) reagents. 12 Recently, CAN has been shown to be an efficient Lewis acid catalyst in the synthesis of β-enaminoketones. 13 Based on this precedent and our previous experience with CAN, we reasoned that highly substituted pyrazoles could be synthesized through the Ce(IV)-initiated reaction of a radicophile and a β-diketone, followed by reaction with an appropriately substituted hydrazine. To test this supposition, an initial experiment was performed using 2,4-pentanedione as the diketone. The diketone was treated with 2.1 equivalents CAN in the presence of 1.3 equivalents allyltrimethylsilane in acetonitrile (MeCN). After loss of the yellow color of Ce(IV), 1.4 equivalents of phenylhydrazine hydrochloride was added to the solution. The reaction was stirred for 3 hours yielding **3a** with a one-pot yield of 68%. This procedure was then applied to a variety of hydrazines providing tetrasubstituted pyrazoles in moderate to good isolated yields as shown in Table 1.

Next, the one-pot method was applied to diaryl β-diketones. Unfortunately, significantly lower yields of pyrazole were obtained. To achieve better conversions, the reaction was run in two steps. First, allylation of the diketone was performed under the one-pot conditions. The allylated diketone was isolated and then added to a solution of 1.4 equivalents hydrazine

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and 3 mol% CAN in MeCN. The solution was refluxed for 3 hours yielding tetrasubstituted pyrazoles in modest overall yields (Table 2).

In addition to examining various diketones, the impact of modifying the radicophile was examined. Dibenzoylmethane was treated with CAN in the presence of methyl allyltrimethylsilane. Rotary evaporation under reduced pressure and washing with water and CH_2Cl_2 resulted in the isolation of dihydrofuran **7** instead of the anticipated **6e**. It is likely that during the workup, olefin **6e** is activated either by Lewis acid interaction with Ce(III) or through protonation by a free ammonium. Addition to the activated olefin by the pendant carbonyl followed by elimination leads to **7**. To circumvent this process and reduce furan production, triethylamine was added dropwise after completion of the reaction to neutralize the acidic medium. Using this alternative workup procedure, production of **7** is minimized, allowing **6e** to be isolated in a 52% yield (Scheme 1). Subsequent reaction of **6e** with either methylhydrazine or *p*-methoxyphenylhydrazine produced pyrazoles **8e** and **8f** in moderate overall yields (Table 2, entries 5 and 6).

Many synthetically relevant pyrazoles possess different substituents at the C3 and C5 positions. In order to effectively synthesize these species from unsymmetric diketones, regioselectivity is required for production of single isomers. To examine the regioselectivity of our approach, benzoylacetone was employed as a model substrate (Table 3). Oxidative allylation, isolation, and subsequent reaction of *p*-methoxyphenylhydrazine hydrochloride in the presence of a catalytic amount of CAN (3 mol%) led to a 16:1 ratio of regioisomers as determined by ^{1}H NMR. Separation of the isomers via flash chromatography and analysis by ^{1}H NMR showed that the major and minor products were **10a** and **10b**, respectively.

To examine the basis of the regioselectivity, a series of 1-phenyl-β-diketones with varied substitution on the hydrazine and the 2-position of the diketone was explored. When methylhydrazine was used, **11a** was formed almost exclusively. Replacement of the 2-allyl group with a methyl substituent was examined next. Reaction of 2-methyl-1-phenyl-1,3-butanedione with *p*-methoxyphenylhydrazine hydrochloride and 3 mol% CAN provided pyrazoles **12a** and **12b** in a 6:1 ratio. An attempt to alter the electronic nature of the diketone through the use of 2-allyl-4,4,4-trifluoro-1-phenyl-1,3-butanedione resulted in a single isomer (Table 3, entry 4). Unfortunately, after extensive analysis using 1D and 2D NMR, the structure of the isomer could not be identified.[14]

Taken together, these limited observations are consistent with product formation resulting from steric interactions encountered upon initial nucleophilic attack of the hydrazine on the diketone. Comparison of entries 1 and 2 in Table 3 shows that altering the size of the substituent on the hydrazine impacts the selectivity. During the course of the reaction, initial reversible formation of the hydrazone is followed by ring closure. Nucleophilic attack of the hydrazine on the carbonyl adjacent to the methyl group of benzoylacetone leads to a hydrazone at the 3-position. Subsequent ring closure places R^3 in close proximity to the 1-phenyl group of the intermediate. A smaller R^3 substituent is likely to lead to ring closure more efficiently than a larger substituent as observed for the relative regioselectivities for **10** and **11**. In the case of the example in entry 3 of Table 3, decreasing the size of the substituent in the 2-position of the diketone from an allyl to a methyl reduces steric crowding around both carbonyls, decreasing the overall selectivity for **12**.

To examine the practical use of this method, the synthesis of propylpyrazole triol (PPT) **14**, an estrogen receptor agonist, was attempted.[9] Dropwise addition of CAN dissolved in MeCN to 1,3-bis(4-methoxyphenyl)-1,3-propanedione (**4d**) and allyltrimethylsilane in MeCN produced diketone **6d** in 66% isolated yield. Refluxing a slight excess of *p*-methoxyphenylhydrazine hydrochloride with **6d** in the presence of 3 mol% CAN provided

8d in a 68% yield. Reduction of **8d** by Pd/C hydrogenation followed by deprotection with Br_3B provided **14** in an overall yield of 30% in four steps.

In conclusion, a variety tetrasubstituted pyrazoles can be synthesized from Ce(IV)-initiated reaction of allyltrimethylsilane and a β-diketone, followed by reaction with an appropriately substituted hydrazine. Both aliphatic and aromatic diketones can be employed with a range of substituted hydrazines leading to highly substituted and complex products from readily available starting materials. [16–18]

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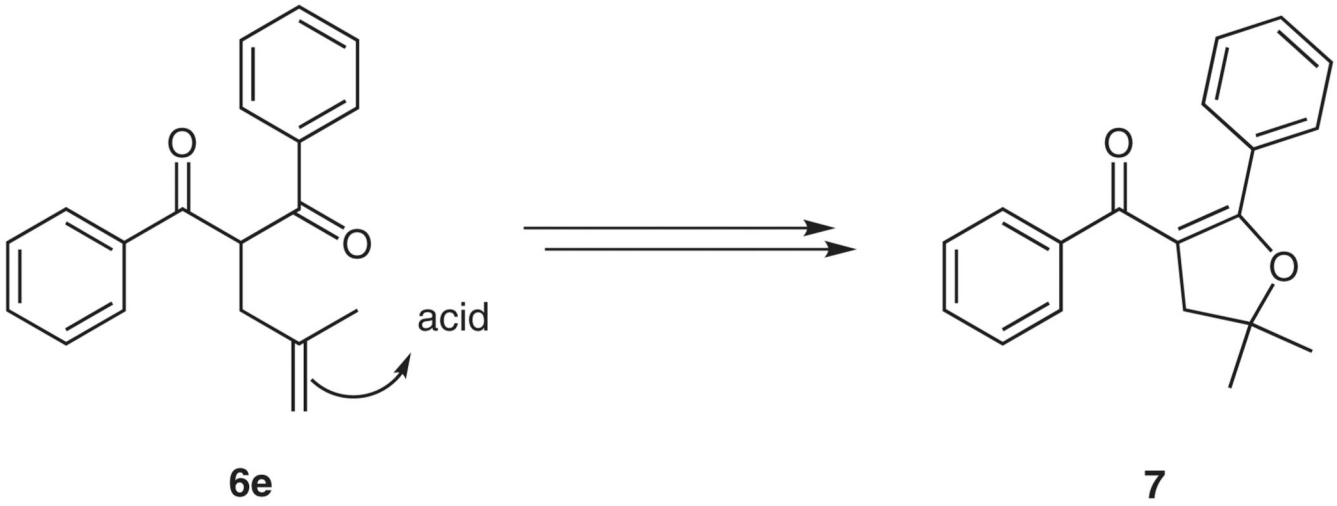
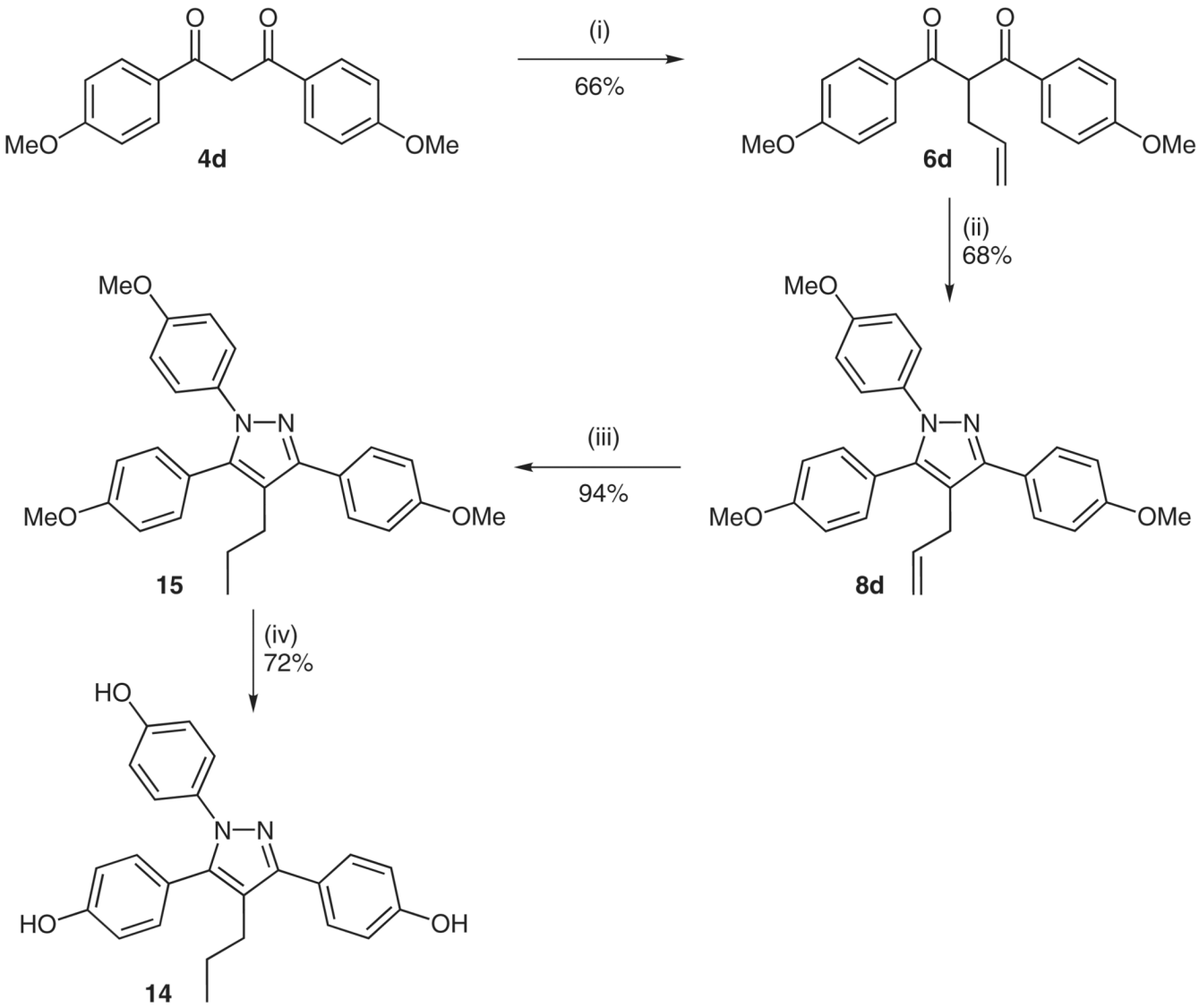
15. All reactions were run at room temperature unless specified otherwise.
16. **One-Pot Procedure for 4-Allyl-1,3,5-trisubstituted Pyrazoles**To a mixture of 1,3-dione (1 equiv) and allyltrimethylsilane (1.3 equiv) in MeCN, CAN (2.1 equiv) dissolved in MeCN was added dropwise. The solution was stirred at r.t. until the color disappeared completely (20–45 min). Hydrazine (1.4 equiv) was added and stirred at r.t. for 3.5–6 h (monitored by GC). Solvent was removed by rotary evaporation. Ice-cold water was added to the solid residue and extracted with CH_2Cl_2. The combined organic extract was dried over $MgSO_4$ and concentrated by rotary evaporation. The residue was purified with SiO_2 column chromatography eluting with hexanes–EtOAc.**4-Allyl-1-(4-methoxy-phenyl)-3,5-dimethyl-1*H*-pyrazole (3c)**Yield 74% (0.89 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.13 (s, 3 H, Me), 2.21 (s, 3 H, Me), 3.14 (d, *J* = 5.0 Hz, 2 H, CH_2), 3.82 (s, 3 H, OMe), 4.98 (d, *J* = 8.5 Hz, 1 H, CH), 4.99 (br s, 1 H, CH), 5.85 (m, 1 H), 6.93 (d, *J* = 8.2 Hz, 2 H, ArH), 7.28 (d, *J* = 8.5 Hz, 2 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.65, 11.87, 27.99, 55.51, 114.09, 114.51, 114.54, 126.36, 133.31, 136.50, 136.61, 147.6, 158.67. HRMS–FAB: *m/z* = calcd for $C_{15}H_{19}N_2O$ $[MH]^+$: 243.1497; found: 243.1488.**4-Allyl-1-(2,4-dinitro-phenyl)-3,5-dimethyl-1*H*-pyrazole (3d)**Yield 63% (0.48 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, Me), 2.16 (s, 3 H, Me), 3.15 (d, *J* = 5.7 Hz, 2 H, CH_2), 4.75 (d, *J* = 17.2 Hz, 1 H, CH), 5.03 (d, *J* = 10.0 Hz, 1 H, CH), 5.85 (m, 1 H), 7.67 (d, *J* = 8.7 Hz, 1 H, ArH), 8.49 (d, *J* = 7.9 Hz, 1 H, ArH), 8.76 (s, 1 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.2, 11.9, 27.56, 115.25, 117.39, 121.0, 127.26, 129.18, 135.25, 137.82, 138.11, 145.44, 145.95, 151.92. HRMS–FAB: *m/z* calcd for $[MH]^+$ $C_{14}H_{15}N_4O_4$: 303.1093; found: 303.1071.**4-Allyl-1-(4-toluenesulfonyl)-3,5-dimethyl-1*H*-pyrazole (3e)**Yield 67% (0.68 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.10 (s, 3 H, Me), 2.36 (br s, 6 H, 2 × Me), 2.98 (d, *J* = 5.7 Hz, 2 H, CH_2), 4.75 (dd, *J* = 1.7, 17.1 Hz, 1 H, CH), 4.92 (dd, *J* = 1.5, 10.1 Hz, 1 H, CH), 5.69 (m, 1 H), 7.25 (d, *J* = 8.4 Hz, 2 H, ArH), 7.77 (d, *J* = 8.8 Hz, 2 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.23, 12.29, 22.6, 27.18, 115.30, 118.79, 127.41, 129.77, 134.74, 135.44, 140.33, 144.91, 153.49. HRMS–FAB: *m/z* calcd for $[MH]^+$ $C_{15}H_{19}N_2O_2S$: 291.1167; found: 291.1178.**4-(4-Allyl-3,5-dimethyl-pyrazol-1-yl)-benzoic Acid (3f)**Yield 65% (0.58 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.26 (s, 3 H, Me), 2.27 (s, 3 H, Me), 3.15 (d, *J* = 5.8 Hz, 2 H, CH_2), 4.98 (d, *J* = 17.1 Hz, 1 H, CH), 5.0 (d, *J* = 10.1 Hz, 1 H, CH), 5.85 (m, 1 H), 7.54 (d, *J* = 8.4 Hz, 2 H, ArH), 8.15 (d, *J* = 8.5 Hz, 2 H, ArH), 9.98 (br s, 1 H, OH). ^{13}C MR (125 MHz, $CDCl_3$): δ = 11.21, 11.73, 27.76, 114.93, 116.53, 123.71, 127.77, 131.13, 135.85, 136.89, 143.92, 149.37, 170.42. HRMS–FAB: *m/z* calcd for $[MH]^+$: $C_{15}H_{17}N_2O_2$: 257.1290; found: 257.1287.**4-Allyl-3,5-diethyl-1-methyl-1*H*-pyrazole (3g)**Yield 76% (0.68 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.5 Hz, 3 H, Me), 1.18 (t, *J* = 7.5 Hz, 3 H, Me), 2.49–2.52 (two quart are overlapping, 2 × 2 H, 2 × CH_2), 3.08 (dd, *J* = 1.6, 4.7 Hz, 2 H, CH_2), 3.71 (s, 3 H, Me), 4.91 (d, *J* = 7.3 Hz, 1 H, CH), 4.93 (d, *J* = 7.8 Hz, 1 H, CH), 5.86 (m, 1 H). ^{13}C NMR (125 MH_Z, $CDCl_3$): δ = 13.55, 13.89, 17.4, 19.81, 27.67, 35.73, 113.1, 114.26, 137.53, 141.92, 151.26. HRMS–FAB: *m/z* calcd for $C_{11}H_{19}N_2$ $[MH]^+$: 179.1548; found: 179.1572.
17. **Typical Procedure for Pyrazole Synthesis**An MeCN soln of 2-substituted diketone (1 equiv), hydrazine (1.4 equiv), and CAN (3 mol%) was refluxed for 3 h. Reaction mixture was cooled down to r.t. Solvent was removed by rotary evaporation. The residue was dissolved with CH_2Cl_2, and washed with H_2O. The organic layer was separated, dried over anhyd $MgSO_4$, and concentrated by rotary evaporation. The crude reaction mixture was purified by SiO_2 column chromatography eluted with hexanes–EtOAc.**4-Allyl-1,3,5-triphenyl-1*H*-pyrazole (8b)**Yield 72% (0.24 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.34 (dd, *J* = 1.9, 3.3 Hz, 2 H, CH_2), 5.02 (dd, *J* = 1.8, 17.0 Hz, 1 H, CH), 5.11 (dd, *J* = 1.8, 10.3 Hz, 1 H, CH), 6.00 (m, 1 H), 7.24–7.25 (m, 1 H, ArH), 7.27–7.30 (m, 4 H, ArH), 7.31–7.33 (m, 6 H, ArH), 7.34 (t, 2 H, *J* = 6.5 Hz, ArH), 7.42 (d, 2 H, *J* = 6.7 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.16, 115.85, 115.93, 124.7, 126.76, 127.7, 127.93, 128.32, 128.37, 128.42, 128.66, 129.91, 130.61, 133.65, 137.61, 140.13, 142.0, 151.48. HRMS–FAB: *m/z* calcd for $C_{24}H_{21}N_2$ $[MH]^+$: 337.1705; found: 303.1721.**4-Allyl-1-(4-methoxyphenyl)-3,5-diphenyl-1*H*-pyrazole (8c)**Yield 76% (0.63 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.34 (br s, 2 H, CH_2), 3.76 (s, 3 H, OMe), 5.00 (d, 1 H, *J* = 18.4 Hz, CH), 5.08 (d, 1 H, *J* = 9.3 Hz, CH), 5.98 (m, 1 H), 6.79 (br d, 2 H, *J* = 6.1 Hz, ArH), 7.22–7.25 (m, 4 H, ArH), 7.29–7.32 (m, 4 H, ArH), 7.42 (br d, 2 H, ArH), 7.81 (d, 2 H, *J* = 6.7 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.22, 55.39, 113.86, 115.44, 115.75, 126.15, 127.59, 127.93, 128.20, 128.34, 128.36, 128.57, 128.86, 129.96, 130.67, 133.52, 133.79, 137.67, 141.98, 151.06, 158.36. HRMS–FAB: *m/z* calcd for $C_{25}H_{23}N_2O$ $[MH]^+$: 367.1810; found: 367.1826.

18. **Alternative Workup Procedure for Methylallylation (8e and 8f only)**Upon completion of allylation, an excess of Et_3N was added dropwise to the reaction mixture. Solvent was removed by rotary evaporation. The residue was dissolved with CH_2Cl_2, and washed with H_2O. The organic layer was separated, dried over anhyd $MgSO_4$, and concentrated by rotary evaporation. The crude reaction mixture was purified by SiO_2 column chromatography eluted with hexanes–EtOAc.**1-Methyl-4-(2-methylallyl)-3,5-diphenyl-1*H*-pyrazole (8e)**Yield 84% (0.24 g), ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.69 (s, 3 H, Me), 3.11 (s, 2 H, CH_2), 3.81 (s, 3 H, Me), 4.61 (s, 1 H, CH), 4.64 (s, 1 H, CH), 7.30 (d, *J* = 6.9 Hz, 1 H, ArH), 7.38–7.45 (m, 7 H, ArH), 7.71 (br d, *J* = 7.2 Hz, 2 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.06, 32.19, 37.26, 111.47, 114.1, 127.23, 127.44, 127.94, 128.26, 128.47, 128.5, 129.48, 130.35, 133.97, 143.01, 145.3, 149.71. HRMS–FAB: *m/z* calcd for $C_{20}H_{21}N_2$ $[MH]^+$: 289.1705; found: 289.1722.**1-(4-Methoxyphenyl)-4-(2-methylallyl)-3,5-diphenyl-1*H*-pyrazole (8f)**Yield 70% (0.79 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.78 (s, 3 H, Me), 3.20 (s, 2 H, CH_2), 3.79 (s, 3 H, OMe), 4.75 (s, 1 H, CH), 4.95 (s, 1 H, CH), 6.81 (d, *J* = 7.2 Hz, 2 H, ArH), 7.25 (m, 4 H, ArH), 7.32 (br t, *J* = 7.1 Hz, 4 H, ArH), 7.42 (d, *J* = 7.4 Hz, 2 H, ArH), 7.81 (d, *J* = 7.1 Hz, 2 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.28, 32.33, 55.39, 111.87, 113.84, 115.78, 126.14, 127.52, 127.70, 128.14, 128.57, 129.68, 129.88, 133.51, 133.74, 142.03, 145.47, 151.19, 158.3. HRMS–FAB: *m/z* calcd for $C_{26}H_{24}N_2O$ $[M]^+$: 380.1889; found: 380.1891.**4-Allyl-1-(4-methoxyphenyl)-3-methyl-5-phenyl-1*H*-pyrazole (10a)**Yield 45% (0.30 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, Me), 3.15 (dt, *J* = 5.6, 1.7 Hz, 2 H, CH_2), 3.75 (s, 3 H, Me), 4.98 (ddt, *J* = 20.0, 1.8, 1.8 Hz, 1 H, CH), 5.03 (ddt, *J* = 10.3, 1.7, 1.7 Hz, 1 H, CH), 5.90 (ddt, *J* = 17.0, 10.0, 5.6 Hz, 1 H, CH), 6.75 (m, *J* = 9.1 Hz, 2 H, ArH), 7.09 (m, *J* = 9.1 Hz, 2 H, ArH), 7.13–7.15 (m, 2 H, ArH), 7.27–7.30 (m, 3 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.01, 27.85, 55.37, 113.82, 114.94, 115.94, 126.03, 127.97, 128.33, 129.75, 130.72, 133.50, 136.83, 140.81, 148.45, 158.12. HRMS–FAB: *m/z* calcd for $C_{20}H_{20}N_2O$ $[M]^+$: 304.1576; found: 304.1570.**4-Allyl-1-(4-methoxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazole (10b)**Yield 27% (0.16 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.21 (s, 3 H, Me), 3.34 (dt, *J* = 5.5, 1.8 Hz, 2 H, CH_2), 3.84 (s, 3 H, Me), 5.02 (ddt, *J* = 17.0, 1.8, 1.8 Hz, 1 H, CH), 5.08 (ddt, *J* = 10.3, 1.8, 1.6 Hz, 1 H, CH), 5.99 (ddt, *J* = 17.3, 10.5, 5.5 Hz, 1 H, CH), 6.97 (m, *J* = 8.9 Hz, 2 H, ArH), 7.30–7.34 (m, *J* = 7.5 Hz, 1 H, ArH), 7.37–7.41 (m, 4 H, ArH), 7.66–7.68 (m, 2 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.85, 28.28, 55.61, 113.83, 114.19, 115.20, 126.63, 127.97, 128.33, 133.17, 133.88, 136.72, 138.05, 150.76, 159.00, 195.65. HRMS–FAB: *m/z* calcd for $C_{20}H_{20}N_2O$ $[M]^+$: 304.1576; found: 304.1577.**4-Allyl-1,3-dimethyl-5-phenyl-1*H*-pyrazole (11a)**Yield 78% (0.63 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.21(s, 3 H, Me), 3.05 (m, 2 H, CH_2), 3.69 (s, 3 H, NMe), 4.88 (dd, *J* = 1.8, 7.0 Hz, 1 H, CH), 4.95 (dd, *J* = 1.7, 11.0 Hz, 1 H, CH), 5.82 (m, 1 H), 7.26–7.28 (m, 2 H, ArH), 7.37–7.45 (m, 3 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.85, 27.81, 36.77, 114.41, 114.61, 128.4, 128.55, 129.6, 130.52, 136.99, 141.85, 146.68. HRMS–FAB: *m/z* calcd for $C_{14}H_{17}N_2$ $[M]^+$: 213.1392; found: 213.1387.**1-(4-Methoxyphenyl)-3,4-dimethyl-5-phenyl-1*H*-pyrazole (12a)**Yield 68% (0.37 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.01 (s, 3 H, CH_3), 2.31 (s, 3 H, Me), 3.71 (s, 3 H, OMe), 6.74 (d, *J* = 7.2 Hz, 2 H, ArH), 7.12 (m, 4 H, ArH), 7.27 (m, 3 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.52, 11.84, 55.21, 113.69, 113.93, 125.91, 127.65, 128.21, 129.63, 130.83, 133.40, 140.13, 148.06, 157.94. HRMS–FAB: *m/z* calcd for $C_{18}H_{18}N_2O$ $[M]^+$: 278.1419; found: 278.1412.**1-(4-Methoxyphenyl)-4,5-dimethyl-3-phenyl-1*H*-pyrazole (12b)**Yield 11% (0.06 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.19 (s, 3 H, Me), 2.23 (s, 3 H, Me), 3.84 (s, 3 H, OMe), 6.96 (d, *J* = 9.0 Hz, 2 H, ArH), 7.27–7.31 (m, 2 H, ArH), 7.37–7.41 (m, 3 H, ArH), 7.71 (d, *J* = 8.0 Hz, 2 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.76, 10.85, 55.58, 114.19, 125.41, 126.59, 127.28, 127.81, 127.90, 128,34, 134.25, 137.34, 150.30, 158.92. HRMS–FAB: *m/z* calcd for $C_{18}H_{18}N_2O$ $[M]^+$: 278.1419; found: 278.1422.**4-Allyl-1-(4-methoxyphenyl)-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazole (13)**Yield 68% (0.49 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.27 (d, *J* = 3.6 Hz, 2 H, CH_2), 3.75 (s, 3 H, Me), 4.94 (d, *J* = 17.2 Hz, 1 H, C=CH), 5.03 (d, *J* = 10.5 Hz, 1 H, C=CH), 5.89 (m, 1 H, C=CH), 6.77 (d, *J* = 8.8 Hz, 2 H, ArH), 7.14 (m, 4 H, ArH), 7.33 (m, 3 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.38, 55.16, 113.98, 115.58, 116.63, 122.25 (q, *J* = 271 Hz, CF_3), 126.40, 128.65, 128.96, 129.07, 129.99, 132.45, 136.43, 141.05 (q, *J* = 37 Hz), 142.83, 159.17. HRMS–FAB: *m/z* calcd for $C_{20}H_{17}F_3N_2O$ $[M]^+$: 358.1293; found: 358.1301.



6e 7

Scheme 1.
Dihydrofuran formation

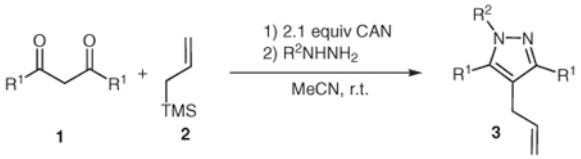


Scheme 2.

Reagents and conditions:[15](i) allyltrimethylsilane (1 equiv), CAN (2.1 equiv), MeCN, 45 min; (ii) *p*-methoxyphenylhydrazine hydrochloride (1.4 equiv), CAN (3 mol%), MeCN, reflux, 3 h; (iii) Pd/C (5 wt%), MeOH, H_2 (100 psi), 14 h; (iv) Br_3B (6 equiv), CH_2Cl_2, −78 °C, 1.5 h.

Table 1

Pyrazoles from Aliphatic Diketones

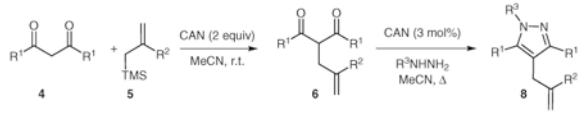


Entry	Product	R^1	R^2	Yield (%)[a]
1	**3a**	Me	Ph	68
2	**3b**	Me	Me	85
3	**3c**	Me	4-$MeOC_6H_4$	71
4	**3d**	Me	2,4-DNP	63
5	**3e**	Me	Ts	67
6	**3f**	Me	4-$COOHC_6H_4$	65
7	**3g**	Et	Me	76

[a] Isolated yield.

Table 2

Two-Step Pathway with Symmetric Aromatic Diketones

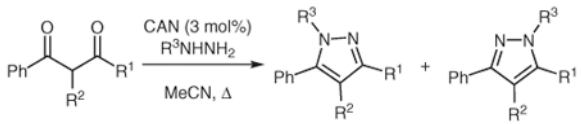


Entry	Product	R^1	R^2	R^3	Yield (%)[a]
1	**8a**	Ph	H	Me	76
2	**8b**	Ph	H	Ph	59
3	**8c**	Ph	H	4-$MeOC_6H_4$	62
4	**8d**	4-$MeOC_6H_4$	H	4-$MeOC_6H_4$	45
5	**8e**	Ph	Me	Me	44
6	**8f**	Ph	Me	4-$MeOC_6H_4$	36

[a]Total isolated yield of pyrazole relative to diketone.

Table 3

Selectivity of Pyrazole Formation[a]



9 10–13a 10–13b

Entry	Product	R^1	R^2	R^3	Yield (%)[b]	Ratio[c]
1	**10**	Me	allyl	4-$MeOC_6H_4$	72	16:1
2	**11**	Me	allyl	Me	61	trace **b**
3	**12**	Me	Me	4-$MeOC_6H_4$	79	6:1
4	**13**	CF_3	allyl	4-$MeOC_6H_4$	68	single isomer

[a] Structure determined by NOESY correlation or analogy.

[b] Total isolated yield.

[c] Determined by ratio of isolated products **a**:**b**.

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