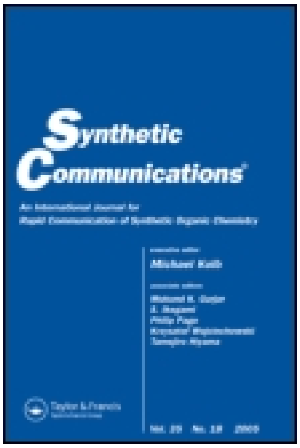

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Silica Sulfuric Acid-Catalyzed Friedel-Crafts Alkylation of Indoles with Nitro Olefins

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Abstract: The 1,4-conjugate addition of indoles to nitro olefins was efficiently carried out using an environmentally benign catalyst, silica sulfuric acid, at ambient temperature.

Keywords: C-C bond formation, conjugate addition reactions, indole, nitro olefins, silica sulfuric acid

INTRODUCTION

Indoles and their derivatives occur in nature and have a variety of biological activities.[1] Because of this, indoles and their derivatives have great importance in synthetic organic chemistry. The 3-position of indole is the preferred site for the electrophillic substitution reaction; 3-alkyl or acyl indoles are versatile intermediates for the synthesis of a wide range of indole derivatives.[2] In recent years, catalytic Michael-type additions of nucleophiles to nitro olefins have emerged as a powerful method for the formation of new C-C bonds in organic synthesis.[3] Nitro olefins are very attractive Michael acceptors because the nitro group is the strongest electron-withdrawing group known[4] and has been widely used in organic

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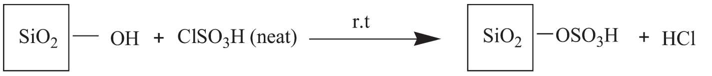


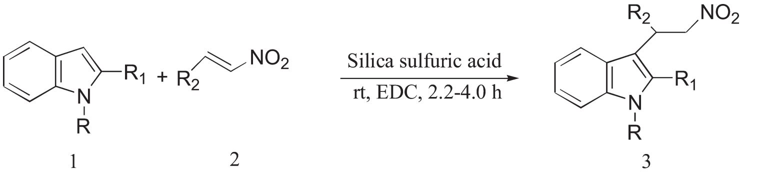
Scheme 1.

synthesis.[5] Among the strongest Michael acceptors,[6] nitro olefins are also attractive because the nitro group can served as a masked functionality.

Recently, silica sulfuric acid is a powerful and an efficient solid acid for various chemical transformations.[7] Silica sulfuric acid was prepared by treating silica gel with chloro sulfonic acid in which sulfuric acid immobilized on the surface of silica gel via a covalent bond (Scheme 1).[8] The acid-catalyzed conjugate addition of indoles has been reported,[9] where many procedures involve careful control of acidity to prevent side reactions such as dimerization or polymerization, require long reaction times, elevated temperatures, and expensive reagents, and result in low yields. To over come these drawbacks, we describe the remarkable catalytic activity of silica sulfuric acid in the conjugate addition of indoles to nitro olefins.

RESULTS AND DISCUSSION

General treatment of the indole with the trans β-nitro styrene (Scheme 2) in the presence of a catalytic amount of the silica sulfuric acid in dichloro ethane gave the corresponding 3-alkylated products in high yields (71–93%) at ambient temperature under optimal reaction conditions. A variety of nitro olefins and indoles were investigated, and the results are summarized in Table 1. Most nitro olefins reacted with indole and its derivatives to produce alkylated indoles in good yields. The reactions were clean, and the products were obtained in high yields without the formation of any side products such as dimers or trimers. This procedure does not require any promoters, activators, or anhydrous conditions. All the products were isolated and characterized by ^{1}H NMR, mass, and IR spectroscopy.

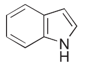
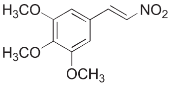
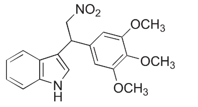
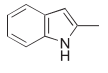
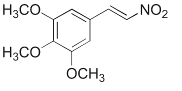
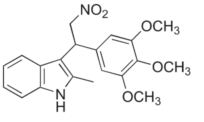
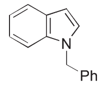
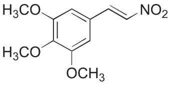
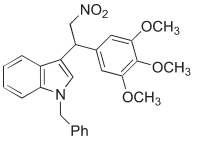
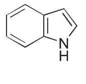
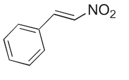
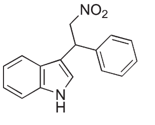
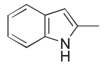
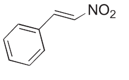
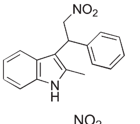
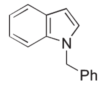
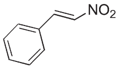
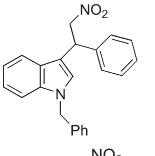
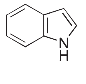
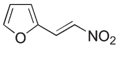
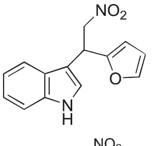
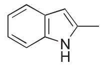
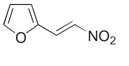
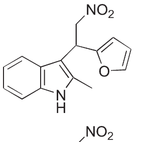
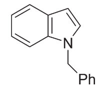
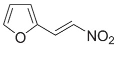
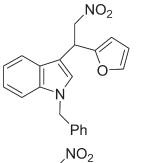
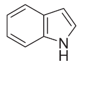
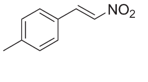
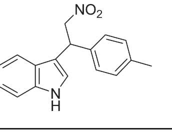


R = H,Bn
R_1 = H, Me

R_2= Ph, 3, 4, 5-tri-OMePh
Furyl, P-OMePh,
P-MePh

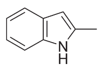
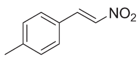
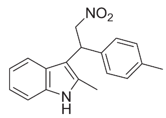
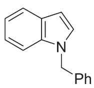
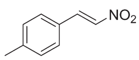
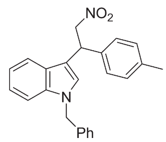
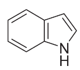
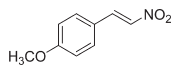
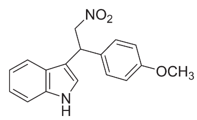
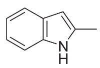
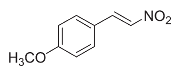
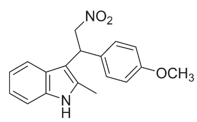
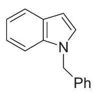
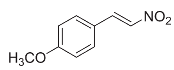
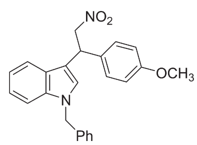
Scheme 2.

Table 1. Silica sulfuric acid–catalyzed addition of indoles with nitro olefins

Entry	Nucleophile	Electrophile	Product[a]	Time (h)	Yield (%)[b]
a				2.5	85
b				2.2	84
c				3.0	80
d				2.5	93
e				2.5	78
f				3.0	79
g				3.0	78
h				3.5	75
i				4.0	72
j				3.0	75

(*continued*)

Table 1. Continued

Entry	Nucleophile	Electrophile	Product[a]	Time (h)	Yield (%)[b]
k				3.0	75
l				3.5	78
m				2.5	75
n				2.5	71
o				3.0	72

[a]All products were characterized by IR, ^{1}H NMR, and mass spectroscopy.
[b]Isolated and unoptimized yields.

CONCLUSION

In summary, we have demonstrated that silica sulfuric acid is a superior acid catalyst for the alkylation of indoles with nitro olefins. This procedure has the advantages of mild reaction conditions, high yields of products, short reaction times, and simple experimental/product-isolation techniques, which make it a useful and attractive process for the synthesis of alkylated indole derivatives.

General Procedure for the Addition of Indoles to Nitro Olefins

A mixture of indole **1** (5 mmol), nitro olefin **2** (5 mmol), and silica sulfuric acid (catalytic, 30 mg) in dichloro ethane (2 ml) was stirred at room temperature for an appropriate time (Table 1). After complete conversion as indicated by thin-layer chromatography (TLC), the compound was purified by column chromatography on silica gel (hexane–ethyl acetate 9:1) to afford the pure products **3** (Table 1).

Selected Data for Compounds

Compound 3b: Solid. Mp: 124–126°C; IR (KBr, cm^{-1}): 3402, 2931, 1591, 1550, 1507, 1459, 1424, 1125, 1003, 745; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 10.45$ (1H, s), 7.48 (1H, d), 7.31 (1H, d), 7.15–6.95 (2H, m), 6.80 (2H, s), 5.30–5.10 (3H, m), 3.78 (9H, s), 2.50 (3H, m); LC-MS m/z: 370 (M^+).

Compound 3e: Solid. Mp: 100–102°C; IR (KBr, cm^{-1}): 3408, 2918, 1550, 1458, 1429, 1377, 1301, 744, 700; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.75$ (1H, s), 7.30–6.90 (9H, m), 5.18–5.03 (3H, m), 2.25 (3H, s); EI-MS m/z: 280 (M^+).

Compound 3h: Pale brown viscous oil. IR (neat, cm^{-1}): 3406, 2919, 1552, 1502, 1460, 1429, 1378, 1302, 1189, 1142, 1032, 742; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.85$ (1H, s), 7.38–6.95 (4H, m), 6.94–6.92 (1H, d), 6.28–6.22 (1H, m), 6.05–6.01 (1H, d), 5.18–4.85 (3H, m), 2.25 (3H, s); EI-MS m/z: 270 (M^+).

Compound 3k: Pale brown viscous oil. IR (neat, cm^{-1}): 3399, 2922, 1617, 1555, 1458, 1218, 1110, 745; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.80$ (1H, s), 7.38–6.78 (8H, m), 5.12–4.96 (3H, m), 2.30 (3H, s), 2.24 (3H, s); LC-MS m/z: 294 (M^+).

Compound 3n: Solid. Mp: 110–111°C; IR (KBr, cm^{-1}): 3406, 2924, 1612, 1550, 1510, 1460, 1377, 1247, 1113, 1029, 745; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.78$ (1H, s), 7.32–7.14 (4H, m), 7.08–6.94 (2H, m), 6.78–6.75 (2H, d), 5.18–4.95 (3H, m), 3.75 (3H, s), 2.37 (3H, s); LC-MS m/z: 310 (M^+).

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