

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 pyrazoles² 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

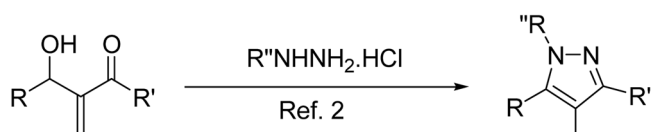
hydrochlorides in 1,2-dichloroethane at refluxing temperature afforded the best results.² As shown in Table 1, the reaction of **2a** with phenylhydrazine hydrochloride, *tert*-butylhydrazine hydrochloride, 2,4-difluorophenylhydrazine hydrochloride afforded **3a-c** in moderate yields (39-75%). In the 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.

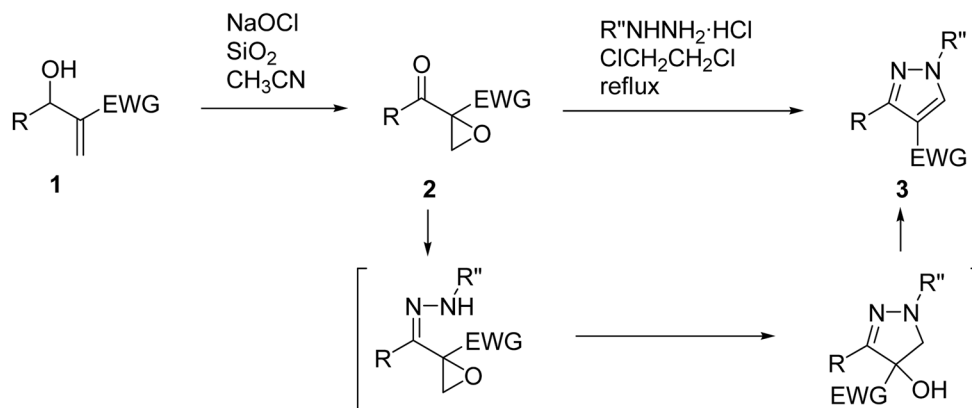
Experimental Section

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/CH₂Cl₂, 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 (film) 3057, 2951, 1722 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.83 (s, 3H), 7.34-7.52 (m, 6H), 7.77-7.80 (m, 2H),

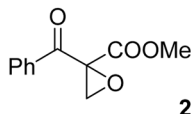
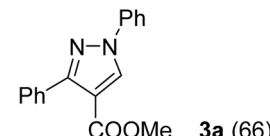
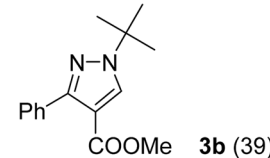
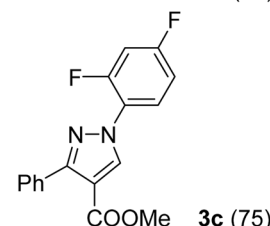
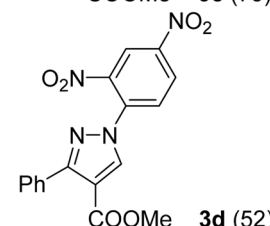
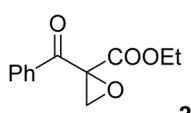
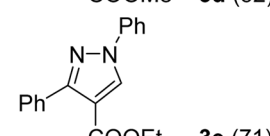
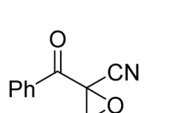
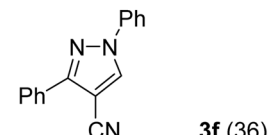
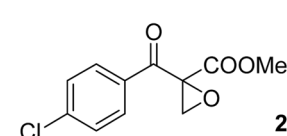
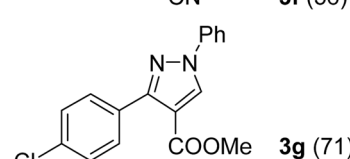
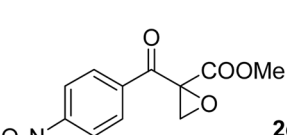
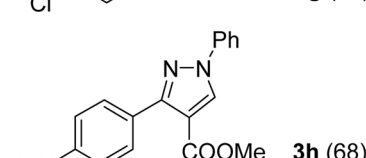


Scheme 1



Scheme 2

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

Entry	Acyloxiranes	Conditions	Pyrazoles (%)
1	 2a	PhNHNH ₂ .HCl (1.5 equiv) ClCH ₂ CH ₂ Cl reflux, 48 h	 3a (66)
2	2a	<i>t</i> -BuNHNH ₂ .HCl (1.5 equiv) ClCH ₂ CH ₂ Cl reflux, 72 h	 3b (39)
3	2a	2,4-F ₂ C ₆ H ₃ NHNH ₂ .HCl (1.5 equiv) ClCH ₂ CH ₂ Cl reflux, 48 h	 3c (75)
4	2a	2,4-(NO ₂) ₂ C ₆ H ₃ NHNH ₂ (1.0 equiv) ClCH ₂ CH ₂ Cl, <i>p</i> -TsOH (1.0 equiv) reflux, 26 h	 3d (52)
5	 2b	PhNHNH ₂ .HCl (1.5 equiv) ClCH ₂ CH ₂ Cl reflux, 48 h	 3e (71)
6	 2c	PhNHNH ₂ .HCl (1.5 equiv) ClCH ₂ CH ₂ Cl reflux, 48 h	 3f (36)
7	 2d	PhNHNH ₂ .HCl (1.5 equiv) ClCH ₂ CH ₂ Cl reflux, 37 h	 3g (71)
8	 2e	PhNHNH ₂ .HCl (1.5 equiv) ClCH ₂ CH ₂ Cl reflux, 48 h	 3h (68)

7.86-7.89 (m, 2H), 8.51 (s, 1H); ¹³C NMR (CDCl₃, 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 C₁₇H₁₄N₂O₂: 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; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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} ; 1H 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} ; 1H 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**: 36%; yellow solid, mp 138-141 °C; IR (flim) 3140, 2238, 1542 cm^{-1} ; 1H 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} ; 1H 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} ; 1H 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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References and Notes

- Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 3, pp 1-75 and further references on the synthesis and biological activities of pyrazole derivatives were cited in Ref. 2.
- Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 6737-6740.
- For the synthesis of similar pyrazole compounds, see: (a) Kamitori, Y.; Hojo, M.; Masuda, R.; Fujishiro, M.; Nakamura, I.; Yamamoto, K. *J. Heterocyclic Chem.* **1993**, *30*, 389-391. (b) Farghaly, A.-R.; El-Kashef, H. *ARKIVOC* **2006** (xi) 76-90. (c) Kaddar, H.; Hamelin, J.; Benhaoua, H. *J. Chem. Res. (S)* **1999**, 718-719. (d) Chornous, V. A.; Bratenko, M. K.; Vovk, M. V.; Sidorchuk, I. I. *Pharm. Chem. J.* **2001**, *35*, 203-205. (e) Hassaniien, A. Z. A.; Mohamed, M. H.; Gohzlan, S. A. S. *J. Chem. Res.* **2005**, 440-445. (f) Sridhar, R.; Perumal, P. T. *Synth. Commun.* **2003**, *33*, 1483-1488. (g) Aurell, M. J.; Domingo, L. R.; Pérez, P.; Contreras, R. *Tetrahedron* **2004**, *60*, 11503-11509. (h) Reddy, G. J.; Manjula, D.; Rao, K. S.; Khalilullah, Md.; Latha, D. *Indian. J. Chem. (B)* **2005**, *44B*, 2412-2415.
- For the synthesis of pyrazoles from acyloxiranes, see: (a) LeBlanc, R.; Dickson, J.; Brown, T.; Stewart, M.; Pati, H. N.; VanDerveer, D.; Arman, H.; Harris, J.; Pennington, W.; Holt, H. L., Jr.; Lee, M. *Bioorg. Med. Chem.* **2005**, *13*, 6025-6034. (b) Bhat, B. A.; Dhar, K. L.; Puri, S. C.; Saxena, A. K.; Shanmugavel, M.; Qazi, G. N. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3177-3180. (c) Bhat, B. A.; Puri, S. C.; Qurishi, M. A.; Dhar, K. L.; Qazi, G. N. *Synth. Commun.* **2005**, *35*, 1135-1142.
- Further references on the synthesis and biological activities of similar pyrazole derivatives, see: (a) Genin, M. J.; Biles, C.; Keiser, B. J.; Poppe, S. M.; Swaney, S. M.; Tarpley, W. G.; Yagi, Y.; Romero, D. L. *J. Med. Chem.* **2000**, *43*, 1034-1040. (b) Lévai, A.; Silva, A. M. S.; Cavaleiro, J. A. S.; Alkorta, I.; Elguero, J.; Jekö, J. *Eur. J. Org. Chem.* **2006**, 2825-2832. (c) Ge, M.; Cline, E.; Yang, L. *Tetrahedron Lett.* **2006**, *47*, 5797-5799. (d) Almirante, N.; Cerri, A.; Fedrizzi, G.; Marazzi, G.; Santagostino, M. *Tetrahedron Lett.* **1998**, *39*, 3287-3290. (e) Peruncheralathan, S.; Khan, T. A.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2005**, *70*, 10030-10035.
- For the review articles on Baylis-Hillman reaction, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811-891. (b) Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 51, pp 201-350. (c) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627-645. (d) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481-1490 and further references cited therein.
- For our recent papers on chemical transformations involving the Baylis-Hillman adducts, see: (a) Gowrisankar, S.; Kim, S. J.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 289-292. (b) Park, D. Y.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 1633-1636. (c) Kim, S. J.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 1069-1072. (d) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron* **2006**, *62*, 4052-4058. (e) Lee, K. Y.; Gowrisankar, S.; Lee, Y. J.; Kim, J. N. *Tetrahedron* **2006**, *62*, 8798-8804. (f) Park, D. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 6641-6645. (g) Park, D. Y.; Kim, S. J.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 6315-6319. (h) Lee, K. Y.; Lee, H. S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2007**, *28*, 333-335. (i) Lee, C. G.; Lee, K. Y.; Kim, S. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2007**, *28*, 719-720. (j) Lee, K. Y.; Park, D. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 1489-1492. (k) Lee, H. S.; Kim, S. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 1063-1066.
- For the synthesis of acyloxiranes, see: (a) Foucaud, A.; le Rouille, E. *Synthesis* **1990**, 787-789. (b) Das, B.; Holla, H.; Venkateswarlu, K.; Majhi, A. *Tetrahedron Lett.* **2005**, *46*, 8895-8897. (c) Chaiyanurakkul, A.; Jitchati, R.; Kaewpet, M.; Rajviroongit, S.; Thebtaranonth, Y.; Thongyoo, P.; Watcharin, W. *Tetrahedron* **2003**, *59*, 9825-9837.