Ceric Ammonium Nitrate (CAN) Promoted Efficient Synthesis of 1,5-Benzodiazepine Derivatives[1]

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Abstract: Ceric ammonium nitrate was found to be an efficient reagent for the preparation of 1,5-benzodiazepine derivatives of a wide range of substituted *o*-phenylenediamines and electronically divergent ketones in moderate to excellent isolated yields (60–98%) under mild conditions using methanol as solvent at ambient temperature.

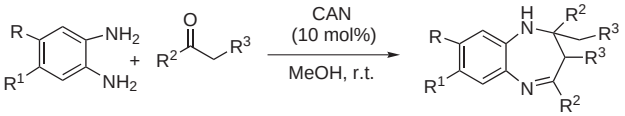
Key words: 1,5-benzodiazepines, ceric ammonium nitrate, *o*-phenylenediamines

Due to their accessibility, easy functionalization and potential pharmacological properties, 1,5-benzodiazepine derivatives have received significant attention and represent a 'privileged scaffold' found in compounds active against a variety of target types including peptide hormones (such as CCK),[2a] interleukin converting enzymes (ICE)[2b] and potassium blockers (I_k).[2c] More recently, the area of biological interest of 1,5-benzodiazepines has been extended to various diseases such as cancer,[3a] viral infection (non-nucleoside inhibitors of HIV-1 reverse transcriptase),[3b] and cardiovascular disorders.[3c,d] In addition, 1,5-benzodiazepines show antidepressive, antifungal, antibacterial, antifeedant, antiinflammatory, analgesic and anticonvulsant activities.[4] Derivatives are also used as dyes for acrylic fibre[5] in photography. Moreover, 1,5-benzodiazepines are valuable synthons used for the preparation of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines.[6]

Despite their importance from a pharmacological, industrial and synthetic point of view, comparatively few methods for their preparation are reported in the literature, a great number of which have appeared only very recently employing $BF_3{\cdot}OEt_2$,[7a] $NaBH_4$,[7b] polyphosphoric acid or SiO_2,[7c] $MgO/POCl_3$,[7d] $Yb(OTf)_3$,[7e] Al_2O_3/P_2O_5 or AcOH under microwave conditions,[7f,g] Amberlyst-15 in ionic liquid,[7h] $CeCl_3{\cdot}7H_2O/NaI$ supported on silica gel,[7i] and $InBr_3$,[7j] 1-butyl-3-methylimidazolium bromide ([bmim]Br),[7k] $Sc(OTf)_3$[7l] as catalysts or as stoichiometric reagents. However, many of these methods have drawbacks such as low yields of the products,[7a,b] high temperatures,[7c] drastic reaction conditions,[7d] long reaction times,[7c] and relatively expensive reagents.[7e,i,j,l] Therefore, there is scope to explore efficient methods for the synthesis of 1,5-benzodiazepines using a milder, non-hazardous and inexpensive reagent.

In continuation of our interest in developing novel synthetic methodologies, particularly carbon–carbon, carbon–heteratom bond formations,[8] and being interested in the use of lanthanide salts as environmentally friendly reagents for organic synthesis, we undertook a study of the utility of several lanthanide salts as catalysts for the synthesis of 1,5-benzodiazepines. Among the various lanthanide salts such as $TbCl_3$, $Sm(NO_3)_3$, $ErCl_3$, $Pr(NO_3)_3$, $YbCl_3$, CAN (ceric ammonium nitrate), $Tb(NO_3)_3$, $La(NO_3)_3$, YCl_3 and $LaCl_3$ studied for this reaction, CAN was found to be the most effective catalyst in terms of conversion and reaction rates. CAN has emerged as powerful single electron transfer reagent in many carbon–carbon bond-forming reactions.[9] However, to the best of our knowledge, there are no earlier reports on the preparation of 1,5-benzodiazepines using CAN to date.[10]

At first, we evaluated the feasibility of *o*-phenylenediamine (*o*-PD) (1 mmol) and acetophenone (2.2 mmol) using CAN (10 mol%, Scheme 1) at ambient temperature in acetonitrile as solvent to afford the corresponding 1,5-benzidiazepine in 45% yield in four hours.



R, R^1 = H; R = Me, R^1 = H;
R = Cl, R^1 = H; R = NO_2, R^1 = H;
R, R^1 = Me; R = Cl, R^1 = Cl;
R = COPh, R^1 = H

(27 examples)

Scheme 1

Encouraged by this result, we studied different reaction parameters. The reaction was performed in different solvents such as MeCN, MeCN–H_2O, $CHCl_3$, MeOH, and H_2O. Methanol (89%) and chloroform (80%) were found to be the best solvents in terms of yields and reaction time. The reaction was also conducted in solvent-free conditions but the yields were poorer compared to the yields obtained in methanol as solvent. Next, the optimization of ceric ammonium nitrate was tested, wherein it was found that 10 mol% of CAN is sufficient to promote reaction. No reaction was observed when *o*-phenylenediamine was reacted with acetophenone under similar conditions in the

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absence of the CAN even after stirring for 2 days, thus highlighting the role of the CAN as a promoter. Any excess of CAN beyond this loading did not show any further increase in conversion and yield. Use of less than the required catalyst loading resulted in poor yields. The optimum yields of the product were obtained when a 1:2.2 ratio of *o*-phenylenediamine to ketone was used.

Having established the optimized reaction conditions, we then successfully synthesized a wide variety of biologically relevant 1,5-benzodiazepines using CAN (10 mol%) in methanol at room temperature, and the results from this study are shown in Table 1. In all cases, the reactions were clean and complete within 2.5–6.5 hours. Water was added to the reaction mixture and the pure product was isolated by extracting with diethyl ether and after usual workup and purification by silica gel column chromatography. Electronically divergent acetophenones were employed as novel substrates for the synthesis of corresponding 1,5-benzodiazepines in good to excellent yields (Table 1). 4-Methoxy acetophenone gave a moderate yield of 66% in 6.5 hours (entry 3). Entries 4 and 5 (Table 1), on reacting with *o*-phenylenediamine resulted corresponding product in 5 hours and 4.5 hours in good yields (85%, 80%, respectively). Acetophenones containing halo substituents, except bromo substituent, reacted rapidly (entry 6, Table 1). The order of the reactivity of the substituted acetophenones towards *o*-phenylenediamine in terms of yields and time is as follows: fluoro > chloro > iodo ~ methyl > hydroxy > nitro > bromo > methoxy. In a similar fashion, substituted *o*-phenylenediamines also reacted well with substituted acetophenones and gave the corresponding 1,5-benzodiazepines in good yields (entries 7–14). For diamines C and D, the reaction did not give the expected products with acetophenone even after stirring for 12 hours under the present experimental conditions. 4,5-Dichloro *o*-phenylenediamine (diamine F) reacted rapidly with acetophenone giving a yield of 92% in 3.5 hours. Likewise, 4,5-dimethyl *o*-phenylenediamine (diamine E) reacted faster than the simple and 4-benzoyl derivatives (see Table 1); whereas 4-methyl *o*-phenylenediamine (diamine B) reacted sluggishly. The order of reactivity of various substituted *o*-phenylenediamines with acetophenone is as follows: F > A > E > G > B. The benzodiazepines were the only products obtained and the rest of the material was essentially starting material. The scope and generality of the present procedure was extended to various aliphatic ketones as well (Table 1). The reaction of *o*-phenylenediamine with acetone when performed under similar conditions gave high yields of 2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine (entry 15a, Table 1). It is noteworthy that, in the reaction with an unsymmetrical ketone such as 2-butanone, the ring closure occurred selectively giving a single product in 2.5 hours (92%, entry 16, Table 1). 3-Pentanone also reacted well to furnish the desired product in 88% yield (entry 17, Table 1). Cyclic ketones such as cyclopentanone and cyclohexanone (entries 18 and 19, Table 1) also reacted efficiently to afford the corresponding fused ring benzodiazepines in excellent yields. To demonstrate the scope of this methodology, the reaction was performed with *o*-phenylenediamine and acetophenone on a 20-mmol scale (entry 1, Table 1) using CAN. The reaction was complete in 3.5 hours affording the corresponding product in 85% yield, thus confirming the possibility of being scaled up, if desired. The mechanism of the reaction probably involves an intramolecular imine–enamine cyclization promoted by CAN, as already reported by Jung and coworkers when using polyphosphoric acid or SiO_2.[7c]

Table 1 CAN-Promoted Synthesis of 1,5-Benzodiazepines

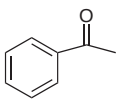
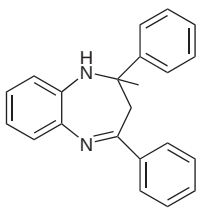
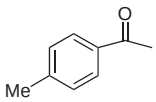
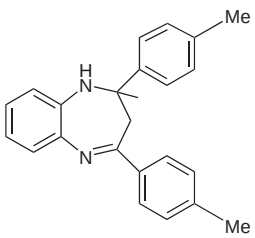
Entry	Diamine	Ketone	Benzodiazepine	Time (h)	Yields (%)[a,b]
1	**A**			3.5	89/85[c,7i]
2	**A**			4.0	87[7i]

Table 1 CAN-Promoted Synthesis of 1,5-Benzodiazepines (continued)

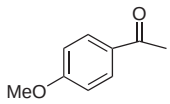
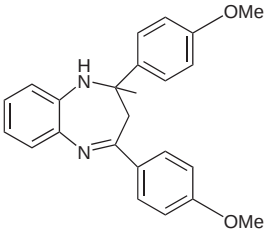
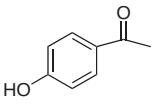
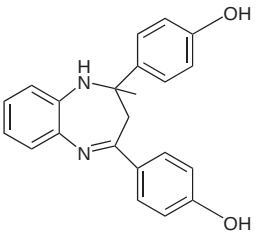
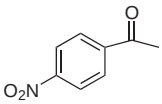
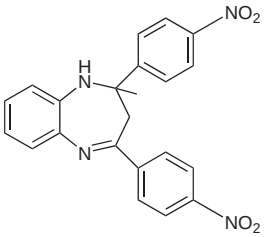
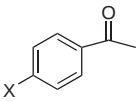
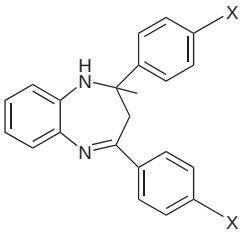
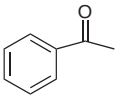
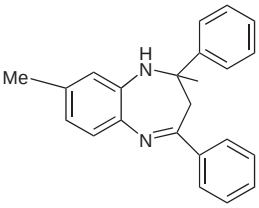
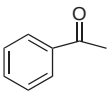
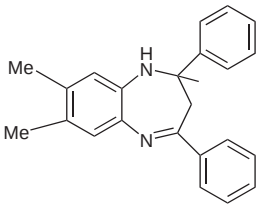
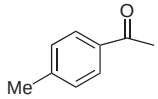
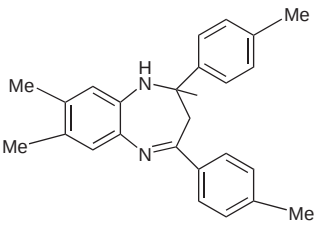
Entry	Diamine	Ketone	Benzodiazepine		Time (h)	Yields (%)[a,b]
3	**A**				6.5	66
4	**A**				5.0	85
5	**A**				4.5	80
6	**A**			X = F X = Cl X = Br X = I	3.5 4.0 6.0 4.5	95 92 74 88
7	**B**				6.0	65[7k]
8	**E**				4.5	85[7g]
9	**E**				4.5	76

Table 1 CAN-Promoted Synthesis of 1,5-Benzodiazepines (continued)

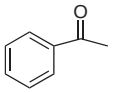
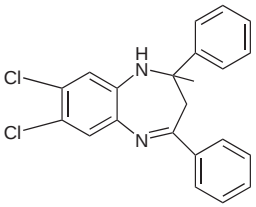
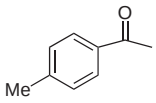
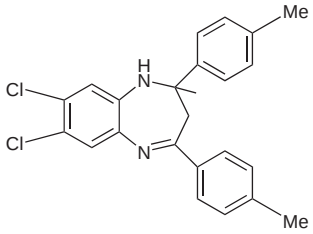
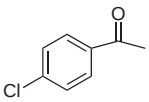
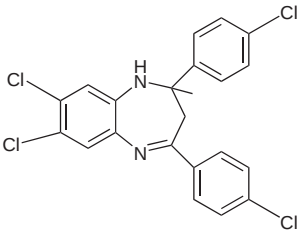
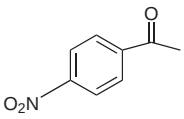
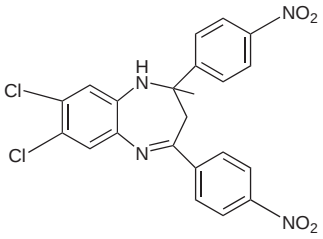
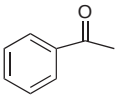
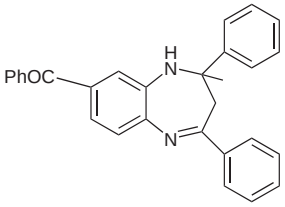
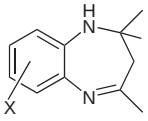
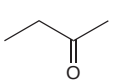
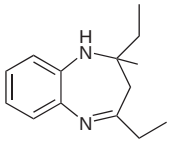
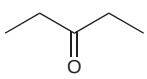
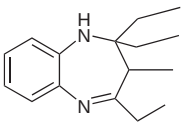
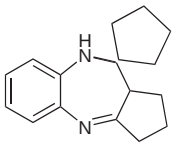
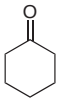
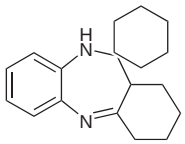
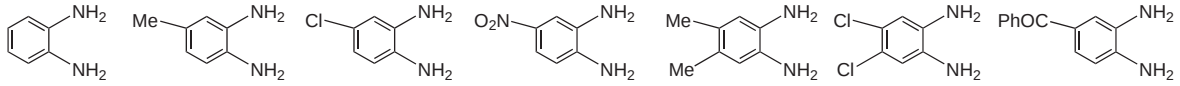
Entry	Diamine	Ketone	Benzodiazepine	Time (h)	Yields (%)[a,b]
10	**F**			3.5	92
11	**F**			4.0	90
12	**F**			6.0	78
13	**F**			4.5	60
14	**G**			5	80[7h]
15	**A** **B** **C** **D** **E** **F**			3.0 4.5 2.5 3.0 3.0 3.5	90[7j] 82[7j] 88[7j] 92[7j] 87[7j] 95
16	**A**			2.5	92[7j]
17	**A**			3.0	88[7h]

Table 1 CAN-Promoted Synthesis of 1,5-Benzodiazepines (continued)

Entry	Diamine	Ketone	Benzodiazepine	Time (h)	Yields (%)[a,b]
18	**A**			3.0	95[7e]
19	**A**			3.5	98[7e]

Diamine: 

A **B** **C** **D** **E** **F** **G**

[a] Yields refer to the isolated pure products after column chromatography.
[b] All novel compounds were characterized by ^{1}H NMR and/or ^{13}C NMR, IR and mass spectra.
[c] Reaction on 20-mmol scale.

In conclusion, we have developed a practical procedure for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines at ambient temperature using ceric ammonium nitrate in methanol. The advantages of the present protocol are mild, short reaction times, study of wide range of electronically divergent substrates, easy work up, low toxicity, inexpensive, and ready availability of the catalyst, that make the procedure an attractive alternative to the existing methods for the synthesis of 1,5-benzodiazepines.

Acknowledgment

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References and Notes

(1) IICT communication no: 050809.
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(10) **Representative Procedure.**
A mixture of *o*-phenylenediamine (1.0 mmol), ketone (2.2 mmol) and CAN (0.055 g, 10 mol%) in MeOH (2 mL) was stirred at r.t. for the time specified in Table 1. After the reaction was over, the reaction mixture was diluted with H_2O and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel with EtOAc and *n*-hexane (2:8) as eluent to afford the corresponding pure 1,5-benzodiazapine. Previously reported materials were characterized by comparison of their NMR and mass spectra with those of authentic samples. All novel compounds gave satisfactory spectroscopic data in accordance to their proposed structures.

Spectral Data for Selected Compounds:

Compound **2**: pale yellow crystalline solid, mp 98–99 °C. IR (KBr): 3318, 1630, 1598 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.72 (s, 3 H), 2.26 (s, 3 H), 2.32 (s, 3 H), 2.98 (d, *J* = 13.38 Hz, 1 H), 3.05 (d, *J* = 13.38 Hz, 1 H), 3.43 (br s, NH), 6.76 (m, 1 H), 7.01 (m, 6 H), 7.23 (m, 1 H), 7.49 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.75, 21.16, 29.85, 42.97, 73.06, 121.28, 121.38, 125.18, 126.03, 127.15, 128.50, 128.67, 128.92, 129.22, 136.45, 137.0, 138.18, 139.76, 140.32, 144.98, 166.82. MS (EI): *m/z* = 340 [M^+].[7i]

Compound **3**: yellowish solid, mp 114–116 °C. IR (neat): 3325, 1135, 1640, 1594 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.71 (s, 3 H), 2.85 (d, *J* = 12.84 Hz, 1 H), 2.98 (d, *J* = 13.60 Hz, 1 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 6.65–6.78 (m, 4 H), 6.95–7.02 (m, 2 H), 7.18–7.25 (m, 2 H), 7.42–7.55 (m, 4 H). MS (EI): *m/z* = 372 [M^+].

Compound **4**: yellow crystalline solid, mp 219–220 °C. IR (KBr): 3339, 1636, 1599 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.65 (s, 3 H), 2.77 (d, *J* = 12.63 Hz, 1 H), 2.89 (d, *J* = 7.43 Hz, 1 H), 4.18 (br s, NH), 6.57–6.64 (m, 4 H), 6.81–7.00 (m, 1 H), 7.10–7.18 (m, 1 H), 7.28–7.55 (m, 4 H). MS (EI): *m/z* = 344 [M^+].

Compound **5**: red crystalline solid, mp 156–158 °C. IR (KBr): 3325, 1642, 1597 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.83 (s, 3 H), 2.96 (d, *J* = 13.38 Hz, 1 H), 3.27 (d, *J* = 13.38 Hz, 1 H), 3.52 (br s, NH), 6.98 (m, 1 H), 7.00 (m, 6 H), 7.22 (m, 1 H), 7.47 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.02, 42.92, 73.37, 121.29, 122.16, 123.53, 123.38, 126.78, 127.57, 127.75, 129.58, 137.23, 138.80, 144.65, 146.95, 148.40, 154.05, 163.82. MS (EI): *m/z* = 402 [M^+].

Compound **6** (X = F): pale-yellow crystalline solid, mp 104–105 °C. IR (KBr): 3271, 1651, 1603, 1231 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.75 (s, 3 H), 2.87 (d, *J* = 13.60 Hz, 1 H), 3.04 (d, *J* = 12.84 Hz, 1 H), 3.30 (br s, NH), 6.75–6.79 (m, 1 H), 6.82–6.92 (m, 4 H), 7.00–7.05 (m, 2 H), 7.19–7.25 (m, 1 H), 7.48–7.62 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.72, 42.94, 73.38, 114.70, 114.79, 114.97, 115.06, 126.22, 127.0, 128.50, 129.20, 135.46, 137.44, 140.36, 143.2, 160.23, 162.22, 165.26, 165.53, 163.50. MS (EI): *m/z* = 348 [M^+].

Compound **9**: pale-yellow crystalline solid; mp 102–103 °C. IR (KBr): 3325, 1636, 1594 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.72 (s, 3 H), 2.26–2.36 (s, 6 H), 2.45 (s, 3 H), 2.58 (s, 3 H), 2.91 (d, *J* = 12.84 Hz, 1 H), 3.03 (d, *J* = 13.60 Hz, 1 H), 3.29 (br s, NH), 6.56 (s, 1 H), 7.02–7.07 (m, 1 H), 7.24–7.28 (m, 4 H), 7.47–7.53 (m, 2 H), 7.83–7.87 (d, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.12, 21.10, 29.88, 43.06, 72.88, 122.34, 125.24, 127.05, 128.44, 128.76, 128.94, 129.58, 129.60, 134.58, 136.56, 137.26, 137.96, 139.68, 166.76. MS (EI): *m/z* = 368 [M^+].

Compound **10**: yellow crystalline solid, mp 158–160 °C. IR (KBr): 3304, 1638, 1603, 761 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.75 (s, 3 H), 2.93 (d, *J* = 13.60 Hz, 1 H), 3.12 (d, *J* = 12.84 Hz, 1 H), 3.49 (br s, NH), 6.88 (s, 1 H), 7.13–7.30 (m, 5 H), 7.36 (s, 1 H), 7.50–7.53 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.97, 43.23, 72.97, 121.90, 124.14, 125.33, 127.30, 128.35, 128.76, 130.13, 137.84, 139.26, 146.83, 168.81. MS (EI): *m/z* = 381 [M^+].

Compound **11**: pale-yellow solid, mp 179–180 °C. IR (KBr): 3434, 1636, 1597, 817 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.75 (s, 3 H), 2.34 (s, 3 H), 2.37 (s, 3 H), 2.95 (d, *J* = 13.60 Hz, 1 H), 3.09 (d, *J* = 13.60 Hz, 1 H), 3.50 (br s, NH), 6.88 (s, 1 H), 7.05–7.09 (t, 3 H), 7.28 (s, 1 H), 7.38–7.44 (t, 3 H), 7.50–7.53 (d, 2 H). MS (EI): *m/z* = 409 [M^+].

Compound **12**: pale-yellow crystalline solid, mp 199–200 °C. IR (KBr): 3325, 1630, 1594 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.77 (s, 3 H), 2.88 (d, *J* = 13.60 Hz, 1 H), 3.11 (d, *J* = 13.60 Hz, 1 H), 3.48 (br s, NH), 6.92 (s, 1 H), 7.21–7.25 (m, 4 H), 7.38 (s, 1 H), 7.45–7.51 (m, 4 H). MS (FAB): *m/z* = 451 [M^+ + 1].

Compound **13**: reddish crystalline solid, mp 218–220 °C. IR (KBr): 3387, 1640, 1585 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.74 (s, 3 H), 2.69 (d, *J* = 9.82 Hz, 1 H), 2.82 (d, *J* = 11.33 Hz, 1 H), 2.93 (br s, NH), 6.92 (s, 1 H), 7.21–7.25 (m, 4 H), 7.38 (s, 1 H), 7.45–7.51 (m, 4 H). MS (FAB): *m/z* = 472 [M^+ + 1].

Compound **15** (R = R^1 = Cl): reddish crystalline solid, mp 92–94 °C. IR (KBr): 3325, 1636, 1590 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 6 H), 2.26 (s, 2 H), 2.34 (s, 1 H), 6.78 (s, 1 H), 7.18 (s, 1 H). MS (EI): *m/z* = 257 [M^+].