Molecular-Iodine-Catalyzed One-Pot Synthesis of 1,5-Benzodiazepine Derivatives under Solvent-Free Conditions

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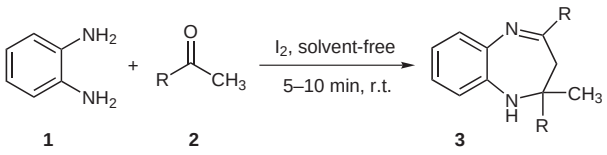
Abstract: 2,3-Dihydro-1*H*-1,5-benzodiazepines have been synthesized from *o*-phenylenediamine (OPDA) and ketones under solvent-free conditions in the presence of a catalytic amount of molecular iodine. All of the ketones, including cyclic ketones and acyclic ketones, reacted smoothly with OPDA to furnish products. Compared to other reaction conditions, this new protocol has the advantage of excellent yield and short reaction time at room temperature.

Key words: benzodiazepine, *o*-phenylenediamine, iodine, ketones, solvent-free

Benzodiazepines are interesting compounds because of their pharmacological properties.[1] Many members of this family are, in fact, nowadays widely used as anti-convulsant, anti-anxiety, analgesic, sedative, anti-depressive, and hypnotic agents.[2] Although the first benzodiazepine was introduced as a drug nearly 30 years ago,[3] research in this area is still very active and is directed towards the synthesis of compounds with enhanced pharmacological activity. It was also found that 1,5-benzodiazepines are valuable synthons used for the preparation of other fused ring compounds such as triazolo-,[4] oxadiazolo-[5], oxazino-[6], or furano-benzodiazepines.[7]

Despite their wide range of pharmacological activity, industrial and synthetic applications, the synthesis of 1,5-benzodiazepines has received little attention, and few methods for their preparation are reported in the literature, a great number of which have appeared only very recently. These include condensation reactions of OPDA with α,β-unsaturated carbonyl compounds, β-haloketones or ketones in the presence of $BF_3{\cdot}OEt_2$,[8] $NaBH_4$,[9] polyphosphoric acid,[10] SiO_2,[10] MgO and $POCl_3$,[11] $Yb(OTf)_3$,[12] Al_2O_3/P_2O_5 under MW,[13] AcOH under MW,[14] and ionic liquid.[15] Many of these processes suffer at least one limitation such as drastic reaction conditions, expensive reagents, low to moderate yields, relatively long reaction times, or occurrence of several side reactions. Most of them make use of an acid catalyst giving rise to tedious work-up procedures for their separation and recycling or disposal.

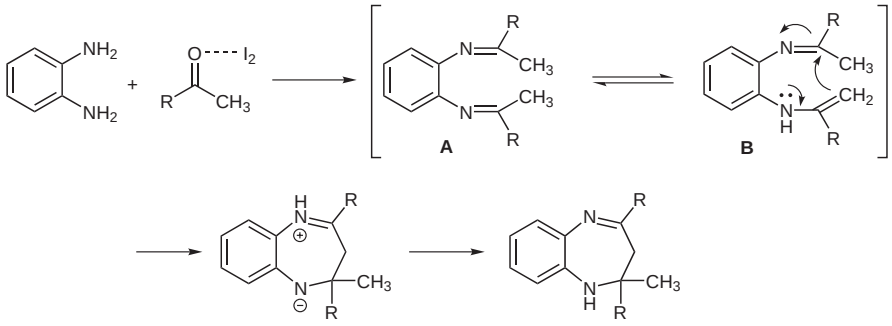
In recent years, molecular iodine has received considerable attention as an inexpensive and easily available catalyst for various organic transformations.[16–18] Given the large number of similar condensation reactions that have been reported to proceed readily under solvent-free conditions,[19,20] we proceeded to examine the synthesis of 1,5-benzodiazepine derivatives in the presence of a catalytic amount of molecular iodine under solvent-free conditions (Scheme 1). The results are summarized in Table 1.



1 2 3

Scheme 1

The reactions were carried out simply by mixing OPDA with a ketone in the presence of a catalytic amount (10 mol%) of iodine under solvent-free condition. The mix-



Scheme 2

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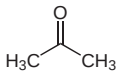
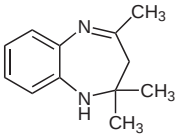
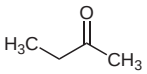
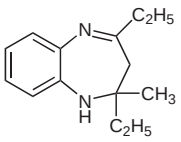
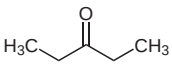
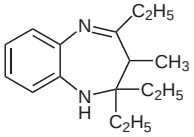
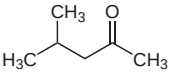
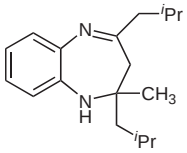
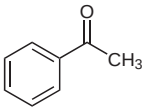
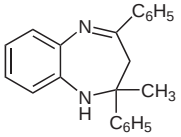
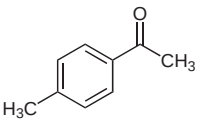
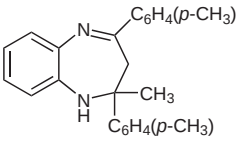
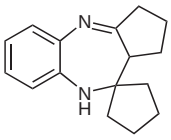
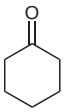
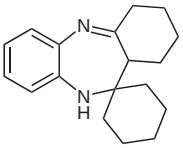
Table 1 Synthesis of 1,5-Benzodiazepine Derivatives Catalyzed by Iodine under Solvent-Free Conditions

Entry	Ketone	Product[a]	Yield (%)[b]	Time (min)
1		 **3a**	95 (97)[c]	5
2		 **3b**	90	5
3		 **3c**	86	6
4		 **3d**	86	8
5		 **3e**	94	10
6		 **3f**	83	10
7		 **3g**	88	8
8		 **3h**	92	8

[a] All products were characterized by NMR spectroscopy.
[b] Isolated yields.
[c] The reaction was carried out on 10 mmol scale.

ture was ground together in a mortar with a pestle at room temperature for several minutes, then purified by column chromatography, and the 1,5-benzodiazepine derivatives were obtained in excellent yields.

As shown in Table 1, OPDA undergoes rapid condensation with ketones having hydrogens at the α-position in the presence of 10 mol% iodine under extremely mild reaction conditions to afford the corresponding 2,3-dihydro-1*H*-1,5-benzodiazepines in excellent yields with high selectivity. Interestingly, both cyclic and acyclic ketones reacted with OPDA to give the corresponding products in good yield, without any significant difference. This method offers several advantages such as high conversions, short reaction times, cleaner reaction profiles, high regioselectivity in the case of unsymmetrical ketones, solvent-free conditions, and simple experimental and work-up procedures.

A possible mechanism for the condensation of OPDA with ketones is shown in Scheme 2; the amino group of OPDA attacks the carbonyl group of the ketone, which is activated by iodine, giving the intermediate diimine **A**. A 1,3-shift of the hydrogen attached to the methyl group then occurs to form an isomeric enamine **B**, which cyclizes to afford a seven-membered ring.

In conclusion, iodine was found to be a mild and effective catalyst for the formation of 1,5-benzodiazepines in excellent yields. The uses of this inexpensive and easily available catalyst under solvent-free conditions make this protocol practical and economically attractive. The simple work-up procedure, mild reaction conditions, selectivity, and very good yields make our methodology a valid contribution to the existing processes in the field of 1,5-benzodiazepine derivatives synthesis.

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(21) **General Experimental Procedure**: A mixture of OPDA (1 mmol), ketone (2 mmol), and iodine (0.1 mmol) were ground together in a mortar with a pestle at room temperature for several minutes. After completion of the reaction (TLC), the reaction was treated with aqueous $Na_2S_2O_3$ to furnish the crude products, which were further purified by column chromatography.
3a: Mp 145–146 °C. IR (KBr): 3341, 1637, 1600 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.37 (s, 6 H), 2.25 (s, 2 H), 2.39 (s, 3 H), 3.44 (br s, 1 H), 6.64–7.41 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 29.4, 30.8, 44.9, 68.1, 121.6, 122.3, 126.1, 126.8, 138.2, 140.9, 171.6.
3b: Mp 137–138 °C. IR (KBr): 3328, 1640, 1608 cm^{-1}.^1H NMR ($CDCl_3$): δ = 0.98 (t, 3 H, *J* = 6.8 Hz), 1.24 (t, 3 H, *J* = 7.1 Hz), 1.72 (q, 2 H, *J* = 6.8 Hz), 2.18 (m, 2 H), 2.34 (s, 3 H), 2.71 (q, 2 H, *J* = 7.1 Hz), 3.28 (br s, 1 H), 6.78–7.33 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 8.8, 11.2, 26.8, 35.9, 36.0, 42.3, 70.8, 121.9, 125.2, 126.4, 126.8, 137.6, 140.9, 175.8.
3c: Mp 142–144 °C. IR (KBr): 3320, 1638, 1596 cm^{-1}.^1H NMR ($CDCl_3$): δ = 0.81–1.15 (m, 10 H), 1.22–1.42 (m, 4 H), 1.52–1.66 (m, 2 H), 2.38–2.56 (m, 2 H), 2.91 (q, 1 H, *J* = 7.0 Hz), 3.78 (br s, 1 H), 6.56–7.38 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 7.6, 7.9, 11.9, 12.4, 28.1, 28.5, 35.5, 46.4, 68.4, 117.6, 118.2, 126.4, 132.7, 139.1, 142.2, 173.9.
3d: Mp 118–120 °C. IR (KBr): 3265, 1651, 1600 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.96–1.085 (m, 12 H), 1.34 (s, 3 H), 1.50–1.52 (m, 2 H), 1.66–1.75 (m, 1 H), 2.07–2.26 (m, 3 H), 2.25 (d, 2 H, *J* = 12.7 Hz), 6.60–7.15 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 22.6, 22.9, 24.1, 24.8, 25.1, 26.2, 28.3, 43.4, 51.7, 51.9, 70.9, 121.4, 121.5, 125.3, 127.4, 137.9, 140.5, 173.9.
3e: Mp 150–152 °C. IR (KBr): 3268, 1640, 1601 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.81 (s, 3 H), 3.01 (d, 1 H, *J* = 12.8 Hz), 3.16 (d, 1 H, *J* = 12.8 Hz) 3.45 (br s, 1 H), 6.56–7.02 (m, 3 H), 7.14–7.40 (m, 7 H), 7.56–7.65 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 29.8, 42.9, 73.5, 121.2, 121.5, 125.3, 126.1, 126.7, 126.9, 127.8, 128.2, 128.5, 129.6, 137.9, 139.4, 139.9, 147.5, 167.6.
3f: Mp 141–143 °C. IR (KBr): 3270, 1644, 1602 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.11 (s, 9 H,), 3.05 (d, 1 H, *J* = 13.6 Hz), 3.17 (d, 1 H, *J* = 13.6 Hz,), 3.60 (br s, 1 H), 7.12–7.61 (m, 11 H). ^{13}C NMR ($CDCl_3$): δ = 21.3, 24.4, 28.4, 29.0, 46.4, 52.5, 114.7, 122.2, 126.2, 127.1, 128.6, 132.7, 133.1, 133.6, 135.5, 136.1, 164.9.
3g: Mp 136–138 °C. IR (KBr): 3342, 1656, 1604 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.29–1.88 (m, 12 H), 2.31–2.58 (m, 3 H), 4.36 (br s, 1 H), 6.71–7.39 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 23.5, 24.1, 24.4, 28.9, 33.4, 38.5, 39.4, 54.4, 67.3, 118.6, 119.5, 126.9, 132.3, 139.3, 143.3, 178.4.
3h: Mp 137–139 °C. IR (KBr): 3321, 1654, 1600 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.88–2.58 (m, 16 H), 2.46–2.79 (m, 3 H), 4.55 (br s, 1 H), 6.65–7.36 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 21.5, 21.7, 23.3, 24.5, 25.4, 33.4, 34.4, 39.3, 40.5, 52.4, 63.2, 121.1, 121.4, 126.3, 129.7, 138.2, 142.4, 178.8.