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SILICA GEL, AN EFFECTIVE CATALYST FOR THE REACTION OF ELECTRON-DEFICIENT NITRO-OLEFINS WITH NITROGEN HETEROCYCLES

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The reaction of electron-deficient olefins with nitrogen heterocycles such as pyrrole and indole was examined in the presence of silica gel at room temperature under stirring at solvent-free conditions. It was found that silica gel is an effective catalyst for this conjugate addition. This work resulted in the formation of monosubstituted pyrroles selectively as a major product except in a few cases where disubstituted pyrroles were also formed as side products. Thus, a simple, rapid, efficient, environmentally benign, and solvent-free method was established.

Keywords: Conjugate addition reaction; indole; nitro-olefins; pyrrole; silica gel

INTRODUCTION

Synthetic methods for *C*-alkyl pyrroles and *C*-alkyl indoles are in demand because of their importance as building blocks for the synthesis of biologically active compounds and natural products.[1] It is well documented that indole has good nucleophilicity from C-3, as pyrrole has from C-2. The conjugate addition of nitrogen heterocycles to electron-deficient olefins is one of the routes toward alkylated pyrroles and indoles and has been developed with various catalysts such as indium trichloride,[2] bismuth trichloride,[3] iodine,[4] sulfamic acid,[5] and aluminium dodecyl sulfate trihydrate $[Al(DS)_3 \cdot 3H_2O]$,[6] ytterbium triflate $[Yb(OTf)_3 \cdot 3H_2O]$,[7] $CeCl_3 \cdot 7H_2O$, and $NaI \cdot SiO_2$.[8] Protic solvents and Lewis acids have some limitations because they involve use of toxic reagents and require careful control of the acidity to prevent side reactions such as dimerization or polymerization. Although recently microwave methodology has been used,[9] there is still a need to develop an environmentally friendly method devoid of toxic acidic reagents and solvents.

Use of silica gel as a solid and mild acidic catalysts is well reported and is receiving considerable attention from synthetic chemists.[10,11] In the present study, we planned to use silica gel for conjugate additions of pyrrole and indole on electron-deficient nitro-olefins.

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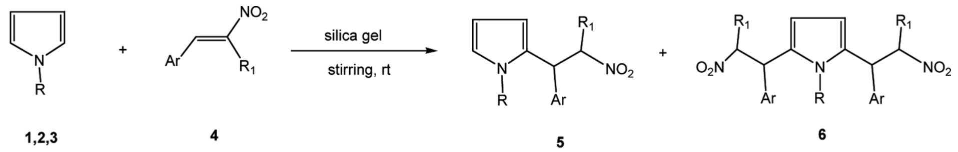
RESULTS AND DISCUSSION

Reaction between pyrrole and β-nitrostyrene **4a** was carried out by loading both of these compounds on silica gel and stirring at room temperature. 2-Alkyl pyrrole **5a** was obtained as a major product in 89% yield along with 2,5-dialkyl pyrrole **6a** in minor amounts 6% (Scheme 1; Table 1, entry 1). Thus, after achieving a successful, high-yielding, rapid Michael addition using silica gel, the reaction was generalized using nitro olefins **4b, 4c**, and **4e**, where surprisingly the reaction was more selective and afforded exclusively 2-alkyl pyrroles (Scheme 1; Table 1, entries 2, 3, and 5). However, during the Michael addition using other nitro olefins **4d, 4f**, and **4g**, 2,5-dialkyl pyrroles were also obtained in very minor amounts along with major monoalkylated products (Scheme 1; Table 1, entries 4, 6, and 7). Reaction of methyl-substituted nitro-olefins **4h, 4i**, and **4j** with pyrrole gave an inseparable



1. R = H
2. R = CH_3
3. R = COPh

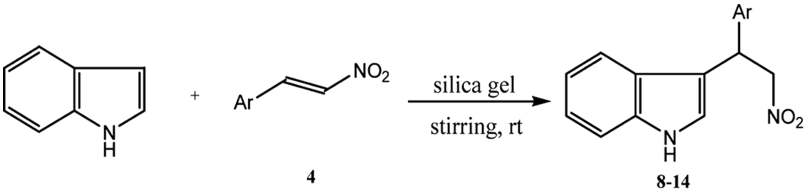
4a, 5a, 6a Ar = Ph; R = R_1 = H
4b, 5b Ar = 3,4-dimethoxyphenyl; R_1 = R = H
4c, 5c Ar = 3,4-methylenedioxyphenyl; R_1 = R = H
4d, 5d, 6d Ar = 2-furyl; R_1 = R = H
4e, 5e Ar = 4-nitrophenyl; R_1 = R = H
4f, 5f, 6f Ar = 2-thienyl; R_1 = R = H
4g, 5g, 6g Ar = 4-methoxyphenyl; R_1 = R = H
4h, 5h Ar = phenyl; R_1 = CH_3, R = H
4i, 5i Ar = 3,4-dimethoxyphenyl; R_1 = CH_3, R = H.
4j, 5j Ar = 4-nitrophenyl; R_1 = CH_3, R = H
4a, 5k Ar = phenyl; R = CH_3, R_1 = H

Scheme 1. Michael addition of pyrroles on nitro-olefins.

Table 1. Time, yield, and mp of Michael adducts from pyrrole

Entry	Michael adducts	Time (h)	2-Alkyl pyrrole **5**		2,5-Dialkyl pyrrole **6**	
			Yield (%)	Mp (°C)	Yield (%)	Mp (°C)
1	**a**	1.5	89	75–77 (lit.[3] mp 77–77.5 °C)	6	Oily liquid
2	**b**	3	83	146–147	—	—
3	**c**	3	80	Oily liquid	—	—
4	**d**	2.5	83	Oily liquid	9	Oily liquid
5	**e**	3	80	123–124	—	—
6	**f**	2.5	79	>250	10	Oily liquid
7	**g**	3	85	Oily liquid	8	Oily liquid
8	**h**	3.5	77	*	—	—
9	**i**	3.5	75	*	—	—
10	**j**	3.5	80	*	—	—
11	**k**	2.5	81	64–66	—	—

Notes. Yield calculated according to the recovered starting electrophile. An asterisk (*) indicates products are mixtures of diastereomers.



4a, 8 Ar = Ph
4b, 9 Ar = 3,4-dimethoxyphenyl
4c, 10 Ar = 3,4-methylenedioxyphenyl
4d, 11 Ar = 2-furyl
4e, 12 Ar = 4-nitrophenyl
4f, 13 Ar = 2-thienyl
4g, 14 Ar = 4-methoxyphenyl

Scheme 2. Michael addition of indole on nitro-olefins.

mixture of diastereomers of the 2-alkyl pyrroles **5h, 5i**, and **5j** as the only products (Scheme 1; Table 1, entries 8–10).

Reactivity of substituted pyrroles was studied using reactions of *N*-substituted pyrroles, namely *N*-methyl pyrrole **2** and *N*-benzoyl pyrrole **3**, with β-nitrostyrene **4a**. In the case of *N*-methyl pyrrole, 2-alkyl pyrrole **5k** was obtained exclusively in 81% yield (Table 1, entry 11) and in the case of *N*-benzoyl pyrrole, no reaction was observed. The latter can be attributed to decreased reactivity of pyrrole due to the electron-withdrawing *N*-benzoyl substituent.

After establishing good catalytic activity of silica gel for Michael additions of pyrroles and substituted pyrroles, indole was used for these reactions. Thus, a mixture of indole and β-nitrostyrene **4a** was loaded on silica gel and was stirred at room temperature for 30 min, affording product **8**, which was fully characterized by spectral techniques. Reactions of various other nitro-olefins **4b–g** and indole under similar reaction conditions furnished products **9–14**. The results are summarized in Scheme 2 and Table 2. The structures of all products were confirmed using infrared (IR), ^{1}H NMR, ^{13}C NMR, and gas chromatography–mass spectrometry (GC-MS).

Table 2. Time, yield, and mp of Michael adducts from indoles

Entry	Michael adducts	Time (h)	Yield (%)	Mp (°C)
1	**8**	0.5	92	99–101 (lit. mp 99 °C)[a]
2	**9**	2.5	79	143–145 (lit. mp 145 °C)[a]
3	**10**	2.5	82	144–146 (lit. mp 145 °C)[a]
4	**11**	0.5	80	69 (lit. mp 69 °C)[a]
5	**12**	2.5	78	143 (lit. mp 142 °C)[a]
6	**13**	0.5	85	93–95 (lit. mp 94 °C)[a]
7	**14**	2.5	87	151 (lit. mp 150–152 °C)[a]

Note. Yield calculated according to the recovered starting electrophile.
[a] Ref. [9b].

CONCLUSION

A simple, efficient, environmentally benign, and solvent-free silica gel–catalyzed method was established for the conjugate addition of pyrrole and indole. All reactions were very clean, and no polymerization was observed, in contrast to earlier reported reactions using different catalysts.

EXPERIMENTAL

Methods

All recorded melting points are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded as δ values in $CDCl_3$ with reference to tetramethylsilane (TMS) as internal standard on a Varian Mercury instrument, 300 MHz and 200 MHz for ^{1}H NMR and 75 MHz and 50 MHz for ^{13}C NMR. Fourier transform (FT)–IR spectra were recorded on a Perkin-Elmer 1600. Mass spectra were recorded on a Shimadzu QP 5050. Elemental analyses were recorded on Flash E.A.1112 Thermo instrument.

General Procedure

A mixture of indole (0.0024 mol) and nitro-olefins **4a–g** (0.002 mol) or pyrrole **1–3** (0.02 mol) and nitro-olefins **4a–j** (0.01 mol) was loaded on silica gel (60–120 mesh) and stirred at room temperature. After the reaction was completed as judged by thin-layer chromatography (TLC), the same silica gel was loaded on a silica-gel column. The chromatographic separation was carried out by using hexane–ethyl acetate to furnish the products.

Selected Data

Compound 5c. Yield 80%. Oily liquid; IR (KBr) (cm^{-1}): 3356, 1551, 1335; ^{1}H NMR (200 MHz, $CDCl_3$): 4.56–4.83 (m, 3H), 5.79 (s, 2H), 5.94 (brs, 1H), 6.02–6.06 (m, 1H), 6.54–6.65 (m, 4H), 7.91 (brs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): 42.7, 53.1, 79.3, 96.2, 101.3, 105.6, 108.2, 108.7, 118.3, 121.3, 128.9, 131.8, 147.4, 148.3; MS: m/z 260 M$^+$, 213 (100%), 200, 183, 92, 77, 65.

Compound 5e. Yield 80%. Mp 123–124 °C; IR (KBr) ν (cm^{-1}): 3404, 1551, 1358; ^{1}H NMR (300 MHz, $CDCl_3$): 4.85 (dd, $J = 11.0$, 15.4 Hz, 1H), 4.95–5.08 (m, 2H), 6.09 (brs, 1H), 6.18 (d, $J = 2.2$ Hz, 1H), 6.72 (brs, 1H), 7.4 (d, $J = 8.5$ Hz, 2H), 7.97 (brs, 1H), 8.17 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 42.6, 78.5, 106.4, 108.9, 118.9, 124.2, 127.0, 128.8, 145.3, 147.3; MS m/z 261 M$^+$, 214 (100%), 201, 167, 139, 115, 93.

Compound 5g. Yield 85%. Oily liquid; IR (KBr) ν (cm^{-1}): 3384, 1517, 1340; ^{1}H NMR (300 MHz, $CDCl_3$): 3.76 (s, 3H), 4.69–4.85 (m, 2H), 4.94 (d, $J = 11.3$, 6.6 Hz, 1H), 6.03 (brs, 1H), 6.12 (q, $J = 5.8$, 2.8 Hz, 1H), 6.64 (t, $J = 2.8$ Hz, 1H), 6.83 (d, $J = 8.8$ Hz, 2H), 7.11 (d, $J = 8.8$ Hz, 2H), 7.82 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 42.2, 55.3, 79.3, 105.4, 108.5, 114.4, 117.9, 128.9, 129.1, 129.7, 159.1; MS: m/z 246 M$^+$, 199 (100%), 186, 92, 77.

Compound 6g. Mixture of diastereomers 8% yield. Oily liquid; IR (KBr) ν (cm^{-1}): 3348, 1575, 1386; ^1H NMR (300 MHZ, $CDCl_3$): 3.76 (s, 6H), 3.77 (s, 6H) 4.61–4.78 (m, 8H), 4.8–4.93 (m, 4H), 5.98 (m, 4H), 6.79–6.83 (m, 8H), 7.03 (d, $J = 8.8$ Hz, 8H), 7.5 (2xbs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 42.1, 55.2, 79.2, 79.3, 105.7, 106.1, 114.1, 114.3, 114.4, 128.7, 128.8, 129.5, 129.57, 129.6, 159.0, 159.1.

Compound 5i. Mixture of two diastereomers in the ratio of 2.5:1. Yield 75%; mp 163–165 °C; IR (KBr), ν (cm^{-1}): 3360, 1550, 1387; ^1H NMR (300 MHz, $CDCl_3$): 1.44 (d, $J = 6.6$ Hz, 3H), 1.66 (d, $J = 6.6$ Hz, 3H), 3.84 (m, 12H, four singlets overlapping), 4.41 (d, $J = 10.17$ Hz, 1H), 4.48 (d, $J = 10.17$ Hz, 1H), 5.04–5.2 (m, 2H), 6.1 (brs, 2H), 6.15 (brs, 2H), 6.6–6.9 (m, 8H), 7.9 (brs, 2H,); ^{13}C NMR (75 MHz, $CDCl_3$): 18.9, 19.1, 48.8, 49.2, 55.7, 55.8, 55.9, 86.8, 86.9, 105.6, 106.5, 108.4, 108.8, 111.0, 111.2, 111.3, 117.7, 119.3, 120.5, 128.3, 129.5, 129.9, 130.7, 148.3, 148.4, 148.9, 149.1; MS m/z 290 M^+, 243, 228, 216 (100%), 200, 154, 142, 130, 77.

Compound 5j. Mixture of two diastereomers in the ratio of 4.7:1. Yield 80%; mp 153–155 °C; IR (KBr) ν (cm^{-1}): 3393, 1524, 1348; ^1H NMR (300 MHz, $CDCl_3$): 1.47 (d, $J = 6.6$ Hz, 3H), 1.69 (d, $J = 6.6$ Hz, 3H), 4.56 (d, $J = 10.45$ Hz, 1H), 4.69 (d, $J = 9.9$ Hz, 1H), 5.21 (m, 2H), 6.14 (brs, 2H), 6.19 (brs, 2H), 6.68 (brs, 2H), 7.38–7.46 (m, 4H), 8.0 (brs, 2H), 8.14 (d, $J = 8.25$ Hz, 2H), 8.2 (d, $J = 8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 18.8, 19.1, 48.9, 49.5, 86.0, 86.6, 106.8, 107.0, 108.9, 109.4, 118.5, 118.6, 124.1, 124.2, 128.5, 129.3, 144.9, 145.6.

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