

Starch–Sulfuric Acid (SSA) as Catalyst for a One-Pot Synthesis of 1,5-Diaryl-1*H*-pyrazoles

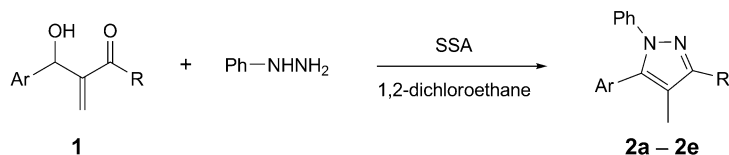
by Farhad Hatamjafari

Department of Chemistry, Faculty of Science, Islamic Azad University-Tonekabon Branch, Tonekabon, Iran (e-mail: hatamjafari@yahoo.com)

Protocols with starch–sulfuric acid (SSA) as reusable catalyst for the synthesis of aryl-1*H*-pyrazoles are described. SSA acted as an efficient and environmentally friendly catalyst for the regioselective condensation of *Baylis–Hillman* adducts **1** with phenylhydrazine hydrochloride leading to the new 1,5-diaryl-1*H*-pyrazole **2a–2e** in excellent yields (*Scheme* and *Table 1*).

Introduction. – Starch–sulfuric acid (SSA) is one of the cheap and heterogeneous biopolymer catalysts, that we designed and used in the synthesis of aryl-1*H*-pyrazoles. It can be easily separated, reused, and does not pollute the environment. Cellulose–sulfuric acid has been used previously as catalyst [4–7]. Aryl-1*H*-pyrazole derivatives belong to an important class of compounds exhibiting a wide range of biological activities as pharmaceuticals, agrochemicals, anti-inflammatories, antivirals, and antibacterials [8–13]. As part of our ongoing research on heterocyclic compounds containing N-atom [14], we report herein starch–sulfuric acid (SSA) as a new catalyst for the one-pot synthesis of 1,5-diaryl-1*H*-pyrazole derivatives **2** by condensation of *Baylis–Hillman* adducts **1** and phenylhydrazine (*Scheme*).

Scheme Condensation of *Baylis–Hillman* Adducts **1** and Phenylhydrazine



Results and Discussion. – The *Baylis–Hillman* adducts **1** were prepared by the reaction of methyl or ethyl vinyl ketone and benzaldehydes [15]. For the synthesis of the 1,5-diaryl-1*H*-pyrazole derivatives **2**, the reaction of a *Baylis–Hillman* adduct **1** and phenylhydrazine hydrochloride in 1,2-dichloroethane was used (*Scheme*). The reactions were complete after almost 1 h at 80° on starch–sulfuric acid (SSA) as solid support and gave **2a–2e** in yields >90% (*Table 1*).

Table 2 shows the optimization for the synthesis of 3-ethyl-4-methyl-5-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole (**2b**) from **1b**. Surprisingly, a significant improvement was observed and the yield of **2b** substantially increased to 97% after stirring; the

Table 1. *Three-Component Synthesis of Some 1,5-Diaryl-1H-pyrazoles 2 from Baylis–Hillman Adducts 1^{a)}*

Entry	R	Ar	Product	Yield [%]
1	Me	Ph	2a	91
2	Et	2-O ₂ N–C ₆ H ₄	2b	97
3	Et	4-O ₂ N–C ₆ H ₄	2c	95
4	Et	3-Cl–C ₆ H ₄	2d	93
5	Et	4-Cl–C ₆ H ₄	2e	90

^{a)} Conditions: **1** (1 mmol), phenylhydrazine hydrochloride (1 mmol), and SSA (0.05 g) in 1,2-dichloroethane (5 ml), at 80° for ca. 1 h.

mixture was stirred for only 1 h (Table 1, Entry 2). With this optimistic result in hand, we investigated the best reaction conditions by using different amounts of SSA (0.05 g of SSA was sufficient to catalyze the reaction effectively, Table 2) and solvents such as H₂O, MeOH, EtOH, MeCN, THF, and 1,2-dichloroethane. Only the latter gave excellent yields of **2b**. We also tested the reaction at different temperatures and established that the best temperature was 80°.

Table 2. *Optimizing the Reaction Conditions for 2b^{a)}*

SSA [g]	Time [h]	Yield [%]
0.00	5	45
0.02	2	85
0.05	1	91
0.10	2	76
0.12	2	69

^{a)} Conditions: **1b** (1 mmol) and phenylhydrazine hydrochloride (1 mmol) in 1,2-dichloroethane (5 ml) at 80°.

Conclusions. – We demonstrated the efficiency of starch–sulfuric acid (SSA) as catalyst for the synthesis of 1,5-diaryl-1H-pyrazoles **2** from Baylis–Hillman adducts **1** and phenylhydrazine hydrochloride in 1,2-dichloroethane giving good to excellent yields. SSA is superior to previously reported heterogeneous catalysts in view of its recovery, efficiency, nontoxicity, cheapness, and environmentally friendly behavior: It gives high yields and is reusable and, therefore, ideal for industrial applications.

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Experimental Part

General. All chemicals were obtained from Merck or Fluka and used without further purification. TLC: silica gel *SILG/UV 254* plates. IR Spectra: *Shimadzu-IR-470* spectrophotometer; $\tilde{\nu}$ in cm^{–1}. ¹H- and ¹³C-NMR Spectra: *Bruker-500-DRX-Avance* instrument; at 500 and 125 MHz, resp.; δ in ppm rel. to Me₄Si as internal standard, *J* in Hz. MS: *Finnigan-MAT 8430* mass spectrometer; ionization potential

70 eV; in m/z . Element analyses (C, H, N): Carlo-Erba-EA-1108 analyzer carried out with a Perkin-Elmer-240c analyzer.

Starch–Sulfuric Acid (SSA). To a magnetically stirred mixture of starch (1.0 g) in CH_2Cl_2 (20 ml), chlorosulfuric acid (ClSO_3H ; 0.2 g, 1.8 mmol) was added dropwise at 0° during 30 min, while HCl gas was removed from the reaction vessel immediately. After the addition was complete, the mixture was stirred for 2 h at 0° . The mixture was then filtered, washed with EtOH (30 ml), and dried at r.t.: starch–sulfuric acid. White powder.

Compounds 2a–2e: General Procedure. A mixture of SSA (0.05 g), Baylis–Hillman adduct **1** (1 mmol), and phenylhydrazine hydrochloride (1 mmol) in 1,2-dichloroethane (5 ml) was heated at 80° until the reaction was complete (ca. 1 h; TLC monitoring). The mixture was diluted with CH_2Cl_2 and washed with H_2O , the org. layer dried (MgSO_4), the solvent evaporated, and the residue purified by column chromatography (silica gel; hexane/AcOEt 8:2): 1*H*-pyrazoles **2a–2e**.

3,4-Dimethyl-1,5-diphenyl-1*H*-pyrazole (2a): Orange oil. IR: 3056, 2974, 1603, 1593, 1495. ^1H -NMR (500 MHz, CDCl_3): 1.36 (t, $J = 7.6$, 3 H); 1.94 (s, 3 H); 2.75 (q, $J = 7.6$, 2 H); 7.21–7.26 (m, 5 H); 7.34 (dd, $J = 7.6$, 1.4, 1 H); 7.55 (dt, $J = 8.1$, 1.4, 1 H); 7.62 (dt, $J = 7.5$, 1.3, 1 H); 7.98 (dd, $J = 8.1$, 1.2, 1 H). ^{13}C -NMR (125 MHz, CDCl_3): 154.4; 149.6; 140.2; 136.1; 133.5; 133.4; 130.0; 129.3; 127.2; 126.7; 125.0; 124.5; 115.3; 20.6; 13.8; 8.5. MS: 248 (M^+). Anal. calc. for $\text{C}_{17}\text{H}_{16}\text{N}_2$: C 82.22, H 6.49, N 11.28; found: C 82.04, H 6.35, N 11.20.

3-Ethyl-4-methyl-5-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole (2b): Orange oil. IR: 3052, 2970, 2965, 2920, 1607, 1552, 1487, 1351, 1455, 900, 750. ^1H -NMR (500 MHz, CDCl_3): 1.38 (t, $J = 7.5$, 3 H); 1.95 (s, 3 H); 2.70 (q, $J = 7.5$, 2 H); 7.20–7.26 (m, 5 H); 7.33 (dd, $J = 7.5$, 1.5, 1 H); 7.58 (dt, $J = 8.5$, 1.5, 1 H); 7.65 (dt, $J = 7.5$, 1.3, 1 H); 8.00 (dd, $J = 8.5$, 1.3, 1 H). ^{13}C -NMR (125 MHz, CDCl_3): 156.4; 148.2; 141.2; 135.7; 132.2; 135.5; 132.0; 129.7; 128.0; 127.4; 125.5; 124.5; 116.8; 21.8; 14.2; 8.8. MS: 307 (M^+). Anal. calc. for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$: C 70.34, H 5.58, N 13.67; found: C 70.25, H 5.48, N 13.53.

3-Ethyl-4-methyl-5-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole (2c): Orange oil. IR: 3055, 2972, 2920, 2821, 1590, 1456, 1519, 1340, 750. ^1H -NMR (500 MHz, CDCl_3): 1.34 (t, $J = 7.2$, 3 H); 2.12 (s, 3 H); 2.79 (q, $J = 7.2$, 2 H); 7.20 (dd, $J = 8.5$, 1.3, 2 H); 7.30–7.38 (m, 3 H); 7.40 (d, $J = 8.5$, 2 H); 8.30 (d, $J = 8.5$, 2 H). ^{13}C -NMR (125 MHz, CDCl_3): 158.0; 148.0; 143.5; 140.8; 135.5; 132.1; 129.2; 128.8; 127.0; 125.9; 120.2; 23.8; 14.5; 8.9. MS: 307 (M^+). Anal. calc. for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$: C 70.34, H 5.58, N 13.67; found: C 70.18, H 5.42, N 13.56.

5-(3-Chlorophenyl)-3-ethyl-4-methyl-1-phenyl-1*H*-pyrazole (2d): Orange oil. IR: 3054, 2962, 2855, 1590, 1568, 1490, 1055, 920, 850, 747, 690. ^1H -NMR (500 MHz, CDCl_3): 1.41 (t, $J = 7.5$, 3 H); 2.40 (s, 3 H); 2.90 (q, $J = 7.5$, 2 H); 7.30 (dt, $J = 7.5$, 1.2, 1 H); 7.25–7.35 (m, 8 H). ^{13}C -NMR (125 MHz, CDCl_3): 158.0; 144.1; 142.2; 137.7; 138.8; 135.5; 132.1; 129.5; 128.8; 128.1; 127.1; 126.0; 115.6; 21.1; 13.5; 9.1. MS: 296 (M^+). Anal. calc. for $\text{C}_{18}\text{H}_{17}\text{ClN}_2$: C 72.84, H 5.77, N 9.44; found: C 72.69, H 5.61, N 9.35.

5-(4-Chlorophenyl)-3-ethyl-4-methyl-1-phenyl-1*H*-pyrazole (2e): Orange oil. IR: 3055, 2964, 2916, 2873, 1605, 1509, 1455, 1732, 763. ^1H -NMR (500 MHz, CDCl_3): 1.38 (t, $J = 7.5$, 3 H); 2.13 (s, 3 H); 2.81 (q, $J = 7.5$, 2 H); 7.14 (d, $J = 7.0$, 2 H); 7.20–7.26 (m, 3 H); 7.31 (m, 2 H); 7.35 (d, $J = 7.0$, 2 H). ^{13}C -NMR (125 MHz, CDCl_3): 158.5; 152.3; 145.4; 138.3; 135.6; 131.4; 128.3; 126.5; 125.5; 124.8; 118.5; 21.0; 13.1; 9.0. MS: 296 (M^+). Anal. calc. for $\text{C}_{18}\text{H}_{17}\text{ClN}_2$: C 72.84, H 5.77, N 9.44; found: C 72.78, H 5.66, N 9.29.

REFERENCES

- [1] P. T. Anastas, J. C. Warner, 'Green Chemistry: Theory and Practice', Oxford University Press, Oxford, UK, 1998; P. T. Anastas, T. Williamson, 'Green Chemistry, Frontiers in Benign Chemical Synthesis and Process', Oxford University Press, Oxford, UK, 1998.
- [2] T. Hiedo, *Jpn. Tokkyo Koho JP* 56005480, 1981 (*Chem. Abstr.* **1981**, 95, 80922b).
- [3] J. P. Poupinel, G. Saint-Ruf, O. Foussard-Blanpin, G. Narcisse, G. Uchida-Ernouf, R. Lacroix, *Eur. J. Med. Chem.* **1978**, 13, 67.
- [4] A. Shaabani, A. Rahmati, Z. Badri, *Catal. Commun.* **2008**, 9, 13.
- [5] H. A. Oskooie, L. Tahershamsi, M. M. Heravi, B. Baghernejad, *E-J. Chem.* **2010**, 7, 717.
- [6] E. Mosaddegh, A. Hassankhani, A. Baghizadehb, *J. Chil. Chem. Soc.* **2010**, 4, 419.

- [7] J. Safari, S. H. Banitaba, S. D. Khalili, *J. Mol. Catal. A: Chem.* **2011**, 335, 46.
- [8] K. Y. Lee, G. Gowrishankar, J. N. Kim, *Tetrahedron Lett.* **2005**, 46, 5387.
- [9] N. Haddad, A. Salvagno, C. Busacca, *Tetrahedron Lett.* **2004**, 45, 5935.
- [10] J. W. Lyga, R. M. Patera, M. J. Plummer, B. P. Halling, D. A. Yuhas, *Pestic. Sci.* **1994**, 42, 29.
- [11] S. Cacchi, G. Fabrizi, A. Carangio, *Synlett* **1997**, 959.
- [12] K. Y. Lee, J. M. Kim, J. N. Kim, *Tetrahedron Lett.* **2003**, 44, 6737.
- [13] Y. R. Huang, J. A. Katzenellenbogen, *Org. Lett.* **2000**, 2, 2833.
- [14] N. P. Peet, E. W. Huber, J. C. Huffman, *J. Heterocycl. Chem.* **1995**, 32, 33.
- [15] M. Shi, J. K. Jiang, C. Q. Li, *Tetrahedron Lett.* **2002**, 43, 127.

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