Microwave-Assisted Solid-Acid-Catalyzed Friedel–Crafts Alkylation and Electrophilic Annulation of Indoles Using Alcohols as Alkylating Agents

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Abstract: Alcohols are considered environmentally benign alkylating agents since the only by-product generated in their reactions is water. Herein, we report a microwave-assisted Friedel–Crafts alkylation and electrophilic annulation of indoles using alcohols as alkylating agents. Alkylation of indoles using *tert*-butyl alcohol gives 3-substituted *tert*-butylindoles. A domino electrophilic annulation/aromatization of indoles using hexane-2,5-diol results in the formation of substituted carbazoles. The reaction is catalyzed by a strong, solid-acid catalyst montmorillonite K-10. The products were obtained in good yields and high selectivities.

Key words: alkylation, carbazoles, indole, *tert*-butyl alcohol, hexane-2,5-diol, montmorillonite K-10, microwave heating, annulation

The indole scaffold is prominent among numerous natural products and biologically active compounds.[1] Therefore, synthesis and functionalization of indoles have attracted considerable attention over the years.[2] The Friedel–Crafts alkylation is extensively used in the chemical industry to produce a vast array of products.[3] It is one of the most fundamental C–C bond-forming reactions and has been explored widely for the functionalization of indoles.[4,5] Although very effective, the traditional Friedel–Crafts chemistry does not conform to the ever stricter contemporary environmental regulations. Thus, the design and development of eco-friendly methods for such transformations is of paramount importance.[6] There are numerous studies, which address the role of the catalyst, and describe the use of environmentally benign, solid Brønsted or Lewis acid catalysts.[6] The majority of these studies still rely on popular alkyl halides as alkylating agents. These reactants, while very reactive and convenient to use, produce corrosive and harmful hydrogen halogenides as by-products and thus cannot be considered as sustainable reagents. To replace these alkylating agents in the design of eco-friendly processes, one can consider alternatives. While alcohols are less reactive than alkyl halides in electrophilic substitutions, they have a long shelf-life and produce water as the only by-product after alkylation. Recently, a few methods have been reported for alkylation of indoles using alcohols.[5] However, the use of expensive, toxic, nonrecyclable, or moisture-sensitive reagents and catalysts does not make these methods attractive for large-scale synthesis.

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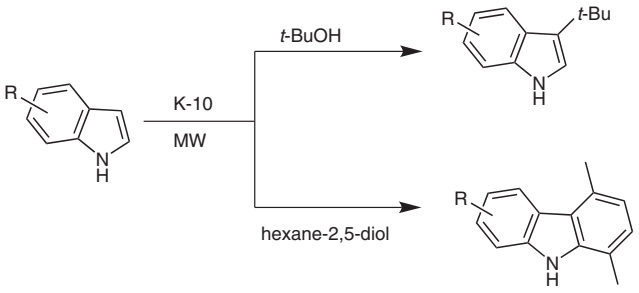
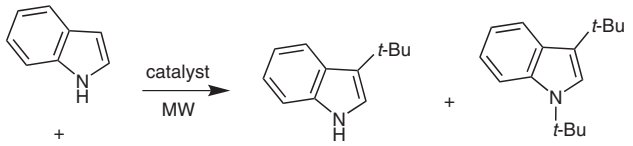
The application of solid-acid catalysis to replace harmful mineral acids is a rapidly growing area in organic synthesis. Solid acids such as natural or modified clays, metal oxides, zeolites, acidic ion-exchange resins have been widely explored to develop greener synthetic methods.[7] Friedel–Crafts alkylations using alcohols as electrophiles have also been reported with solid-acid catalysts such as modified K-10[8] and anionic clays.[9] The catalyst of choice in this work is montmorillonite K-10. It offers a range of advantages over liquid acids. It is a noncorrosive, inexpensive, and easily reusable stable solid. Most importantly, it is commercially available and can be used without any pretreatment. These benefits along with physical characterization of K-10 have been discussed in several reviews.[6,7,10] It is also an excellent catalyst for microwave-assisted organic synthesis (MAOS).[10]

In order to continue our efforts towards developing greener protocols for synthesis, herein we report the application of alcohols as alkylating agents in a solid-acid-catalyzed Friedel–Crafts alkylation of indoles (Scheme 1). The reactions were carried out in a CEM Discover microwave reactor and, for comparison, in a pressure vessel under conventional heating. The reaction of indole and *tert*-butyl alcohol under solvent-free conditions[11] served as a probe. Optimization reactions were carried out to study the effect of catalyst, temperature and time. The results are presented in Table 1. Initial results indicated that higher molar amount (1.5 equiv) of *tert*-butyl alcohol gave optimum yields. The reaction could be completed under mild conditions in a matter of minutes. We have observed the formation of two major products; the expected 3-substituted product **1** and 1,3-disubstituted indole **2**. The best selectivity for product **1** was observed at 130 °C after 10 minutes (Table 1, entry 2). Both longer reaction times and higher temperatures increased the formation of the 1,3-dialkylated product **2** (entries 3, 4, and 5). Different acid-



Scheme 1 Montmorillonite K-10 catalyzed Friedel–Crafts alkylation of indoles using *tert*-butyl alcohol and hexane-2,5-diol

Table 1 Effect of Experimental Variables on the Alkylation of Indole Using *tert*-Butyl Alcohol[a]



Entry	Catalyst	Conditions	Temp (°C)	Time (min)	Yield (%)[b] **1/2**
1	K-10	MW[c]	120	10	35/0
2	K-10	MW[c]	130	10	86/7
3	K-10	MW[c]	130	15	80/15
4	K-10	MW[c]	140	10	62/31
5	K-10	MW[c]	150	10	42/55
6	$H_3[PW_{12}O_{40}]$	MW[c]	130	10	3/10
7	$H_3[PMo_{12}O_{40}]$	MW[c]	130	10	10/0
8	K-10	CH[d]	130	60	36/25
9	HCl	CH[d]	80	60	34/53

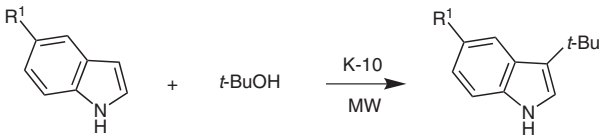
[a] Indole (1 mmol) and *t*-BuOH (1.5 mmol) were used.
[b] GC yields.
[c] Microwave heating.
[d] Conventional heating.

catalysts were screened (entries 6, 7, and 9) and K-10 was found to show the best performance in the alkylation of indole. To determine the beneficial effect of microwaves, a reaction under conventional heating conditions was also carried out. Conventional heating resulted in significantly longer reaction time at 130 °C with reduced yield and selectivity (entry 8).

To explore the scope of our approach, we used a variety of substituted indoles. Table 2 summarizes the results of the *tert*-butylation reactions. Almost all indoles gave the corresponding alkylated products in good yields. It is worth mentioning that the conversion of the starting materials is close to complete and the decrease in yield is usually due to the formation of the dialkylated products. Indoles with electron-withdrawing groups gave better yields as compared to those with electron-donating groups. This behavior can be accounted for by the fact that the first alkylation significantly increases the already high reactivity of indoles and therefore indoles with electron-donating groups readily undergo a second alkylation unlike those with electron-withdrawing groups. Reaction times were further optimized in the case of some indoles (Table 2, entries 4, 5, 7, and 8).

The fact that first alkylation increases the reactivity of indoles triggered the possibility of using a diol, which can act as a bifunctional electrophile. Intermolecular or intramolecular Friedel–Crafts cyclizations with bidentate electrophiles can lead to biologically important compounds. In the intramolecular pathway, the reacting moieties can undergo cyclization due to the closed spatial arrangement. On the contrary, in intermolecular reactions, the bidentate nature of electrophiles may lead to side reactions. However, the substantially higher reactivity of N-heterocycles such as indoles make the use of a bifunctional electrophile appealing.

Table 2 Microwave-Assisted Alkylation of Indoles[a]



Entry	R^1	Temp (°C)	Time (min)	Yield (%)[b,c]
1	H	130	10	86/62
2	Cl	130	10	91/68
3	NO_2	130	10	85/73
4	CN	130	15	77/63
5	CO_2Me	130	15	78/67
6	OMe	130	10	67/50
7	OH	130	8	68/52
8	Me	130	8	66/47

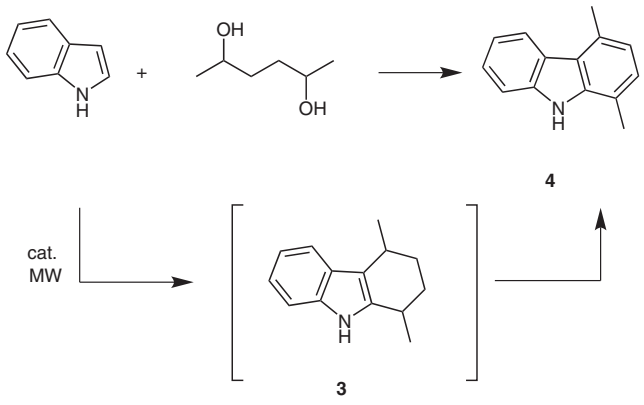
[a] Indole (1 mmol) and *t*-BuOH (1.5 mmol) were used.
[b] GC yields.
[c] Isolated yields.

Our previous investigations have shown that electrophilic annulation can be used to build indoles or carbazoles in one-pot domino reactions.[12] Carbazoles, which are ubiquitous in biologically active natural products[13] and material science,[14] have been a target of interest for synthetic chemists.[12,15]

To explore the possibility of the use of a diol as an alkylating agent, the reaction of indole and hexane-2,5-diol was tested under the previously optimized conditions (130 °C, 10 min). The results are summarized in Table 3. However, no reaction was observed under these experimental conditions most likely due to the lower reactivity of secondary alcohol as compared to tertiary alcohol. Upon increasing the temperature, the formation of tetrahydrocarbazole **3** was observed at 140 °C. Interestingly, the aromatic product **4** also formed in 11% yield.

While the oxidative aromatization via dehydrogenation in the presence of K-10[16] is not unprecedented, it raised the opportunity to synthesize carbazoles in a one-pot domino approach. The best selectivity for the formation of carbazole was observed at 160 °C (Table 3, entry 4). Further increase in temperature resulted in decomposition of the product even at reduced reaction time (entry 5). For comparison, the test reaction was also carried out without solvent in a pressure vessel by conventional heating. As

Table 3 Effect of Experimental Variables on the Synthesis of 1,4-Dimethylcarbazole[a]



Entry	Catalyst	Conditions	Temp (°C)	Time (h)	Yield (%)[b] **3/4**
1	K-10	MW[c]	130	1	0/0
2	K-10	MW[c]	140	1	82/11
3	K-10	MW[c]	150	1	22/63
4	K-10	MW[c]	160	1	0/96
5	K-10	MW[c]	170	0.5	0/82
6	K-10	CH[d]	160	16	22/56

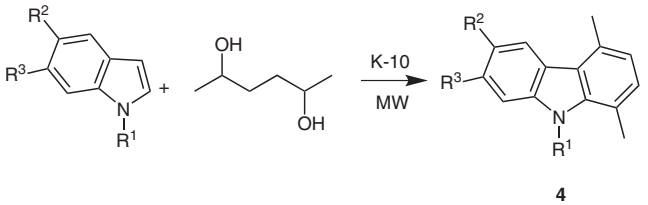
[a] Indole (1 mmol) and hexane-2,5-diol (1.5 mmol) were used.
[b] GC yields.
[c] Microwave heating.
[d] Conventional heating.

expected, even after 16 hours of heating, the formation of carbazole was only 56% (entry 6).

We decided to test the scope of our approach by applying a variety of substituted indoles. The results are tabulated in Table 4. Various substituted indoles readily underwent annulation/oxidative aromatization with hexane-2,5-diol to form corresponding dimethylcarbazoles. As indicated, the reaction conditions can tolerate various functional groups such as alkyl, alkoxy, carbmethoxy, nitro and halogens. 6-Methyl, 5-carboxymethyl, and *N*-methylindoles required higher reaction temperature (Table 4, entries 4, 6, and 9).

Scheme 2 shows the proposed mechanism for the synthesis of 1,4-dimethylcarbazole from indole and hexane-2,5-diol. In the first step, hexane-2,5-diol is protonated by K-10. This is followed by condensation of the protonated species to form 2,5-dimethyltetrahydrofuran.[17] 2,5-Dimethyltetrahydrofuran is protonated again facilitating nucleophilic attack by C-3 of indole, which upon opening leads first to alkylation of indole. This is followed by a second nucleophilic attack by indole to form a cyclic tetrahydrocarbazole intermediate.[18] We have reported earlier that, mostly under microwave-assisted conditions, K-10 was able to execute aerobic oxidative dehydrogenation, including amine oxidation[19] or oxidative aromatization.[16] This is exactly what we have observed here as well. In the last step the tetrahydrocarbazole intermediate underwent an oxidative aromatization producing the corresponding carbazole.

Table 4 Microwave-Assisted Synthesis of Substituted Carbazoles[a]



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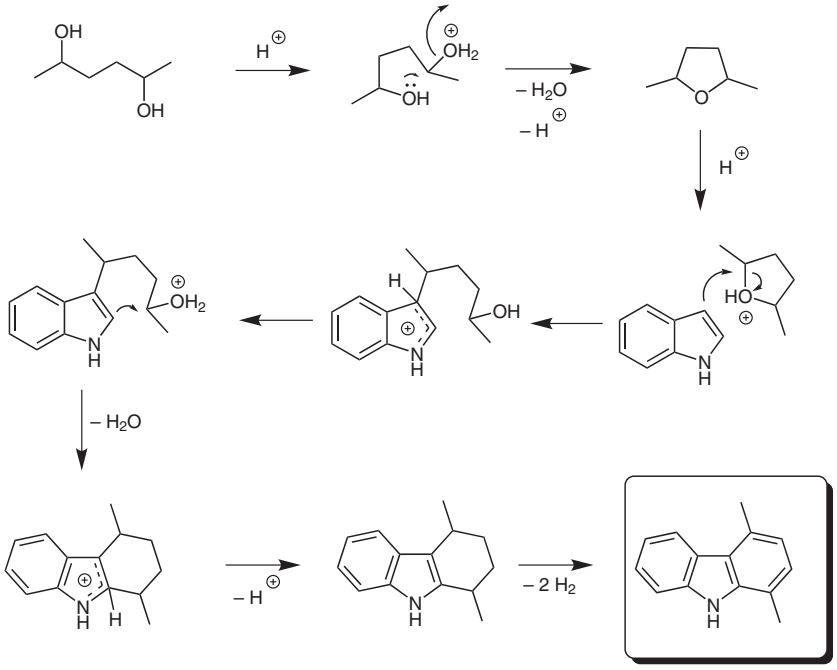
Entry	R^1	R^2	R^3	Temp (°C)	Time (h)	Yield (%)[b,c]
1	H	H	H	160	1	96/83
2	H	Cl	H	160	1	83/72
3	H	Br	H	160	1	65/52
4	H	H	Me	170	0.5	78/68
5	H	Me	H	160	1	77/70
6	H	CO_2Me	H	170	0.5	87/79
7	H	NO_2	H	160	1	82/75
8	H	OMe	H	160	1	71/59
9	Me	H	H	170	0.5	70/62

[a] Indole (1 mmol) and hexane-2,5-diol (1.5 mmol) were used.
[b] GC yields.
[c] Isolated yields.

In conclusion, we have successfully applied alcohols as alkylating agents in the Friedel–Crafts alkylation of indoles. The K-10 catalyzed, microwave-assisted method provides products in good yields and high selectivities in short reaction times as compared to conventional heating. The approach was also extended to the synthesis of dimethylcarbazoles by a domino reaction of indole and hexane-2,5-diol. Solid-acid catalysis, use of diol as an alkylating agent, and microwave-assisted synthesis make the approach attractive for environmentally benign synthesis design.

Indoles, *t*-BuOH, hexane-2,5-diol, and montmorillonite K-10 were purchased from Aldrich and were used without further purification or pretreatment. The reactions were carried out at constant temperature in a Discover Benchmate microwave reactor with continuous stirring. The temperature was measured and controlled by a built-in infrared detector. The ^1H, and ^{13}C NMR spectra were recorded on a 300 MHz Varian NMR spectrometer, in $CDCl_3$, TMS, or the residual solvent signal was used as internal reference. The MS identification of the products have been carried out by an Agilent 6850 GC & 5973 MS system (70 eV electron impact ionization) using a 30 m long DB-5 type column (J & W Scientific). The melting points are uncorrected and were recorded on a MEL-TEMP apparatus.

All products were characterized by mass spectrometry, ^1H, and ^{13}C NMR spectroscopy. The obtained spectra were in agreement with the expected structures and in case of known compounds with the



Scheme 2 Proposed mechanism for the synthesis of 1,4-dimethylcarbazole from indole and hexane-2,5-diol

literature data. Here, the spectral data and other characterization are only listed for the previously unknown compounds.

Alkylation of Indoles Using *tert*-Butyl Alcohol; General Procedure

The appropriate indole (1 mmol) and *t*-BuOH (111 mg, 1.5 mmol) were dissolved in CH_2Cl_2 (10 mL). Montmorillonite K-10 (500 mg) was added and the mixture stirred at r.t. for 2 min. The solvent was evaporated under vacuum. The dry mixture was then transferred to a reaction vial and placed into the cavity of the microwave reactor. The mixture was irradiated at the desired temperature for a preset time at atmospheric pressure in an open system. The progress of the reaction was monitored by GC-MS. After the completion of the reaction, the product was dissolved in CH_2Cl_2 (3 mL) and the catalyst removed by filtration. The solvent was evaporated under vacuum. The crude products were purified by flash chromatography (98:2 hexane–EtOAc) (Table 2).

3-*tert*-Butyl-5-chloro-(1*H*)-indole (Table 2, Entry 2)

Colorless oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.79 (br s, 1 H), 7.77 (s, 1 H), 7.21 (d, *J* = 8.4 Hz, 1 H), 7.10 (dd, *J* = 8.4, 2.1 Hz, 1 H), 6.90 (d, *J* = 2.4 Hz, 1 H), 1.41 (s, 9 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 135.4, 126.8, 126.5, 124.3, 121.6, 120.6, 120.5, 112.1, 31.4, 30.6.

MS: *m*/*z* (%) = 207 (M^+, 24), 192 (100), 177 (8), 157 (21), 141 (7), 128 (5), 117 (6), 102 (4).

3-*tert*-Butyl-5-nitro-(1*H*)-indole (Table 2, Entry 3)

Yellow crystals; mp 122–123 °C.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 8.79 (d, *J* = 1.8 Hz, 1 H), 8.62 (br s, 1 H), 8.09 (dd, *J* = 9.0, 2.1 Hz, 1 H), 7.41 (d, *J* = 9 Hz, 1 H), 7.12 (d, *J* = 2.4 Hz, 1 H), 1.47 (s, 9 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 140.7, 140.3, 129.2, 125.1, 122.5, 118.4, 117.1, 111.2, 31.5, 30.7

MS: *m*/*z* (%) = 218 (M^+, 22), 203 (100), 187 (8), 170 (4), 157 (41), 142 (9), 128 (11), 115 (10), 102 (4).

3-*tert*-Butyl-(1*H*)-indole-5-carbonitrile (Table 2, Entry 4)

Colorless crystals; mp 117–118 °C.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 8.31 (br s, 1 H), 8.09 (s, 1 H), 7.33 (m, 2 H), 6.99 (d, *J* = 2.4 Hz, 1 H), 1.36 (s, 9 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.8, 127.6, 126.8, 125.6, 124.2, 121.4, 116.8, 112.1, 101.5, 31.5, 30.6.

MS: *m*/*z* (%) = 198 (M^+, 19), 183 (100), 168 (7), 155 (16), 143 (10), 127 (4), 116 (4), 101 (2).

Methyl 3-*tert*-Butyl-(1*H*)-indole-5-carboxylate (Table 2, Entry 5)

Colorless crystals; mp 118–119 °C.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 8.59 (s, 1 H), 8.22 (br s, 1 H), 7.88 (dd, *J* = 8.7, 1.5 Hz, 1 H), 7.35 (d, *J* = 8.8 Hz, 1 H), 6.99 (d, *J* = 2.4 Hz, 1 H), 3.94 (s, 3 H), 1.47 (s, 9 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.6, 140.2, 128.3, 125.6, 124.3, 123.0, 120.9, 117.1, 111.1, 52.0, 31.7, 31.0.

MS: *m*/*z* (%) = 231 (M^+, 23), 216 (100), 200 (7), 184 (11), 168 (2), 157 (12), 143 (9), 128 (5), 115 (5), 99 (2).

3-*tert*-Butyl-5-methoxy-(1*H*)-indole (Table 2, Entry 6)

Brown oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.77 (br s, 1 H), 7.26 (d, *J* = 2.1 Hz, 1 H), 7.22 (d, *J* = 8.7 Hz, 1 H), 6.89 (d, *J* = 2.4 Hz, 1 H), 6.84 (dd, *J* = 8.7, 2.4 Hz, 1 H), 3.87 (s, 3 H), 1.43 (s, 9 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 153.1, 132.4, 126.2, 120.2, 111.8, 111.1, 103.8, 102.1, 56.0, 31.4, 30.5.

MS: *m*/*z* (%) = 203 (M^+, 23), 188 (100), 173 (11), 157 (6), 145 (10), 130 (6), 115 (7), 104 (4).

3-*tert*-Butyl-(1*H*)-indol-5-ol (Table 2, Entry 7)

Brown oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.75 (br s, 1 H), 7.23 (d, *J* = 2.4 Hz, 1 H), 7.19 (d, *J* = 8.7 Hz, 1 H), 6.90 (d, *J* = 2.7 Hz, 1 H), 6.74 (dd, *J* = 8.7, 2.4 Hz, 1 H), 4.73 (s, 1 H), 1.41 (s, 9 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 148.4, 132.4, 126.4, 126.0, 120.4, 111.7, 111.1, 105.9, 31.4, 30.5.

MS: *m*/*z* (%) = 189 (M^+, 29), 174 (100), 159 (8), 145 (6), 133 (7), 118 (2), 104 (3).

3-*tert*-Butyl-5-methyl-(1*H*)-indole (Table 2, Entry 8)
Colorless crystals; mp 53–54 °C.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.74 (br s, 1 H), 7.59 (s, 1 H), 7.24 (d, *J* = 8.1 Hz, 1 H), 6.99 (dd, *J* = 8.2, 1.2 Hz, 1 H), 6.89 (d, *J* = 2.1 Hz, 1 H), 2.47 (s, 3 H), 1.44 (s, 9 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 135.4, 127.8, 126.2, 126.0, 122.9, 120.9, 119.3, 110.9, 31.5, 30.6, 21.7.

MS: *m*/*z* (%) = 187 (M^+, 24), 172 (100), 157 (10), 144 (7), 130 (7), 117 (5), 102 (3).

Substituted Carbazoles; General Procedure
The same procedure described above was applied using appropriate indole (1 mmol) and hexane-2,5-diol (177 mg, 1.5 mmol). The crude products were purified by flash chromatography (95:5 hexane–EtOAc). The spectra of the isolated products were in agreement with the literature data[12] (Table 4).

1,4-Dimethyl-6-nitro-(9*H*)-carbazole (Table 4, Entry 7)
Yellow crystals; mp 170–172 °C.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 9.06 (d, *J* = 2.1 Hz, 1 H), 8.46 (br s, 1 H), 8.36 (dd, *J* = 8.8, 1.5 Hz, 1 H), 7.50 (d, *J* = 8.4 Hz, 1 H), 7.24 (d, *J* = 7.5 Hz, 1 H), 7.05 (d, *J* = 7.5 Hz, 1 H), 2.89 (s, 3 H), 2.57 (s, 3 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.2, 138.1, 131.0, 127.9, 127.1, 125.9, 125.2, 122.5, 121.6, 119.2, 118.1, 110.0, 20.3, 16.7.

MS: *m*/*z* (%) = 240 (M^+, 100), 225 (10), 210 (24), 194 (45), 178 (12), 167 (14), 152 (12), 115 (7), 96 (10).

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