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Regioselective synthesis of 1,3,4,5-tetrasubstituted pyrazoles from Baylis–Hillman adducts

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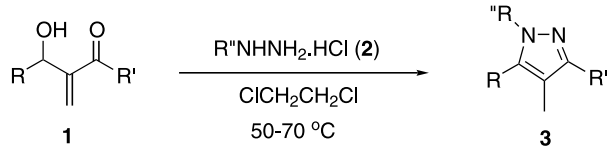
Abstract—Tetrasubstituted pyrazole derivatives **3a–j** were synthesized regioselectively in good yields from the reaction of Baylis–Hillman adducts **1a–f** and hydrazine hydrochlorides **2a–d** in 1,2-dichloroethane.

The pyrazole moiety is present in a wide variety of biologically active compounds.[1–4] Numerous compounds containing pyrazole moiety have been shown to exhibit antihyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial, hypoglycemic, sedative-hypnotic activity.[1–4] Thus, continuous efforts have been devoted to the development of more general and versatile synthetic methodologies to this class of compounds.[1–4] Usually they can be prepared from the reaction of hydrazines and 1,3-dicarbonyls.[1] However, the appealing generality of this method is somewhat vitiated by the severe reaction conditions or the multi-step sequence usually required to access the starting materials.[2]

1,5-Diarylpyrazole derivatives are important in medicinal and pesticidal chemistry.[3–5] Recently, it was known that some 1,5-diarylpyrazole derivatives showed nonnucleoside HIV-1 reverse transcriptase inhibitory activities.[3a] Extensive studies have been devoted to the 1,5-diarylpyrazole derivatives including Celecoxib, the famous cyclooxygenase-2 inhibitor.[5] For the synthesis of these compounds, appropriately substituted 1,3-dicarbonyl compounds were needed. However, the synthesis of these starting materials must suffer from multi-step synthesis and low yields of products as mentioned above.

We are recently interested in the synthesis of aromatic and heteroaromatic compounds from Baylis–Hillman adducts, which included quinolines or naphthalenes.[6] In these respects, we intended to develop an efficient synthetic method for pyrazole derivatives from Baylis–Hillman adducts. The reaction of the Baylis–Hillman adduct and phenylhydrazine would afford 3,4-dimethyl-1,5-diphenylpyrazole via the successive hydrazone formation, cyclization, and double bond isomerization sequence (Scheme 1).

Initially, we examined the reaction of **1a** and free phenylhydrazine in 1,2-dichloroethane or methanol. However, the reaction was found to be very complex and we could not obtain any pyrazole derivatives in appreciable yields. Instead, intractable complex mixtures were observed on TLC. After many trials we finally find out an efficient condition for the synthesis of 3,4-dimethyl-1,5-diphenylpyrazole (**3a**) in good yield. The reaction of the Baylis–Hillman alcohol **1a** and phenylhydrazine hydrochloride (**2a**) in dichloroethane afforded the desired compound **3a** in 89% yield after heating the reaction mixture at 50–60°C for 6 h. When the reaction was carried out with phenylhydrazine hydrochloride in other solvent such as methanol or aqueous ethanol showed complex mixtures also. Use of acetonitrile in the reaction gave somewhat lower yield (65%) of **3a**. Some representative results are summarized in Table 1.[7]



Scheme 1.

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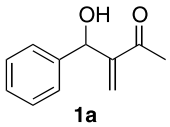
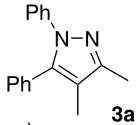
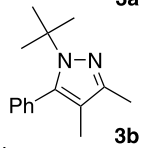
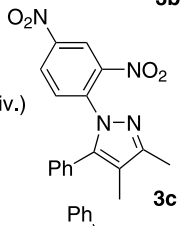
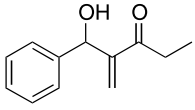
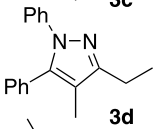
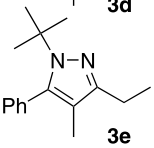
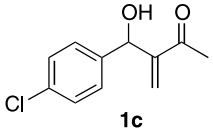
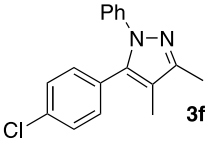
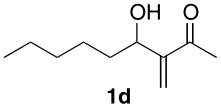
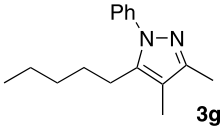
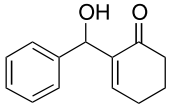
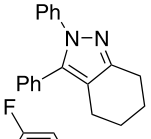
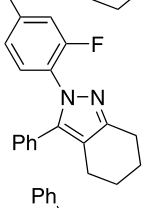
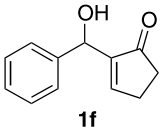
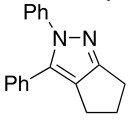
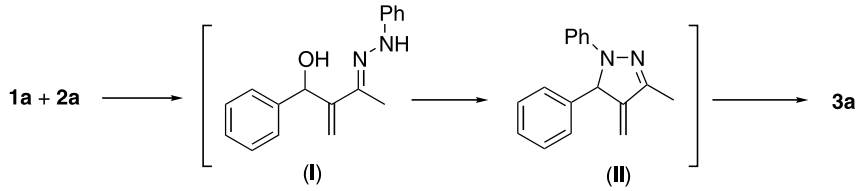
Table 1. Synthesis of 1,3,4,5-tetrasubstituted pyrazole derivatives **3**

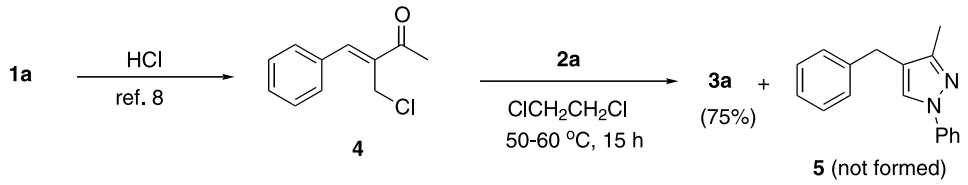
Entry	B-H adduct	Conditions	Product	Yield (%)[a]
1	 **1a**	$PhNHNH_2$·HCl (**2a**) $ClCH_2CH_2Cl$ 50-60 °C, 6 h	 **3a**	89 (oil)
2	**1a**	$(CH_3)_3CNHNH_2$·HCl (**2b**) $ClCH_2CH_2Cl$ 50-60 °C, 20 h	 **3b**	86 (102-103)
3	**1a**	2,4-$(NO_2)_2C_6H_3NHNH_2$ (**2c**) $ClCH_2CH_2Cl$, TsOH (1.0 equiv.) 60-70 °C, 15 h	 **3c**	59 (184-185)
4	 **1b**	**2a** $ClCH_2CH_2Cl$ 50-60 °C, 11 h	 **3d**	91 (oil)
5	**1b**	**2b** $ClCH_2CH_2Cl$ 50-60 °C, 3 days	 **3e**	61 (53-54)
6	 **1c**	**2a** $ClCH_2CH_2Cl$ 50-60 °C, 8 h	 **3f**	93 (oil)
7	 **1d**	**2a** $ClCH_2CH_2Cl$ 50-60 °C, 12 h	 **3g**	87 (oil)
8	 **1e**	**2a** $ClCH_2CH_2Cl$ 50-60 °C, 10 h	 **3h**	51 (oil)
9	**1e**	2,4-$F_2C_6H_3NHNH_2$·HCl (**2d**) $ClCH_2CH_2Cl$ 60-70 °C, 20 h	 **3i**	48 (oil)
10	 **1f**	**2a** $ClCH_2CH_2Cl$ 50-60 °C, 13 h	 **3j**	57 (oil)

[a]Mp was written in the parenthesis.

The starting Baylis–Hillman alcohols **1a–f** were prepared from the reaction of aldehydes and activated alkenes as previously reported.[6] We used four hydrazines: phenylhydrazine hydrochloride (**2a**), *tert*-butylhydrazine hydrochloride (**2b**), 2,4-dinitrophenylhydrazine (**2c**), and 2,4-difluorophenylhydrazine hydrochloride (**2d**). For the reaction with 2,4-dinitrophenylhydrazine, we used *p*-toluenesulfonic acid as the acid catalyst. The formation of pyrazole **3a** could be explained as shown in Scheme 2: Conversion of Baylis–Hillman adduct **1a** into the corresponding hydrazone derivative (**I**), acid-catalyzed cyclization to (**II**), and subsequent 1,3-hydrogen transfer gave the pyrazole **3a**.



Scheme 2.



Scheme 3.

As shown in Table 1, we could synthesize the pyrazoles **3h–j** fused to cyclopentane or cyclohexane rings. Similar compounds were prepared previously as the minor products by adopting the classical cyclocondensation procedure from 1,3-dicarbonyl compounds as the starting materials.[4] The synthesis of **3a** could also be carried out in 75% yield from the reaction of cinnamyl chloride derivative **4**, which was synthesized from **1a** by the reported procedure.[8] We could not obtain the benzyl substituted pyrazole derivative **5** from the reaction (Scheme 3).

In conclusion, we prepared some pyrazole derivatives regioselectively in good yields from the Baylis–Hillman adducts. The biological activities of the prepared compounds are currently under investigation including their herbicidal and fungicidal activities and will be reported in due course.

Acknowledgements

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7. Synthesis of 3,4-dimethyl-1,5-diphenylpyrazole (**3a**) is typical. A stirred mixture of **1a** (100 mg, 0.57 mmol) and phenylhydrazine hydrochloride (**2a**, 83 mg, 0.57 mmol) in 1,2-dichloroethane (4 mL) was heated to 50–60°C for 6 h. The reaction mixture was diluted with methylene chloride and washed with water. After removal of solvent and flash chromatography (hexane/ether, 10:1), desired **3a** was obtained, 126 mg (89%). Some selected spectroscopic data of prepared pyrazoles is as follows. **3a**:[3a] oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03 (s, 3H), 2.33 (s, 3H), 7.12–7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.51, 11.93, 114.56, 124.41, 126.25, 127.77, 128.29, 128.53, 129.65, 130.91, 140.09, 140.12, 148.61; Mass (70 eV) m/z (rel. intensity) 77 (23), 144 (12), 206 (17), 232 (8), 247 (84), 248 (M^+, 100). **3b**: white solid, mp 102–103°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.66 (s, 3H), 2.23 (s, 3H), 7.24–7.27 (m, 2H), 7.38–7.40 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.08, 11.94, 31.15, 60.16, 114.76, 127.99, 128.06, 130.79, 134.55, 140.77, 143.97; Mass (70 eV) m/z (rel. intensity) 130 (19), 171 (70), 172 (100), 213 (23), 228 (M^+, 29); Anal. calcd for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.82; H, 8.94; N, 12.22. **3c**:[9] yellow solid, mp 184–185°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.30 (s, 3H), 7.15–7.19 (m, 2H), 7.29 (d, J=8.7 Hz, 1H), 7.35–7.40 (m, 3H), 8.26 (dd, J=8.7 and 2.7 Hz, 1H), 8.62 (d, J=2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.53, 12.13, 117.03, 120.80, 126.86, 128.92, 128.96, 129.03, 129.07, 129.58, 138.33, 141.31, 144.75, 145.17, 152.52. **3d**: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J=7.5 Hz, 3H), 2.05 (s, 3H), 2.73 (q, J=7.5 Hz, 2H), 7.13–7.34 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.49, 13.47, 20.22, 113.90, 124.54, 126.26, 127.80, 128.32, 128.58, 129.80, 131.04, 140.25, 140.26, 153.92; Anal. calcd for $C_{17}H_{14}N_4O_4$: C, 60.35; H, 4.17; N, 16.56. Found: C, 60.50; H, 4.26; N, 16.48. **3e**: white solid, mp 53–54°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J=7.5 Hz, 3H), 1.40 (s, 9H), 1.68 (s, 3H), 2.63 (q, J=7.5 Hz, 2H), 7.24–7.28 (m, 2H), 7.38–7.40 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.06, 13.76, 20.31, 31.13, 60.16, 113.86, 127.95, 127.99, 130.87, 134.65, 140.74, 149.29; Anal. calcd for $C_{16}H_{22}N_2$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.46; H, 9.10; N, 11.53. **3f**: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.32 (s, 3H), 7.07–7.32 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.54, 11.92, 114.83, 124.54, 126.58, 128.68, 128.74, 129.41, 130.95, 133.91, 138.94, 139.93, 148.79; Anal. calcd for $C_{17}H_{15}ClN_2$: C, 72.21; H, 5.35; N, 9.91. Found: C, 72.31; H, 5.43; N, 9.92. **3g**: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, J=6.9 Hz, 3H), 1.17–1.23 (m, 4H), 1.39–1.44 (m, 2H), 1.99 (s, 3H), 2.24 (s, 3H), 2.59 (t, J=7.8 Hz, 2H), 7.31–7.46 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.21, 11.84, 13.83, 22.13, 24.51, 28.54, 31.33, 112.59, 125.40, 127.30, 128.92, 140.38, 140.86, 147.92; Anal. calcd for $C_{16}H_{22}N_2$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.24; H, 9.31; N, 11.52. **3h**:[2c] oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74–1.94 (m, 4H), 2.60 (t, J=6.3 Hz, 2H), 2.82 (t, J=6.3 Hz, 2H), 7.16–7.31 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.44, 23.30, 23.49, 23.50, 116.80, 124.74, 126.53, 127.68, 128.34, 128.68, 129.18, 130.80, 138.39, 140.36, 150.29; Mass (70 eV) m/z (rel intensity) 77 (25), 246 (44), 273 (42), 274 (M^+, 100). **3i**: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76–1.94 (m, 4H), 2.62 (t, J=6.3 Hz, 2H), 2.80 (t, J=6.3 Hz, 2H), 6.75–6.92 (m, 2H), 7.13–7.16 (m, 2H), 7.24–7.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.45, 23.15, 23.42, 23.50, 104.49, 104.81, 105.15, 111.45, 111.50, 111.75, 111.80, 115.94, 127.88, 128.37, 129.77, 129.89, 130.12, 140.33, 151.13, 154.99, 155.16, 158.37, 158.53, 160.22, 160.37, 163.54, 163.69; Anal. calcd for $C_{19}H_{16}F_2N_2$: C, 73.53; H, 5.20; N, 9.03. Found: C, 73.70; H, 5.17; N, 9.26. **3j**: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45–2.54 (m, 2H), 2.77–2.87 (m, 4H), 7.18–7.40 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.78, 24.79, 29.93, 125.10, 126.76, 126.80, 127.62, 128.41, 128.53, 128.82, 130.97, 136.24, 140.91, 162.28; Mass (70 eV) m/z (rel. intensity) 77 (26), 259 (72), 260 (M^+, 100); Anal. calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 83.19; H, 6.07; N, 10.92.

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