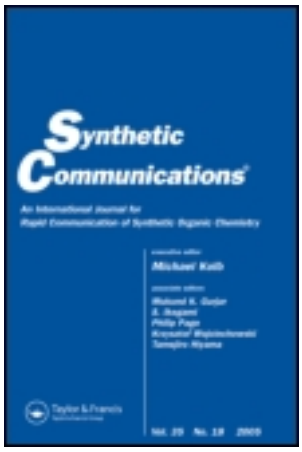

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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Molecular Iodine Catalyzed Highly Rapid Synthesis of 1,5-Benzodiazepine Derivatives Under Mild Conditions

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Version of record first published: 21 Aug 2006.

To cite this article: B. P. Bandgar , Sampada V. Bettigeri & Neeta S. Joshi (2004): Molecular Iodine Catalyzed Highly Rapid Synthesis of 1,5-Benzodiazepine Derivatives Under Mild Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:8, 1447-1453

To link to this article: http://dx.doi.org/10.1081/SCC-120030695

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 8, pp. 1447–1453, 2004

Molecular Iodine Catalyzed Highly Rapid Synthesis of 1,5-Benzodiazepine Derivatives Under Mild Conditions

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ABSTRACT

Rapid reaction of *o*-phenylenediamines with both cyclic and acyclic ketones in the presence of catalytic amount of iodine afforded 1,5-benzodiazepine derivatives in excellent yields at room temperature.

Key Words: 1,5-Benzodiazepine; Molecular iodine; *o*-Phenylenediamine; Catalyst.

Benzodiazepines are very important class of heterocyclic bioactive compounds.[1,2] Most of the members of this family have wide applications in

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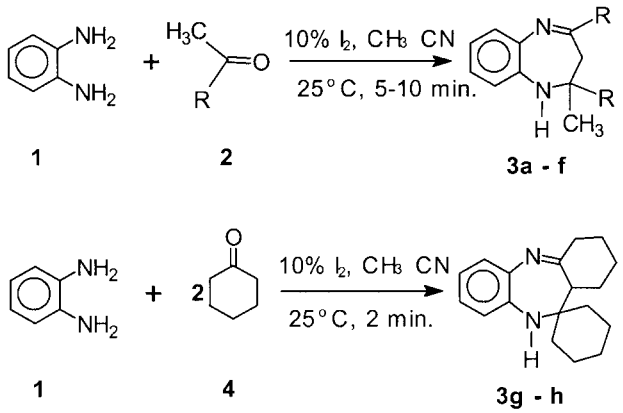
DOI: 10.1081/SCC-120030695 0039-7911 (Print); 1532-2432 (Online)

medicinal chemistry such as tranquilizing, anticonvulsant, antianxiety, and hypnotic agents. In addition, 1,5-benzodiazepines are used as starting materials for the preparation of fused ring compounds such as triazolo-,[3,4] oxazino-,[4] or furano-benzodiazepine.[4,5] Benzodiazepine derivatives also find commercial use as dyes for acrylic fibers[6] and as anti-inflammatory agents.[7]

Despite their importance from a pharmaceutical, industrial, and synthetic point of view, comparatively few methods for their preparation are reported in the literature,[8–11] a great number of which have appeared only very recently.[12–16] These include condensation reactions of *o*-phenylenediamines with α-β-unsaturated carbonyl compounds,[8] β-haloketones[9] or ketones in the presence of BF_3-etherate,[10] $NaBH_4$,[11] polyphosphoric acid,[12] SiO_2,[12] MgO and $POCl_3$,[13] $Yb(OTf)_3$,[14] Al_2O_3/P_2O_5,[15] AcOH[16] under microwave (MW) irradiation and ionic liquid.[17] Many of these processes suffer from one or other limitations such as drastic reaction conditions, expensive reagents and low to moderate yields, relatively long reaction times, and the occurrence of several side reactions. Almost all of them make use of an acid catalyst giving rise to tedious work-up procedures.

In recent years, molecular iodine has received considerable attention as an inexpensive and readily available catalyst for effecting various organic transformations.[18] We now report here the synthesis of 1,5-benzodiazepine derivatives by condensation of *o*-phenylenediamine with both cyclic and acyclic ketones using molecular iodine in CH_3CN as an efficient catalyst under mild condition (25°C) in a very short time (Sch. 1).

The results are summarized in Table 1. The syntheses were carried out simply by mixing *o*-phenylenediamine (1 mmol) with the ketone (2 mmol) in the presence of a catalytic amount (10%) of iodine in CH_3CN, whereupon



Scheme 1.

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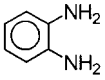
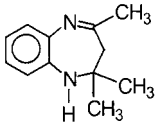
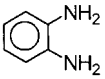
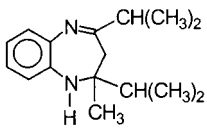
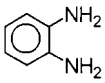
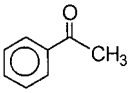
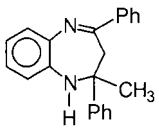
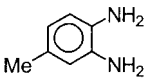
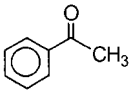
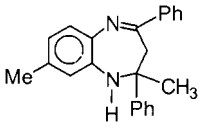
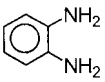
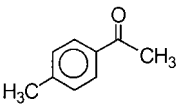
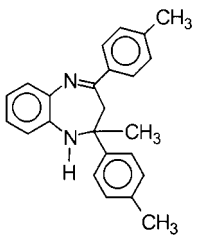
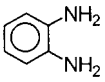
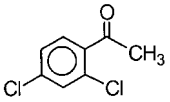
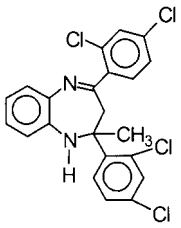
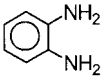
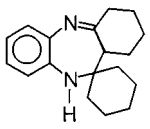
Table 1. I_2 catalyzed synthesis of 1,5-benzodiazepines.

Entry	Substrate	Ketone	Benzodiazepines	Time (min)	Yield[a,b] (%)
a		CH_3COCH_3		5	99
b		$H_3C{-}COCH(CH_3)_2$		10	96
c				10	98
d				10	97
e				10	98
f				10	98
g				02	99

(*continued*)

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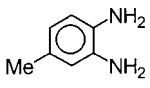
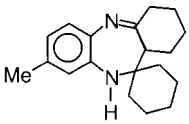
Table 1. Continued.

Entry	Substrate	Ketone	Benzodiazepines	Time (min)	Yield[a,b] (%)
h				02	99

[a]Yields of pure isolated products.
[b]Products were characterized by IR, ^{1}H NMR, ^{13}C NMR, elemental analysis, and by comparison with authentic samples.

the benzodiazepine derivatives were obtained in almost quantitative yield. It is highly rapid method as compared to literature reported methods for the synthesis of benzodiazepines. It was ascertained that a minimum 10% of the catalyst, I_2 is required to achieve optimum conversion. No reaction was observed when *o*-phenylenediamine was treated with acetone under similar conditions in the absence of a catalyst. When the amount of catalyst used was less than 10%, yields of benzodiazepine derivatives were decreased due to incomplete conversion of substrates and any excess of catalyst beyond this proportion (>10%) did not show any further increase in conversion and yield.

In conclusion, we have developed a new and efficient method for the regioselective synthesis of 1,5-benzodiazepines in excellent isolated yields at room temperature in short reaction times. The easy work-up procedure, mild reaction conditions, neutral, inexpensive, and readily available catalyst makes the method amenable for scale-up operations.

GENERAL PROCEDURE

A mixture of *o*-phenylenediamine or 4-methyl *o*-phenylenediamine (1 mmol), methylketone or cyclohexanone (2 mmol), and iodine (0.1 mmol) in acetonitrile (10 mL) was stirred at room temperature. After completion of the reactions (TLC), the solvent was removed under reduced pressure and the crude product obtained was further purified by column chromatography (pet. ether : ethyl acetate = 9 : 1).

3a. M.p. = 82°C, IR (KBr): 1597 (Ar), 1637 (C=N), 3289 (NH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 6H, 2 × CH_3), 2.25 (s, 2H, $-CH_2$), 2.33 (s, 3H, CH_3), 3.45 (brs, 1H, NH), 6.60–7.25 (m, 4H). Anal. calcd for $C_{12}H_{16}N_2$ (188.26): C, 76.56%; H, 8.56%; N, 14.87%; Found: C, 76.77%, H, 4.48%; N, 14.80%.

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3b. M.p. = 119°C, IR (KBr): 1605 (Ar), 1665 (C═N), 32,689 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, 6H, $J = 7.8$ Hz, $CH(CH_3)_2$), 1.15 (s, 3H, CH_3), 1.42 (d, 6H, $J = 7.2$ Hz, N═C–$CH(CH_3)_2$), 1.85 (m, 1H, $CH(CH_3)_2$), 2.1 (m, 1H, $CH(CH_3)_2$), 2.52 (d, 1H, $J = 16.0$ Hz, CH_2^a), 2.60 (d, 1H, $J = 16$ Hz, CH_2^b), 3.65 (brs, 1H, NH), 6.75–7.40 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7, 16.5, 23.5, 29.4, 36.3, 40.5, 113.8, 118.7, 123.0, 127.5, 132.81, 137.0, 164.5. Anal. calcd for $C_{16}H_{24}N$: C, 78.64%; H, 9.90%; N, 11.46%; Found: C, 78.51%; H, 9.81%; N, 11.54%.

3c. M.p. = 121°C, IR (KBr): 1651 (C═N), 3270 (NH) cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (s, 3H, CH_3), 3.01 (d, 1H, $J = 13.2$ Hz, CH_2^a), 3.18 (d, 1H, $J = 13.2$ Hz, CH_2^b), 3.50 (brs, 1H, NH), 6.75–6.85 (m, 14H, Ar-H). Anal. calcd for $C_{22}H_{20}N_2$ (312.40): C, 84.58%; H, 6.45%; N, 8.96%; Found: C, 84.38%, H; 6.38%; N, 8.90%.

3d. M.p. = 91–92°C, IR (KBr): 1660 (C═N), 3280 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.80 (s, 3H, CH_3), 2.41 (s, 3H, Ar-CH_3), 3.02 (d, 1H, $J = 13.0$ Hz, CH_2^a), 3.15 (d, 1H, $J = 13.0$ Hz, CH_2^b), 3.50 (brs, 1H, NH), 6.70–7.50 (m, 13H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 28.5, 46.0, 51.0, 113.5, 124.0, 125.5, 126.0, 127.0, 128.1, 128.4, 128.6, 128.8, 129.0, 131.0, 131.5, 135.0, 137.0, 165.5. Anal. calcd for $C_{23}H_{22}N_2$ (326.42): C, 84.63%; H, 6.79%; N, 8.58%; Found: C, 84.75%; H, 6.68%; N, 8.65%.

3e. M.p. = 143°C; IR (KBr): 1600 (Ar), 1645 (C═N), 3265 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.1 (s, 9H, 3 × Ar-CH_3), 3.05 (d, 1H, $J = 13.5$ Hz, CH_2^a), 3.17 (d, 1H, 13.5 Hz, CH_2^b), 3.60 (brs, 1H, NH), 7.1–7.5 (m, 11H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 24.5, 28.2, 29.1, 46.2, 52.7, 114.7, 122.3, 126.2, 127.1, 128.5, 132.7, 133.0, 133.7, 135.5, 136.1, 164.7. Anal. calcd for $C_{24}H_{22}N_2$ (338.44): C, 85.18%; H, 6.55%; N, 8.27%. Found: C, 85.12%, H, 6.50%; N, 8.19%.

3f. M.p. = 132°C; IR (KBr): 1610 (Ar), 1670 (C═N), 3250 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.75 (s, 3H, CH_3), 2.41 (s, 3H, Ar-CH_3), 2.95 (d, 1H, CH_2^a), 3.1 (d, 1H, CH_2^b), 3.60 (brs, 1H, NH), 7.2–7.6 (m, 9H, Ar-H). Anal. calcd for $C_{22}H_{16}N_2Cl_4$ (450.19): C, 58.77%; H, 3.58%; N, 6.22%; Cl, 31.50%; Found: C, 58.56%; H, 3.62%; N, 6.98%; Cl, 31.41%.

3g. M.p. = 94°C; IR (KBr): 1655 (C═N), 3260 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.90–2.65 (m, 16H, 8 × CH_2), 2.90–3.25 (m, 3H, N═C–CH and N═C–CH_2), 4.80 (brs, 1H, NH), 7.2–7.6 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 23.8, 26.3, 27.7, 33.2, 34.8, 43.7, 47.6, 113.1, 123.5, 127.3, 128.5, 132.4, 134.1, 165.2. Anal. calcd for $C_{18}H_{24}N_2$ (268.39): C, 80.56%; H, 9.01%; N, 10.43%; Found: C, 80.66%; H, 9.11%; N, 10.55%.

3h. M.p. = 138°C; IR (KBr): 1665 (C═NH), 3260 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.1–2.75 (m, 19H, 8 × CH_2 and Ar-CH_3), 2.90–3.30 (m, 3H, N═C–CH and N═C–CH_2)), 4.95 (brs, 1H, NH), 7.00–7.50 (m, 3H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2, 21.0, 23.7, 26.7, 27.5,

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33.0, 35.0, 43.8, 47.5, 113.5, 123.5, 127.5, 128.5, 132.7, 134.0, 164.5. Anal. calcd for $C_{19}H_{26}N_2$: C, 80.80%; H, 9.28%; N, 9.92%; Found: C, 80.88%; H, 9.19%; N, 9.85%.

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Received in India November 15, 2003