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$KHSO_4 \cdot H_2O/SiO_2$-Catalyzed, One-Pot, Solvent-Free Synthesis of Pyrazolines, Tetrahydrocarbozoles and Indoles using Microwave Irradiation

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$KHSO_4 \cdot H_2O/SiO_2$-Catalyzed, One-Pot, Solvent-Free Synthesis of Pyrazolines, Tetrahydrocarbozoles and Indoles using Microwave Irradiation

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Abstract: A new high-yielding, operationally simple, solvent-free, and mild method for preparation of pyrazolines, tetrahydrocarbazoles, and indoles has been developed using $KHSO_4 \cdot H_2O$ impregnated on SiO_2. The reactions have been probed under microwave irradiation (MWI), and ultrasonic and thermal conditions, employing different solid supports. The data revealed that $KHSO_4 \cdot H_2O$ impregnated on SiO_2 under MWI provides the best yields in a shorter time under solvent-free reaction conditions.

Keywords: Indoles, $KHSO_4 \cdot H_2O/SiO_2$, MWI, pyrazolines, sonication, tetrahydrocarbazoles

INTRODUCTION

Among a wide range of biologically active heterocycles, a significant amount of research activity has been directed toward the study of pyrazolines, tetrahydrocarbazoles, and indoles, owing to their wide variety of therapeutic activities.[1–4] A classical synthesis of these compounds involves formation of hydrazones obtained from ketones and arylhydrazines, which can subsequently be cyclized to products in the presence of acid catalysts[5] like acetic acid, $ZnCl_2$, H_2SO_4, HCl, *p*-toluenesulfonic acid, PCl_3, PPA, BF_3,

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sulphosalicylic acid, and $CuCl_2 \cdot KHSO_4 \cdot H_2O/SiO_2$ has been used in many organic transformations such as deprotection,[6] oxidation,[7] dehydration,[8] esterification,[9] and acetylation.[10] It has also proven to be a good catalyst for synthesis of some heterocyclic compounds.[11–13] We thought that the use of this reagent[14] to prepare pyrazolines, tetrahydrocarbazles, and indoles might be a smart choice in terms of efficiency, convenience, and less hazardous handling.

RESULTS AND DISCUSSION

An initial examination was carried out for condensation of cyclohexanone with phenylhydrazine in the presence of $KHSO_4 \cdot H_2O$ adsorbed on different solid supports and in different solvents, and the results are shown in Table 1. When the experiments were carried out under microwave irradiation (MWI), no solvent was used. From the data it is clear that SiO_2 is a better adsorbent, and the best results were obtained when for 2 molar equiv of the substrates (i.e., ketones) and 1 molar equiv of $KHSO_4 \cdot H_2O$ as KHSO4 $\cdot H_2O$ impregnated on SiO_2 was used either thermally or under MW $\cdot KHSO_4 \cdot H_2O$ alone could also bring about the reaction, but in this case the reactions took longer to reach completion. Sonication also effected the reaction but the time taken for completion of reaction was comparatively longer (Table 1).

The use of a SiO_2 support facilitates the workup of the reaction mixtures[15] and gave better yields of products, presumably by acting as a carrier to increase the surface area in the reaction. In the case of α,β-unsaturated ketones as substrates, the required pyrazolines **1a**–**e** were formed under MWI and solvent-free conditions (Table 2). At room temperature and under ultrasonication, only hydrazones were formed and their further cyclization to products did not occur even after 24 h. The structures of all products have been confirmed by spectral means (IR, ^{1}H NMR, and high resolution mass spectrometry (HRMS)) and by comparison with the literature data.

A variety of ketones were reacted under similar conditions to produce products in more than 90% isolated yields except for 3-pentanone (entry 6), where the reaction was performed at room temperature in acetonitrile (Table 3).

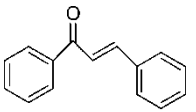
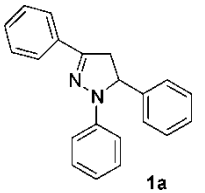
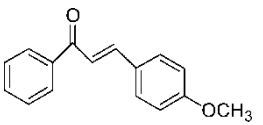
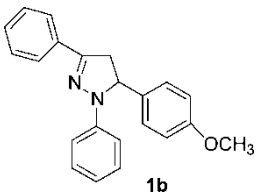
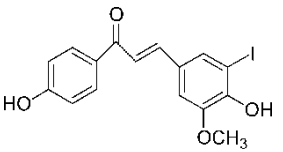
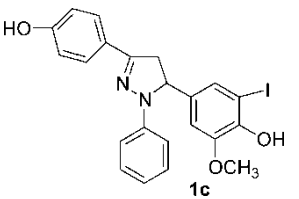
CONCLUSIONS

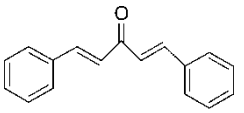
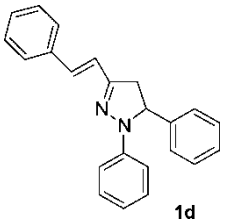
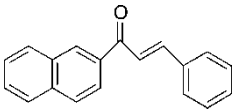
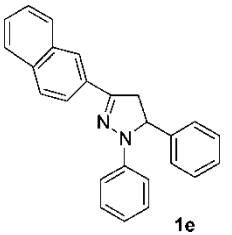
In summary, this work demonstrates a new high-yielding, operationally simple, solvent-free, and mild method for preparation of pyrazolines, tetrahydrocarbazoles, and indoles using $KHSO_4 \cdot H_2O$ impregnated on SiO_2.

Table 1. Scrutiny of the solid supports and solvents for the condensation reactions

Adsorbent	Solvent	Substrate reagent ratio	Time (yield %)		
			Thermally	MW (no solvent)	Sonication
Silica gel	CH_3CN	1.0	50 min (50)	10 min (50)	3 h (40)
Silica gel	CH_3CN	0.5	30 min (decomposition)	2 min (decomposition)	—
Silica gel	CH_3CN	2.0	15 min (94)	1 min (98)	2.5 h (90)
Silica gel	THF	2.0	1 h (76)	—	3 h (60)
Silica gel	Dioxane	2.0	1 h (70)	—	2.5 h (55)
Silica gel	CH_2Cl_2	2.0	1.5 h (60)	—	4 h (48)
Neutral alumina	CH_3CN	2.0	20 min (70)	1 min (85)	2.5 h (78)
Bentonite	CH_3CN	2.0	20 min (76)	2.5 min (80)	4 h (67)
No adsorbent	CH_3CN	2.0	1.5 h (82)	8 min (70)	4 h (62)

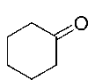
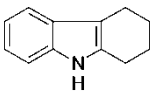
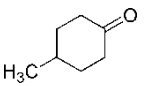
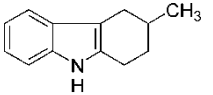
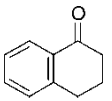
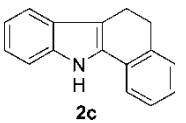
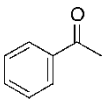
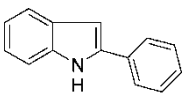
Table 2. Synthesis of pyrazolines

Entry	Substrate	Product	MW time (min), no solvent	Yield (%)	MP (°C) Exp.	MP (°C) Lit.
1		 **1a**	2.5	94	128–130	138[16]
2		 **1b**	3.5	98	78–80	80–82[16]
3		 **1c**	5.0	94	108	107–110[17]

4		 **1d**	4.5	96	87–89	—
5		 **1e**	3.5	97	168	167–168[18]

Notes: All compounds were characterized by ^{1}H NMR, IR, and finally by comparison with authentic samples prepared by known methods. Blank spaces indicate that no reference has been found; MWI was performed at power level 3 (400 W) with a 20-s pause after every 30-s.

Table 3. Synthesis of tetrahydrocarbazoles and indoles

Entry	Substrate	Product	Time		Yield (%)	MP (°C)	
			MW (min), no solvent	RT in CH_3CN (h)		Exp.	Lit.
1		 **2a**	0.83	4	99	115	114[16]
2		 **2b**	1	5	95	258	260[19]
3		 **2c**	2	6.5	94	162	163[20]
4		 **2d**	2.5	6	98	184	186[16]

5		**2e**	4.2	8	93	123	125[19]
6		**2f**	—	7	94	65	65[19]
7		**2g**	4	7	92	93	93[21]
8		**2h**	2.5	5.5	90	73	72[22]

Notes: All compounds were characterized by ^{1}H NMR, IR, and finally by comparison with authentic samples prepared by known methods. Blank space indicates that reaction has not been done. MWI was performed at power level 3 (400 W) with pause of 20-s. after every 30-s.

EXPERIMENTAL

Melting points were measured in open capillaries on a Perfit melting-point apparatus and are uncorrected. IR on KBr were recorded on Brucker-4800 infrared spectrometer. ^{1}H NMR and HRMS spectra were recorded on Bruker AC-200 (200-MHz) spectrometer and JEOL D-300 mass spectrometer at 70 eV respectively. TLC was performed on 0.5-mm-thick plates using BDH silica gel G as adsorbent. The plates were developed with iodine vapors, ceric ammonium sulfate in H_2SO_4, and the compounds were observed as black spots. All solvents were distilled before use. Recrystallization was achieved with aqueous MeOH.

General Procedure for the Preparation of 1a–e and 2a–h

Phenylhydrazine (10 mmol), the appropriate ketone (10 mmol), and $KHSO_4 \cdot H_2O/SiO_2$ (5 mmol with respect to $KHSO_4 \cdot H_2O$) were mixed thoroughly in a 100-mL beaker with glass rod. The mixture was irradiated in a microwave oven at power level 3 until the completion of the reaction (TLC monitored). The resultant mixture was cooled and stirred with EtOAc (40-mL) and filtered through Celite under suction. The filtrate was washed with cold water (10-mL), saturated $NaHCO_3$ (10-mL), and brine (10-mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo, and products were recrystallized from aqueous methanol (yield 90–95%).

1,5-diphenyl-3-[(E)]-2-arylethenyl]-4,5-dihydro-1H-pyrazoline **(1d)**. Yield: 96%. Mp 87–89°C; IR: 2920, 1660, 1606, 1558, 1274, 1168, 139, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.88 (dd, 1H, $J = 16$ and 14 Hz), 3.32 (dd, 1H, $J = 16$ and 10 Hz), 4.17 (dd, 1H, $J =$ 14 and 10 Hz), 6.52 (d, 1H, $J = 17$ Hz), 7.10 (d, 1H, $J = 17$ Hz), 7.24–7.68 (m, 15 H); HRMS: m/z at 324.4188 (M^+) 100% (calc. for $C_{23}H_{20}N_2$, 324.4184).

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