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Short communication

(Bromodimethyl) sulfonium bromide: An efficient catalyst for solvent-free synthesis of 1,5-benzodiazepines☆

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Abstract

An efficient solvent-free synthesis of 1,5-benzodiazepines by condensation of *o*-phenylenediamines with ketones in the presence of catalytic amount of (bromodimethyl) sulfonium bromide has been accomplished. The condensation occurred at room temperature and the products were formed in high yields.

Keywords: 1,5-Benzodiazepine; *o*-Phenylenediamine; Ketone; (Bromodimethyl) sulfonium bromide; New catalyst; Solvent-free conditions

Benzodiazepines have recently received attention as medicinally important compounds possessing analgesic, hypnotic, sedative, antianxiety, anticonvulsant, antidepressant and anti-inflamatory properties [1]. These compounds are also commercially employed as dyes for acrylic fibres [2]. Additionally, they are useful synthons for the synthesis of various fused-ring compounds such as triazolo-, oxazino-, oxadiazolo- and furano-benzodiazepines [3]. Due to such wide range of pharmacological, industrial and synthetic applications the preparation of benzodiazepines is highly necessary.

1,5-Benzodiazepines are generally synthesized by condensation of *o*-phenylenediamines with ketones in the presence of a catalyst such as BF_3-OEt_2, MgO/$POCl_3$, Yb$(OTf)_3$, polyphosphoric acid-SiO_2, HOAc-microwaves, $NaBH_4$, $InBr_3$ and ionic liquids [4]. However, many of these methods are associated with several drawbacks such as applications of expensive reagents, drastic reaction conditions, extended reaction times, occurrence of side products, unsatisfactory yields and complex experimental procedure. Hence, there is a need to develop a convenient, efficient and practically useful process for the synthesis of 1,5-benzodiazepines.

We report here for the first time a simple method for the condensation of *o*-phenylenediamines (**1**) with ketones (**2**) using (bromodimethyl) sulfonium bromide [5] (10 mol%) as a catalyst under solvent-free conditions to synthesize 1,5-benzodiazepines (**3**) (Scheme 1).

The scope and generality of the above process is illustrated with respect to different *o*-phenylenediamines and a wide range of ketones (Table 1). Both aromatic and aliphatic ketones equally underwent the conversion. Different acyclic and cyclic ketones were successfully applied. However, the ketones should contain an α-hydrogen. Cyclic ketones such as cyclopentanone and cyclohexanone afforded fused-ring 1,5-benzodiazepines (entries 3d and 3e). The diamines having electron-donating as well as electron-with drawing groups on the aromatic rings worked well. The conversion proceeded at room temperature and in relatively short reaction time (1 h). No any solvent was added to the reaction mixture. The experimental procedure is simple. The yields of the desired 1,5-benzodiazepines were found to be very high. With unsymmetrical ketones high regioselectivity was also observed. The structure of the products were settled from their spectral (^{1}H NMR and MS) data.

The catalyst (bromodimethyl) sulfonium bromide [5] is an inexpensive reagent. It worked actively in the present conversion under very mild reaction conditions. No product was formed in absence of this catalyst. The catalyst was used earlier for some synthetic conversions [5] but its utilities have not been fully explored. The present conversion is a good example, where the catalyst has been utilized efficiently. Compared to other acid catalysts such as $InCl_3$, $CeCl_3 \cdot 7H_2O$, In$(OTf)_3$, Cu$(OTf)_2$, etc. (bromodimethyl) sulfonium bromide was found to be superior

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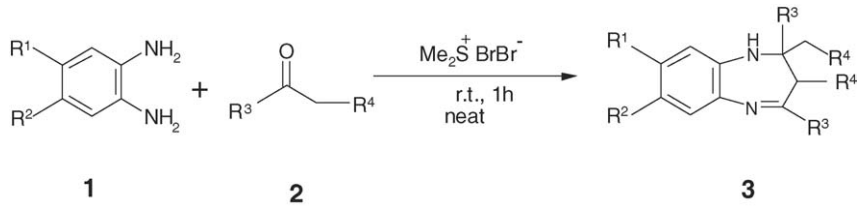
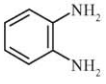
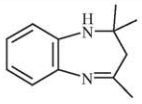
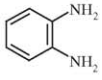
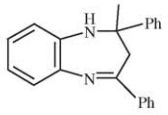
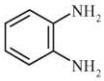
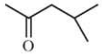
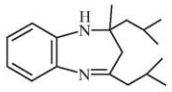
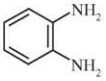
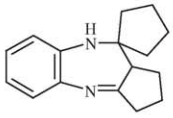
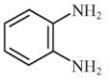
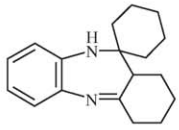
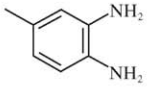
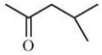
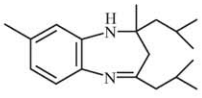
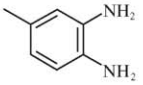
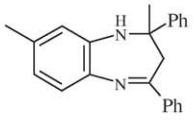
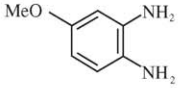
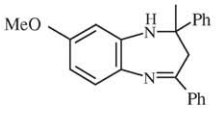
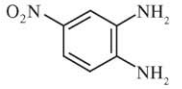
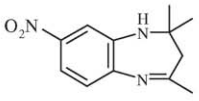
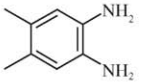
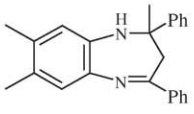
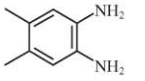
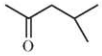
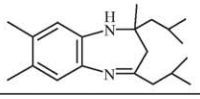


Scheme 1.

Table 1
(Bromodimethyl) sulfonium bromide catalyzed synthesis of 1,5-benzodiazepines[†]

Entry	Diamine 1	Ketone 2	Product 3	Isolated yield (%)	Reference
a		CH_3COCH_3		96	4g
b		$PhCOCH_3$		91	4g
c				94	4g
d				85	4h
e				89	4g
f				95	4i
g		$PhCOCH_3$		93	4g
h		$PhCOCH_3$		84	4h
i		CH_3COCH_3		79	4i
j		$PhCOCH_3$		86	4f
k				95	4i

[†] The structures of the 1,5-benzodiazepines prepared were determined from their spectral (^{1}H NMR and MS) data.

in terms of conversion, reaction rate and required amount of the catalyst [4h]. No any bromination product was obtained using this catalyst.

In conclusion, we have demonstrated a novel efficient solvent-free process for the synthesis of 1,5-benzodiazepines using (bromodimethyl) sulfonium bromide as a catalyst. The simple experimental procedure, mild reaction conditions, short reaction time and high yields and regioselectivity are the advantages of the present protocol. The process is eco-friendly and economically viable. We feel the process will be practically useful for the preparation of a wide variety of biologically active 1,5-benzodiazepines.

1. Experimental section

1.1. General procedure for the synthesis of 1,5-benzodiazepines

To a mixture of *o*-phenylenediamine (1 mmol) and ketone (2.2 mmol) (bromodimethyl) sulfonium bromide (10 mol%) (prepared by reported method [5b]) was added and the mixture was stirred at room temperature. The reaction was monitored by TLC and it was found to be completed by 1 h. The reaction mixture was then quenched with water (5 ml) and extracted with EtOAc (3× 5 ml). The extract was concentrated and the residue was subjected to column chromatography over silica gel using EtOAc:hexane (1:4) as eluent to afford pure 1,5-benzodiazepine.

All the products gave satisfactory spectroscopic (^{1}H NMR and MS) analyses in accord with their assigned structures.

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