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NBS as an efficient catalyst for the synthesis of 1,5-benzodiazepine derivatives under mild conditions

Chun-Wei Kuo, Shivaji V. More and Ching-Fa Yao*

Department of Chemistry, National Taiwan Normal University, 88, Sec. 4, Tingchow Road, Taipei 116, Taiwan, ROC

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Abstract—Various biologically important 1,5-benzodiazepine derivatives were efficiently synthesized in excellent yields using catalytic amounts of NBS (10 mol %). This inexpensive, nontoxic, and readily available catalyst efficiently catalyzes the condensation of several aromatic as well as aliphatic ketones with substituted *o*-phenylenediamines.

Benzodiazepines have recently attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceuticals. These compounds are widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, hypnotic agents[1] as well as anti-inflammatory agents.[2] Other than their biological importance, benzodiazepine derivatives are also commercially used as dyes for acrylic fibers.[3] Moreover, 1,5-benzodiazepine derivatives are valuable synthons that can be used in the preparation of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines.[4] As a result, research in this area is still very active and is directed toward the synthesis of compounds with enhanced pharmacological activity. Generally, these compounds are synthesized by the condensation of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds,[5] β-haloketones, or ketones.[6] A variety of reagents, such as BF_3-etherate, $NaBH_4$, polyphosphoric acid, or SiO_2, $MgO/POCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, Al_2O_3/P_2O_5, or AcOH under microwave and ionic liquids[7] are utilized for this condensation reaction. Most recently, this condensation has also been reported to proceed in the presence of CAN, (bromodimethyl) sulfonium bromide, organic acids, and $AgNO_3$.[8]

The use of organic molecules as catalysts has become an attractive alternative to traditional metal-catalysts. Interest in the field of organocatalysis has increased spectacularly in the last few years as the result of both the novelty of the concept and, more importantly, the fact that the efficiency and selectivity of many organocatalytic reactions meet the standards of established organic reactions.[9] NBS is one such catalyst, which has recently received considerable attention as a catalyst in various organic transformations,[10] and is widely used as a brominating reagent. Furthermore, it is also used in oxidation and free radical reactions under mild and convenient conditions to afford the desired products in excellent yields and with high selectivities. However, there are no examples of the use of NBS as a catalyst for the synthesis of 1,5-benzodiazepines. As part of our ongoing research concerning the use of economically and easily available materials as catalysts for various organic transformations,[11] we wish to report here on the simple, efficient use of NBS as a catalyst for synthesis of 1,5-benzodiazepines derivatives, under mild conditions.

Initially, the reaction was performed by reacting *o*-phenylenediamine (1 equiv) and acetone (2.2 equiv) in the presence of 2 mol % NBS as a catalyst without any solvent at room temperature. Under these conditions, 1,5-benzodiazepine was obtained in 30% yield after a 2 h reaction. The conditions for this transformation were optimized and the results are shown in Table 1. Only a trace amount of product was obtained in the absence of a catalyst (Table 1, entry 1) even when the reaction time was extended to 24 h, thus demonstrating the importance of NBS. The effect of the amount of acetone used (4–10 equiv) was also examined (Table 1, entries 3

* Corresponding author. Tel./fax: +886 2 29309092; e-mail: cheyaocf@scc.ntnu.edu.tw

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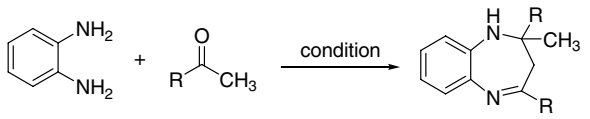
Table 1. Optimization of reaction condition



1 2 3

Entry	R (equiv)	Condition	Yield (%)[a]
1	CH_3 (2.2)	rt/24 h	tr
2	CH_3 (2.2)	2 mol % NBS rt/2 h	30
3	CH_3 (4)	2 mol % NBS rt/2 h	40
4	CH_3 (10)	2 mol % NBS rt/2 h	45
5	CH_3 (10)	5 mol % NBS rt/2 h	53
6	CH_3 (10)	10 mol % NBS rt/2 h	95
7	CH_3 (10)	20 mol % NBS rt/2 h	96
8	CH_3 (4)	10 mol % NBS rt/2 h	95
9	CH_3 (2.2)	10 mol % NBS rt/2 h	75
10	Ph (2.2)	10 mol % NBS rt/24 h	50
11	Ph (2.2)	10 mol % NBS 40 °C/6 h	73
12	Ph (4)	10 mol % NBS rt/24 h	86
13	Ph (4)	10 mol % NBS 40 °C/2 h	90

[a] Isolated yield.

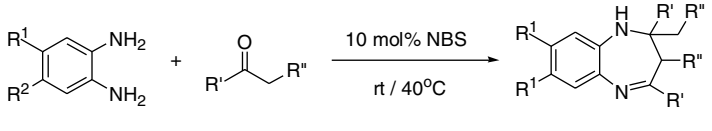
and 4), but this permitted the yield to be increased only to 45%. From this result, the amount of catalyst required for the transformation was investigated by the use of 5–20 mol % of catalyst without any solvent. Under these conditions, the yield of product was in the range of 53–96% (Table 1, entries 5–7), but the amount of acetone (10 equiv) used for this reaction remained as a problem. Reducing the amount of ketone to 4 equiv and the use of 10 mol % NBS gives best results with a 95% yield for a 2 h reaction at room temperature (Table 1, entry 8). However, when 2.2 equiv of acetone was reacted with *o*-phenylenediamine only a 75% yield was obtained, after stirring for 2 h at room temperature (Table 1, entry 9). When the same reaction conditions were applied to acetophenone (Table 1, entry 12), a good yield was obtained but the time required for completion of the reaction was longer. By heating the reaction mixture at 40 °C, however, the reaction time could be reduced to 2 h with the product being produced in excellent yield (90%).

Thus, under the optimized reaction conditions, *o*-phenylenediamine **1** (1 mmol) and ketone **2** (4 mmol) were mixed with NBS (0.1 mmol) and stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), a simple work up followed by column chromatography afforded 2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzadiazepine **3**[12] in good to excellent yields. To investigate the feasibility of this synthetic method for preparing benzodiazepine derivatives, the reactions of *o*-phenylenediamine with various ketones were examined in the presence of 10 mol % NBS at room temperature or 40 °C (Scheme 1). As shown in Table 2, both aromatic and aliphatic ketones reacted readily with *o*-phenylenediamine to afford the corresponding 1,5-benzodiazepines in 64–95% yields.

It is noteworthy that starting from an unsymmetric ketone such as 2-butanone (**3b**, Table 2), the ring closure occurs selectively only from one side of the carbon skeleton to afford a single product. In the case of the strong electron donating 4-methoxy acetophenone, a longer reaction time was required and the yield of the product was moderate (**3e**, Table 2). No such effect of electron donating and electron withdrawing groups on other acetophenones was observed, and all gave good to excellent yields. Heterocyclic ketones such as 2-acetylthiophene also gave good yields (80%, 6 h) with only a slightly longer reaction time (**3k**, Table 2). We also studied the reactions of substituted *o*-phenylenediamines, by treating various substituted *o*-phenylenediamines **4** such as 4-ChloroOPD, 4-methylOPD, 4,5-dichloroOPD, and 4,5-dimethylOPD with various ketones **5** (Table 3). No observable substituent effects of electron donating and electron withdrawing groups on OPD were noted for yields and rate, except for 4,5-dichloroOPD, which required a longer reaction time. Some substituted *o*-phenylenediamines gave inseparable mixtures of regioisomers (Table 3, entries p, q, r, and s). In all cases, the reactions were clean and the products were obtained in high yields with a short time. Compared to existing methods in the literature, this method has several advantages, which include milder reaction conditions, cheap and readily available reagents, wider substrate scope with higher selectivity and improved product yields.

The mechanism of the condensation reaction could involve an intramolecular imine–enamine cyclization promoted by NBS, as shown in Scheme 2. The amine of *o*-phenylenediamine is first activated by NBS[10c] and then attacks the carbonyl group of the ketone, giving intermediate diimine **6**. A 1,3-shift of the hydrogen attached to the methyl group then occurs to form an isomeric enamine **7**, which cyclizes to afford the seven-membered ring.

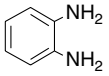
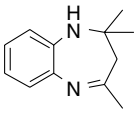
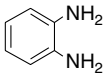
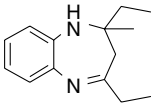
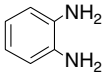
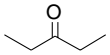
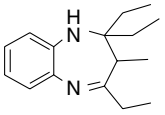
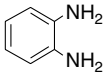
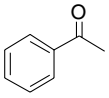
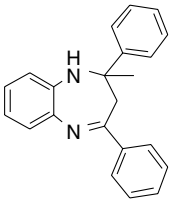
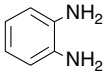
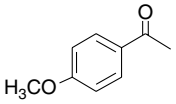
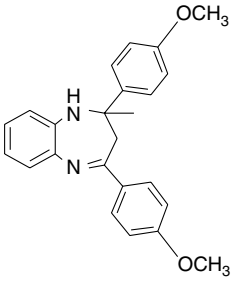
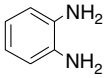
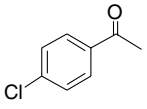
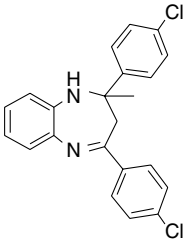
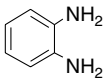
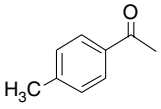
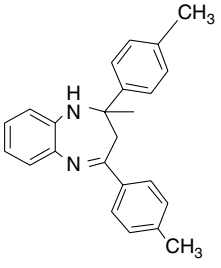
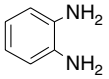
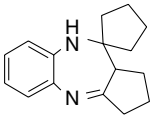
In conclusion, we successfully developed a simple, efficient method for the synthesis of 1,5-benzodiazepine derivatives from various substituted *o*-phenylenediamines (OPD) under mild conditions by the rapid condensation of various aromatic, aliphatic acyclic and cyclic ketones using cheap and readily available NBS as a catalyst. This simple procedure is efficient and can be applied to the synthesis of a wide variety of 1,5-benzodiazepines in good to excellent yields. Further applications of this simple catalytic system are currently underway.



4 5 3

Scheme 1.

Table 2. Synthesis of 1,5-benzodiazepines from OPD and different ketones

Entry	Diamine	Ketone	Product[a]	Time (h)	Yield (%)[b]
a				2	95
b				2.5	85
c				2.5	83
d				2	90
e				6	64
f				2	95
g				2	90
h				2.5	80

(*continued on next page*)

Table 2 (*continued*)

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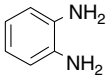
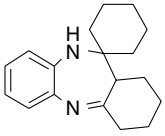
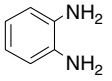
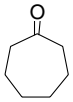
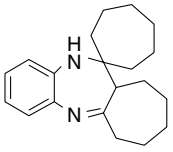
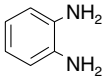
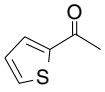
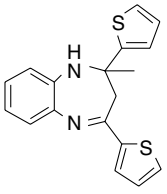
i				2.5	82
j				2.5	81
k				6	80

[a] All product were characterized by ^{1}H NMR, ^{13}C NMR spectral data, and melting point compared with literature values.
[b] Yields of isolated products.

Table 3. Synthesis of 1,5-benzodiazepines from substituted OPD and different ketones

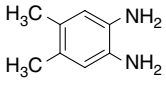
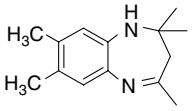
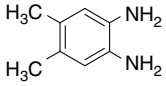
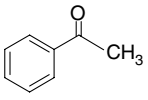
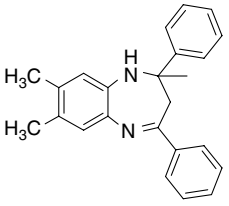
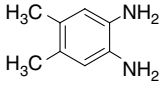
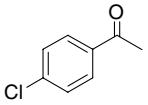
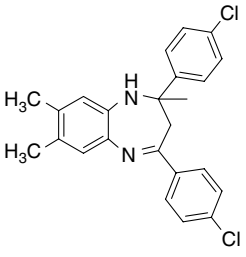
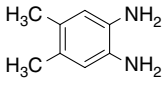
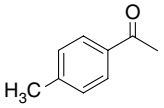
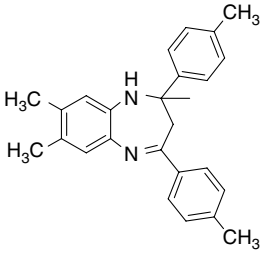
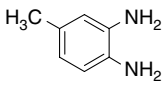
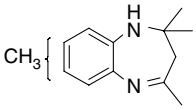
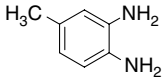
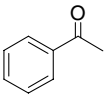
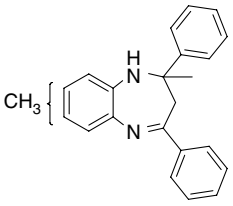
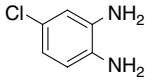
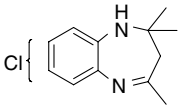
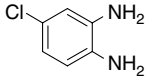
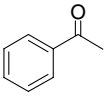
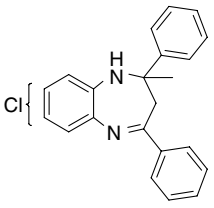
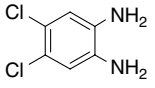
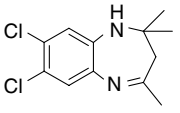
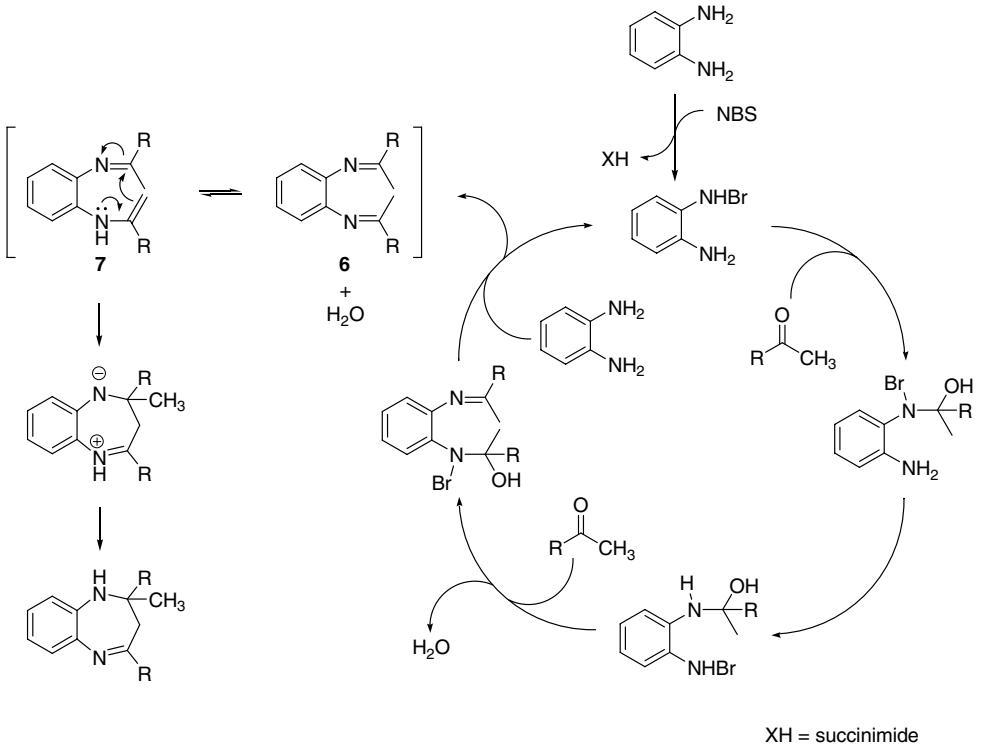
Entry	Diamine	Ketone	Product[a]	Time (h)	Yield (%)[b]
l				2	85
m				2	92
n				2	83
o				2	86

Table 3 (*continued*)

Entry	Diamine	Ketone	Product[a]	Time (h)	Yield (%)[b]
p				2	75 (50:50)[c]
q				2	70 (50:50)[c]
r				2	80 (70:30)[c]
s				3	70 (60:40)[c]
t				5	70

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR spectral data, and melting points compared with literature values.
[b] Yields of isolated products.
[c] Inseparable regioisomers and product ratio.



Scheme 2. Proposed mechanism for the NBS catalyzed reaction.

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12. *General procedure for the synthesis of 2,3-dihydro-1,5-benzodiazepine derivatives* **3***:* A mixture of *o*-phenylenediamine (1 mmol), ketone (4 mmol), and 10 mol % *N*-bromosuccinimide was stirred at ambient temperature (for **3a, 3l**, **3p**, **3r**, **3t** at rt; **3b–k**, **3m–o**, **3q**, **3s** at 40 °C) for the appropriate times (Tables 2 and 3). After completion of the reaction (as monitored by TLC), the reaction mixture was diluted with H_2O and extracted with EA. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in a vacuum. The resulting product was purified by flash column chromatography with EA/hexane as the eluent to afford pure compound **3**.
2,2,4-Trimethyl-2,3-dihydro-1H-1,5-benzadiazepine **3a** *(Table 2):* Light yellow solid; mp 135–137 °C (lit. 136–138 °C);[10] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 6H), 2,18 (s, 2H), 2.33 (s, 3H), 3.02 (br s, 1H, NH), 6.67–6.70 (m, 1H), 6.93–6.96 (m, 2H), 7.10–7.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.55, 30.19, 44.87, 67.99, 121.48, 121.69, 125.25, 126.59, 137.78, 140.39, 172.06. EIMS: *m*/*z* (%) 188 (M+, 30).
2-Methyl-2,4-di(thiophen-2-yl)-2,3-dihydro-1H-1,5-benzodiazepines **3k** *(Table 2):* Brown solid; mp 92–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82 (s, 3H), 2.99 (d, 1H, $J = 13.2$ Hz), 3.06 (d, 1H, $J = 13.2$ Hz), 3.59 (br s, 1H, NH), 6.79–6.81 (m, 1H), 6.90–6.93 (m, 2H), 7.02–7.10 (m, 5H), 7.27–7.30 (1H), 7.36–7.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.57, 44.28, 72.49, 122.00, 122.51, 122.73, 124.13, 126.09, 126.81, 127.47, 127.90, 128.18, 130.06, 137.10, 140.77, 146.53, 153.25, 162.21; LCMS (EI): *m*/*z* (%) 325 (M+1, 100), 201(30).
2,7,8-Trimethyl-2,4-di(4-chlorophenyl)-2,3-dihydro-1H-1,5-benzodiazepine **3n** *(Table 3):* Yellow solid; mp 182–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 3H), 2.24 (s, 6H), 2.88 (d, 1H, $J = 13.2$ Hz), 3.08 (d, 1H, $J = 13.2$ Hz), 3.33 (br s, 1H, NH), 6.63 (s, 1H), 7.10 (s, 1H), 7.18–7.20 (m, 4H), 7.45–7.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.79, 19.39, 29.79, 43.13, 27.97, 122.36, 127.04, 128.23, 128.32, 128.88, 129.61, 129.71, 130.02, 132.94, 135.33, 135.37, 135.86, 137.32, 137.90, 146.01, 165.28; LCMS (EI): *m*/*z* (%) 409 (M+1, 100), 257 (10).
2,7,8-Trimethyl-2,4-di(p-tolyl)-2,3-dihydro-1H-1,5-benzodiazepine **3o** *(Table 3):*Yellow solid; mp 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70 (s, 3H), 2.24 (s, 6H), 2.30 (s, 3H), 2.32 (s, 3H), 2.97 (d, 1H, $J = 13.2$ Hz), 3.07 (d, 1H, $J = 13.2$ Hz), 3.33 (br s, 1H, NH), 6.60 (s, 1H), 7.05–7.11 (m, 5H), 7.49 (d, 2H, $J = 8.4$ Hz), 7.54 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.78, 19.36, 20.86, 21.25, 29.88, 43.06, 72.83, 122.30, 125.22, 127.06, 128.43, 128.75, 128.93, 129.23, 129.55, 134.61, 135.96, 136.54, 137.22, 137.88, 139.68, 145.24, 166.77; EIMS: *m*/*z* (%) 368 (M^+, 25), 353 (30), 277 (30), 250 (10), 236 (100), 211 (10), 117 (25).
2,2,4-Trimethyl-2,3-dihydro-7,8-dichloro-1H-1,5-benzodiazepine **3t** *(Table 3):* Red solid; mp 110–112 °C (lit. 113 °C);[10] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 6H), 2.26 (s, 2H), 2.35 (s, 3H), 3.05 (br s, 1H, NH), 6.81 (s, 1H), 7.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.87, 30.54, 45.32, 67.73, 122.19, 124.53, 128.20, 128.33, 137.71, 139.59, 174.10; EIMS: *m*/*z* (%) 257 (M^+, 45), 241 (100), 200 (80), 165 (15).