A New and Efficient Procedure for Synthesis of 1,5-Benzodiazepine Derivatives in Solution and under Solvent-Free Conditions

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Borax/phosphorous oxychloride (BPO) efficiently catalyzes the preparation of 1,5-benzodiazepine derivatives of *o*-phenylenediamines and ketones in solvent-free and solution conditions. The reaction proceeds efficiently under ambient conditions giving excellent yields of the products. This new protocol allows the recycling of catalyst with no loss in its potency.

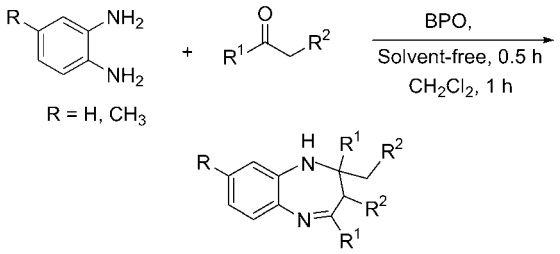
Keywords 1,5-benzodiazepine, *o*-phenylenediamine, borax, phosphorus oxychloride

Introduction

The preparation of benzodiazepines and their polycyclic derivatives is important due to their pharmacological and industrial properties.[1,2] 1,5-Benzodiazepines are useful precursors for the preparation of some fused ring compounds such as triazolo-,[3] oxadiazolo-,[4] oxazino-,[5] furano,[5,6] or tricyclic derivatives.[7] Several methods have been reported in the literature for the synthesis of benzodiazepines. These include condensation reactions of *o*-phenylenediamines (OPD) 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 or SiO_2,[12] MgO and $POCl_3$,[13] $Yb(OTf)_3$,[14] Al_2O_3/P_2O_5 or CH_3COOH under MW,[15,16] $Sc(OTf)_3$,[17] clay-supported polyoxometalates,[18] polymer supported ferric chloride,[19] and tetranitrile-silver complex.[20] Many of these processes suffer from one or other limitations such as requiring harsh condition, expensive reagents, long reaction times, low yields and occurrence of several side products. Moreover, the main disadvantages of almost all existing methods are that the used catalysts are expensive or destroyed in the work-up procedure and cannot be recovered or reused. Surface-mediated solid phase reactions are of growing interest,[21-24] because of their ease of set-up and work-up, mild reaction conditions, rate of the reaction, selectivity, high yields, lack of solvent and the low cost of the reactions in comparison with their homogeneous counterparts.

This paper describes a facile synthesis of benzodiazepines by condensation of ketones with *o*-phenylenediamines in the presence of $Na_2B_4O_7/POCl_3$ (BPO) (Scheme 1).

Scheme 1 BPO catalyzed synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines from ketones and *o*-phenylenediamines under both solvent-free and in solution conditions



Results and discussion

To find the optimal conditions, a mixture of 1,2-phenylenediamine and acetone was stirred under various reaction conditions (Table 1). The reaction did not occur in the absence of catalyst after 5 h (Table 1, Entry 1). Best results were obtained using 0.1 g of BPO, 2 mmol *o*-phenylenediamine and 5 mmol acetone, and any excess of BPO did not lead to an increase in the conversion and yield. It is interesting to note that no reaction was observed in the presence of $POCl_3$ or borax (Table 1, Entries 2—5).

As shown in Table 2, both acyclic and cyclic ketones react without any significant difference to give the corresponding 2,4-dihydro-1*H*-1,5-benzodiazepines under optimal conditions. The benzodiazepines **3** were the

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Table 1 Reaction of *o*-phenylenediamine with acetone in various conditions

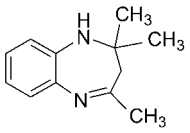
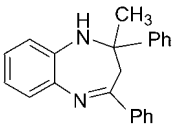
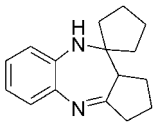
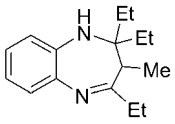
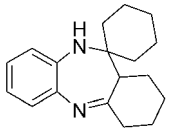
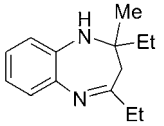
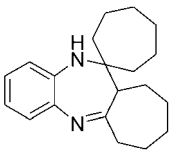
Entry	Catalyst (g)	Solvent	Time/h	Yield[a]/%
1	—	CH_2Cl_2	5	0
2	$POCl_3$ (0.2)	CH_2Cl_2	5	0
3	Borax (0.2)	CH_2Cl_2	5	0
4	$POCl_3$ (0.2)	—	5	0
5	Borax (0.2)	—	5	0
6	BPO (0.2)	CH_3CN	1	85
7	BPO (0.2)	CH_2Cl_2	1	93
8	BPO (0.2)	MeOH	1	90
9	BPO (0.05)	CH_2Cl_2	1	65
10	BPO (0.1)	CH_2Cl_2	1	90
11	BPO (0.1)	—	0.5	92

[a] Isolated yields.

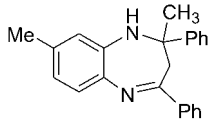
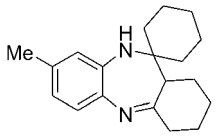
only products obtained. The reactions were carried out in solution and we found that solvent-free conditions were more suitable in term of reaction rate. It is noteworthy to mention that by starting from an unsymmetrical ketone, such as 2-butanone (Table 2, Entry f), the ring closure occurs selectively only from one side of carbonyl group yielding a single product.

The recovery and reusability of the catalyst have been investigated. The condensation of OPD and acetone with BPO afforded the corresponding 1,5-benzodiazepine in 90%, 81%, 65% and 43% yields over four cycles in dichloromethane at room temperature. But in the reaction of 1,2-phenylenediamine and acetone with BPO under solvent-free conditions, the recovered catalyst has been charged to the reaction mixture for four runs without any observable loss of its catalytic activity (Table 3).

Table 2 $Na_2B_4O_7/POCl_3$ catalyzed formation of 2,3-dihydro-1*H*-1,5-benzodiazepines

Entry	Reactant	Product **3**	Yield[a,b]/%	m.p.	
				Found	Reported (Ref.)
a	OPD Acetone		92 (90)	136—139	137—139[10]
b	OPD Acetophenone		95 (91)	150—151	150—152[19]
c	OPD Cyclopentanone		93 (90)	138—140	138—139[10]
d	OPD 3-Pentanone		94 (93)	142—144	143—145[19]
e	OPD Cyclohexanone		92 (88)	139—140	137—139[14]
f	OPD 2-Butanone		91 (92)	135—136	137—139[18]
g	OPD Cycloheptanone		87 (84)	136—138	136—137[14]

Continued

Entry	Reactant	Product **3**	Yield[a,b]/%	m.p.	
				Found	Reported (Ref.)
h	4-Methyl-*o*-phenylenediamine Acetophenone		92 (90)	90—91	92[25]
i	4-Methyl-*o*-phenylenediamine Cyclohexanone		91 (89)	136—138	137—139[25]

[a] Isolated yields. [b] The data in parenthesis are yields in solution.

Table 3 Recycling of BPO in reaction of *o*-phenylenediamine and acetone with BPO

Run	Yield[a,b]/%	
	Solvent-free[c]	Solution[d]
1	92	90
2	90	81
3	88	65
4	89	43

[a] Isolated yields. [b] The recovered catalyst was washed with diethyl ether and dried. [c] Reaction conditions: *o*-phenylenediamine (2 mmol), acetone (5 mmol), BPO (0.1 g), room temperature, 0.5 h. [d] Reaction conditions: *o*-phenylenediamine (2 mmol), acetone (5 mmol), BPO (0.1 g), CH_2Cl_2 (5 mL), room temperature, 1 h.

Experimental

Preparation of BPO

A mixture of $POCl_3$ (1.5 g) and anhydrous borax (2 g) were combined in a mortar and pestle by grinding them together until a fine, homogeneous powder was obtained (15—20 min).

General procedure for the synthesis of 1,5-benzodiazepine derivatives under solvent-free conditions

A mixture of *o*-phenylenediamine or 4-methyl-1,2-phenylenediamine (2 mmol), ketone (5 mmol) and BPO (0.1 g) was well stirred at room temperature. After 0.5 h 10 mL of CH_2Cl_2 was added to the reaction mixture and the catalyst was recovered by filtration. The organic layer was concentrated and the products were purified by silica gel column chromatography (100—200 mesh) and eluted with *V*(EtOAc)∶*V*(*n*-hexane)=2∶8 to afford the pure compounds in 87%—95% yields. The wet catalyst was recycled and no appreciable change in its activity was achieved after four runs. The spectral data of some of the compounds are given below.

3b: m.p. 150—151 ℃; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.78 (s, 3H), 2.90 (d, J=13 Hz, 1H), 3.15 (d, J=13 Hz, 1H), 3.4 (br s, 1H), 6.63—7.05 (m, 3H), 7.10—7.32 (m, 7H), 7.50—7.63 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 167.0, 145.5, 140.4, 140.0, 138.5, 129.7, 128.5, 128.4, 127.9, 127.0, 126.8, 126.2, 125.5, 121.5, 121.2, 73.7, 42.8, 30.0; IR v: 3330, 1650 cm^{-1}.

3i: m.p. 90—91 ℃; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.78 (s, 3H), 2.40 (s, 3H), 2.98 (s, 1H), 3.13 (s, 1H), 3.4 (br s, 1H), 6.63—7.68 (m, 13H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 164.6, 136.5, 133.4, 131.3, 130.5, 128.7, 128.5, 128.3, 128.2, 128.0, 127.5, 126.0, 125.5, 123.5, 113.4, 50.9, 45.8, 28.5, 20.6; IR v: 3295, 1665 cm^{-1}.

The other products were characterized by spectral (IR, ^{1}H and ^{13}C NMR) data and also by the mixed melting points with the authentic samples.

General procedure for the synthesis of 1,5-benzodiazepine derivatives in solution

A mixture of *o*-phenylenediamine or 4-methyl-1,2-phenylenediamine (2 mmol), ketone (5 mmol) and BPO (0.1 g) was well stirred at room temperature in 5 mL of CH_2Cl_2. After 1 h catalyst was recovered by filtration. The filtrate was concentrated and the products were purified by silica gel column chromatography (100—200 mesh) and eluted with *V*(EtOAc)∶*V*(*n*-hexane)=2∶8 to afford the pure compounds in 84%—93% yields.

Conclusion

We have developed a simple, convenient and effective method for easy synthesis of 2,3-dihydro-1,5-benzodiazepines by the condensation of ketones with *o*-phenylenediamines using borax-supported $POCl_3$ as catalyst in both solvent-free and solution conditions. The catalyst can be prepared easily with available inexpensive reagents and works under heterogeneous conditions. The simple procedure combined with ease of

recovery and reuse of the catalyst make this method economical, benign and is a waste-free chemical process for the synthesis of 1,5-benzodiazepines. Studies for the application of the catalyst for several reactions are under investigation in our laboratory.

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