Expeditious Synthesis of 1,3,4-Trisubstituted Pyrazoles from Baylis-Hillman Adducts

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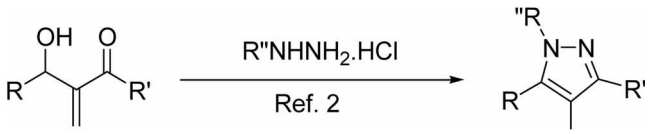
The pyrazole nucleus is present in a wide variety of biologically interesting compounds, which exhibit anti-hyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial, hypoglycemic, sedative-hypnotic activity.[1-5] Thus, continuous efforts have been devoted to the development of more general and versatile synthetic methodologies to this class of compounds.[1-5]

Recently we have reported on the regio-selective synthesis of 1,3,4,5-tetrasubstituted pyrazole derivatives from the reaction of Baylis-Hillman adducts of alkyl vinyl ketone and hydrazine derivatives (Scheme 1).[2] During the continuous studies on the chemical transformations of Baylis-Hillman adducts[6,7] including the synthesis of pyrazoles[2] we presumed that we could synthesize 1,3,4-trisubstituted pyrazoles from the reaction of hydrazine derivatives and acyloxiranes,[8] which could be synthesized easily from Baylis-Hillman adducts (Scheme 2).

According to the reported method, the required acyloxiranes **2a-e** were synthesized in moderate yields from the corresponding Baylis-Hillman adducts **1** by NaOCl in the presence of silica gel in acetonitrile.[8] With these acyloxiranes **2a-e** in our hands, we examined the synthesis of corresponding pyrazoles under a variety of conditions, and we found that the reaction of **2a-e** and various hydrazine hydrochlorides in 1,2-dichloroethane at refluxing temperature afforded the best results.[2] As shown in Table 1, the reaction of **2a** with phenylhydrazine hydrochloride, *tert*-butylhydrazine hydrochloride, 2,4-difluorophenylhydrazine hydrochloride afforded **3a-c** in moderate yields (39-75%). In the reaction of 2,4-dinitrophenylhydrazine (entry 4), we used *p*-toluenesulfonic acid as the acid catalyst. Other acyloxiranes **2b-e** showed similar results in the reactions of phenylhydrazine hydrochloride (36-71%, entries 5-8). Although we isolated the products in moderate yields in most cases, however, the yields of **3b** and **3f** were relatively low due to the formation of many intractable side products.

In summary, we disclosed an expeditious synthesis of 1,3,4-trisubstituted pyrazoles from the reaction of hydrazine derivatives and the acyloxiranes, which were prepared from Baylis-Hillman adducts.

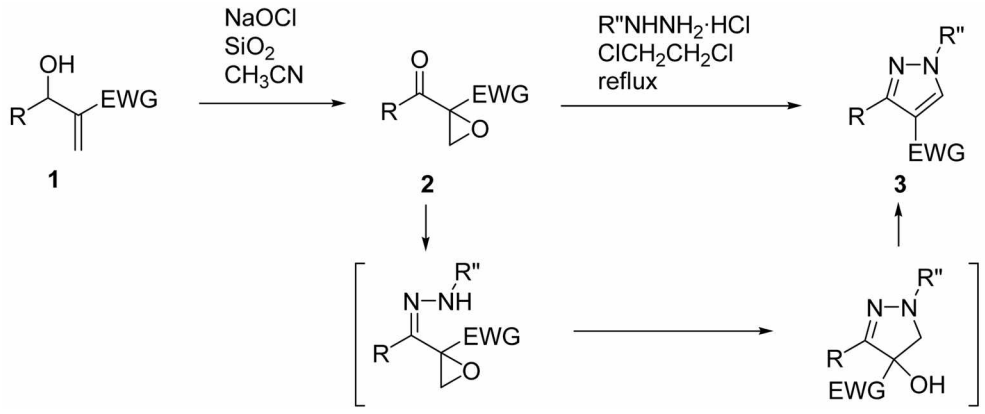


Scheme 1

Experimental Section

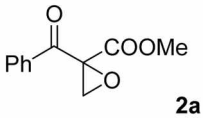
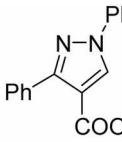
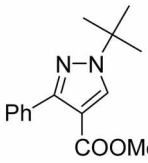
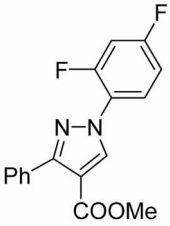
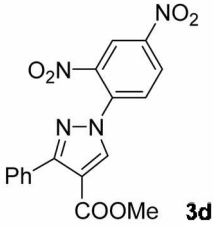
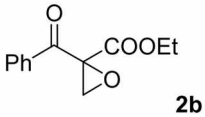
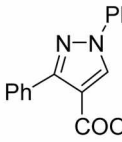
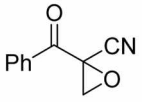
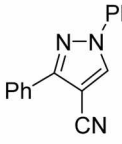
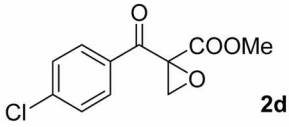
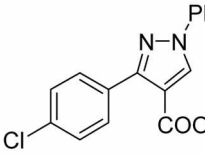
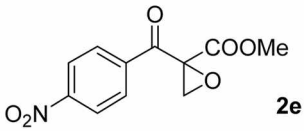
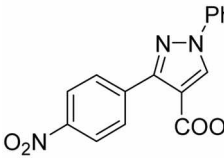
Typical procedure for the synthesis of 3a: A mixture of **2a** (206 mg, 1.0 mmol)[8] and phenylhydrazine hydrochloride (217 mg, 1.5 mmol) in 1,2-dichloroethane (5 mL) was heated to reflux for 48 h. After removal of solvent desired product was separated by column chromatographic purification process (hexanes/EtOAc/CH_2Cl_2, 12:1:2) as a yellow solid, 184 mg (66%). The spectroscopic data of products **3a-h** are as follows.

Compound **3a**:[3d,3e,3g] 66%; yellow solid, mp 103-104 °C; IR (flim) 3057, 2951, 1722 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.83 (s, 3H), 7.34-7.52 (m, 6H), 7.77-7.80 (m, 2H),



Scheme 2

Table 1. Synthesis of 1,3,4-trisubstituted pyrazoles

Entry	Acyloxiranes	Conditions	Pyrazoles (%)
1	 **2a**	$PhNHNH_2$.HCl (1.5 equiv) $ClCH_2CH_2Cl$ reflux, 48 h	 **3a** (66)
2	**2a**	*t*-$BuNHNH_2$.HCl (1.5 equiv) $ClCH_2CH_2Cl$ reflux, 72 h	 **3b** (39)
3	**2a**	2,4-$F_2C_6H_3NHNH_2$.HCl (1.5 equiv) $ClCH_2CH_2Cl$ reflux, 48 h	 **3c** (75)
4	**2a**	2,4-$(NO_2)_2C_6H_3NHNH_2$ (1.0 equiv) $ClCH_2CH_2Cl$, *p*-TsOH (1.0 equiv) reflux, 26 h	 **3d** (52)
5	 **2b**	$PhNHNH_2$.HCl (1.5 equiv) $ClCH_2CH_2Cl$ reflux, 48 h	 **3e** (71)
6	 **2c**	$PhNHNH_2$.HCl (1.5 equiv) $ClCH_2CH_2Cl$ reflux, 48 h	 **3f** (36)
7	 **2d**	$PhNHNH_2$.HCl (1.5 equiv) $ClCH_2CH_2Cl$ reflux, 37 h	 **3g** (71)
8	 **2e**	$PhNHNH_2$.HCl (1.5 equiv) $ClCH_2CH_2Cl$ reflux, 48 h	 **3h** (68)

7.86-7.89 (m, 2H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.40, 113.27, 119.46, 127.46, 127.90, 128.70, 129.30, 129.53, 132.01, 132.26, 139.18, 154.01, 163.31; ESIMS *m/z* 279 (M^++1). Anal Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.51; H, 5.29; N, 9.98.

Compound **3b**: 39%; colorless oil; IR (flim) 2978, 2941, 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.64 (s, 9H), 3.77 (s, 3H), 7.32-7.45 (m, 3H), 7.78-7.81 (m, 2H), 8.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.58, 51.10, 59.35, 110.34, 127.81, 128.20, 129.26, 131.60, 132.89, 152.30, 163.85; ESIMS *m/z* 259 (M^++1).

Compound **3c**: 75%; yellow solid, mp 79-80 °C; IR (flim) 3070, 2952, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.82 (s, 3H), 6.99-7.07 (m, 2H), 7.38-7.48 (m, 3H), 7.82-7.86 (m, 2H), 7.93-8.01 (m, 1H), 8.50 (d, J = 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.46, 104.84, 105.16, 105.19, 105.51, 112.13, 112.18, 112.43, 112.48, 113.41, 124.05, 124.10, 124.17, 124.22, 125.71, 125.84, 127.94, 128.86, 129.29,

131.59, 136.11, 136.24, 152.03, 152.19, 153.89, 155.38, 155.54, 159.65, 159.80, 162.98, 163.11. Anal Calcd for $C_{17}H_{12}F_2N_2O_2$: C, 64.97; H, 3.85; N, 8.91. Found: C, 64.75; H, 3.94; N, 8.76.

Compound **3d**: 52%; yellow solid, mp 172-174 °C; IR (flim) 3094, 2955, 1741 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.84 (s, 3H), 7.40-7.45 (m, 3H), 7.74-7.79 (m, 2H), 7.86 (d, J = 9.0 Hz, 1H), 8.37 (s, 1H), 8.52 (dd, J = 9.0 and 2.4 Hz, 1H), 8.74 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.80, 115.52, 121.26, 126.15, 127.65, 128.04, 129.29, 129.42, 130.59, 135.31, 136.49, 143.45, 146.26, 155.88, 162.37.

Compound **3e**: 71%; yellow solid, mp 61-63 °C; IR (flim) 3060, 2981, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, J = 7.2 Hz, 3H), 4.29 (q, J = 7.2 Hz, 2H), 7.33-7.52 (m, 6H), 7.76-7.81 (m, 2H), 7.84-7.89 (m, 2H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.26, 60.34, 113.74, 119.50, 127.44, 127.85, 128.66, 129.39, 129.55, 132.12, 132.23, 139.26, 154.03, 162.93.

Compound **3f**:[3h] 36%; yellow solid, mp 138-141 °C; IR (flim) 3140, 2238, 1542 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.56 (m, 6H), 7.73-7.77 (m, 2H), 8.06-8.10 (m, 2H), 8.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 91.78, 114.15, 119.72, 126.79, 128.16, 128.91, 129.63, 129.74, 130.37, 133.50, 138.76, 153.88; ESIMS *m/z* 246 (M^++1).

Compound **3g**: 71%; yellow solid, mp 144-145 °C; IR (flim) 2916, 2850, 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.83 (s, 3H), 7.34-7.44 (m, 3H), 7.47-7.53 (m, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.81 (d, J = 9.0 Hz, 2H), 8.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.52, 113.28, 119.53, 127.66, 128.16, 129.62, 130.50, 130.68, 132.44, 134.78, 139.12, 152.88, 163.23; ESIMS *m/z* 313 (M^++1).

Compound **3h**: 68%; yellow solid, mp 174-176 °C; IR (flim) 3140, 2955, 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.86 (s, 3H), 7.37-7.43 (m, 1H), 7.49-7.55 (m, 2H), 7.76-7.79 (m, 2H), 8.14 (d, J = 9.0 Hz, 2H), 8.30 (d, J = 9.0 Hz, 2H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.69, 113.75, 119.57, 123.14, 128.00, 129.70, 130.18, 132.77, 138.43, 138.89, 147.80, 151.56, 162.94.

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