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

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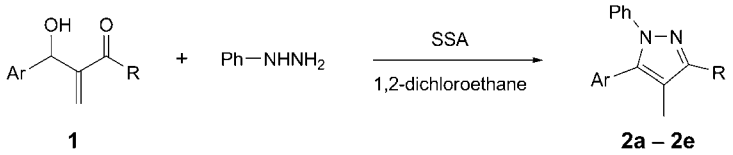
Protocols with starch–sulfuric acid (SSA) as reusable catalyst for the synthesis of aryl-1*H*-pyrazoles are described. SSA acted as an efficient and environmentally friendly catalyst for the regioselective condensation of *Baylis–Hillman* adducts **1** with phenylhydrazine hydrochloride leading to the 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*



1 **2a – 2e**

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-dicloroethane 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-1*H*-pyrazoles* **2** *from* Baylis–Hillman *Adducts* **1**[a])

Entry	R	Ar	Product	Yield [%]
1	Me	Ph	**2a**	91
2	Et	2-O_2N–C_6H_4	**2b**	97
3	Et	4-O_2N–C_6H_4	**2c**	95
4	Et	3-Cl–C_6H_4	**2d**	93
5	Et	4-Cl–C_6H_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 H_2O, 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-1*H*-pyrazoles **2** from *Baylis–Hillman* adducts **1** and phenylhydrazine hydrochloride in 1,2-dicloroethane 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 ^{13}C-NMR Spectra: *Bruker-500-DRX-Avance* instrument; at 500 and 125 MHz, resp.; δ in ppm rel. to Me_4Si 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. ^{1}H-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 $C_{17}H_{16}N_2$: 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. ^{1}H-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 $C_{18}H_{17}N_3O_2$: 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. ^{1}H-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 $C_{18}H_{17}N_3O_2$: 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. ^{1}H-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 $C_{18}H_{17}ClN_2$: 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. ^{1}H-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 $C_{18}H_{17}ClN_2$: C 72.84, H 5.77, N 9.44; found: C 72.78, H 5.66, N 9.29.

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