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Kaolin: A Recyclable Catalyst for the Synthesis of 1,5-Benzodiazepines

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ABSTRACT: *2,3-Dihydro-1*H*-1,5-benzodiazepines are synthesized by the condensation of o-phenylenediamine and various ketones in the presence of kaolin as a recyclable catalyst in dichloroethane.*
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INTRODUCTION

Benzodiazepines are an important class of pharmacologically active compounds and are used as anticonvulsing, antianxiety, and hypnotic agents [1,2]. Its derivatives are also commercially used as dyes for acrylic fibers [3] and as anti-inflammatory agents [4]. Moreover, they are key intermediates for the preparation of other fused ring compounds such as triazolo- [5], oxazino- [6], oxadiazolo- [7], or furano-benzodiazepines [8]. However, only few methods are reported for their preparation. In the literature, these include condensation reaction of *o*-phenylenediamine as freebase or hydrochloride salts, with α-β-unsaturated carbonyl compounds [9], β-haloketones [10], or ketones [11] in the presence of conventional acid catalyst, Lewis acid catalysts such as BF_3-etherate [11], $NaBH_4$ [12], and polyphosphoric acid [13]. Furthermore, the synthesis of 1,5-benzodiazepine derivatives, catalyzed by $MgO/POCl_3$ [14], $Yb(OTf)_3$ [15], ionic liquid [16], sulfated zirconia [17], $AgPW_{12}O_{40}$ [18], and zeolit [19], has been reported recently. Unfortunately, many of these processes suffer because of some major or minor limitations, such as drastic reaction conditions, low yields, tedious work up procedures, and co-occurrence of several side reactions.

RESULTS AND DISCUSSION

In recent years, considerable emphasis has been placed on improvement in the environmental impact of industrial chemical processes. It is well recognized that solids can play a significant role in the development of cleaner technologies through their abilities to act as catalyst, support reagents, entrain by products, and influence product selectivity [20]. Aluminosilicate clays are well characterized by their surface acidities, which render them efficient, versatile supports, or catalysts [21,22]. Although montmorillonite (bentonites) is widely used, kaolin-based reagents or kaolin-assisted reactions appear to be extremely limited [23–25]. Kaolin, owing to its acidic nature, can be a suitable replacement for various homogeneous acid catalysts. It has been used in the protection reaction of carbonyl compounds [23], alkylation of benzene [24], and bromination and chlorination of aromatic compounds [25].

In view of the importance of heterogeneous solid acids as reusable catalysts in organic synthesis and in continuation of ongoing research using solid supports in our laboratory [26], in this communication we report a facile method for the synthesis of

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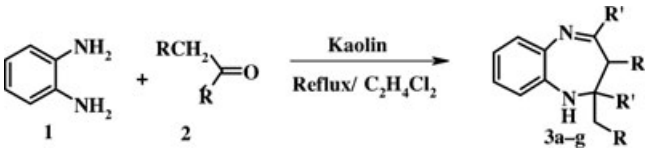

SCHEME 1

2,3-dihydro-1*H*-1,5-benzodiazepines by the condensation of *o*-phenylenediamine with ketones in the presence of catalytic amount of kaolin under refluxing dichloroethane (Scheme 1).

The syntheses were carried out simply by refluxing a mixture of *o*-phenylenediamine (1 mmol), ketone (2.1 mmol), and a catalytic amount of kaolin in dichloroethane, whereupon the benzodiazepine derivatives were obtained in almost quantitative yields. The results are summarized in Table 1.

Cyclic and acyclic ketones and substituted aryl ketones have been used for the synthesis of 1,5-benzodiazepine derivatives. Kaolin is not soluble in dichloroethane, so it can facilitate the separation of products from the catalyst.

We investigated the reusability of the catalyst. For this purpose, we first carried out the reaction of *o*-phenylenediamine and acetophenone in the presence of the catalyst. After completing the reaction, the catalyst was removed by a simple filtration and washed with diethyl ether and subjected to a second run of the reaction process with the same substrate. The results of the first experiment and subsequent experiments were almost consistent in yields after three runs (86%, 84%, 81%).

In summary, a simple work-up procedure, convenient and efficient protocol for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines via the condensation of *o*-phenylenediamine with different ketones, using kaolin as a recyclable heterogeneous catalyst, is reported. The simple experimental procedure together with ease of recovery and reuse of the catalyst makes this method quite simple, more convenient, and environmentally benign.

TABLE 1 Kaolin-Catalyzed Synthesis of 1,5-Benzodiazepines

Entry	*Ketone*	*Time (h)*	*Yield*
1	Acetone	3	90
2	Acetophenone	4	90
3	4′-Methyl acetophenone	3.5	87
4	4′-Nitroacetophenone	5	85
5	4′-Hydroxy acetophenone	5	84
6	Ethyl methyl ketone	3.5	92
7	Cyclohexanone	6	90

EXPERIMENTAL

A mixture of ketone (2.1 mmol), *o*-phenylenediamine (1 mmol), and kaolin (0.05 g) was refluxed in dichloroethane. After completion of reaction (monitored by TLC), the reaction mixture was filtered. After evaporation of solvent, products were obtained in good yields. More purification was done by column chromatography. They were identified through comparing with authentic samples. The recovered catalyst was washed with diethyl ether and was reused.

All products gave satisfactory spectral data in accordance with the assigned structures. For example, for entry 1: light yellow solid: mp 138°C (136–138°C [18]). IR (KBr): 3340, 1650, 1600 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7–7.25 (m, 4H, Ar-H), 3.5 (br s, 1H, N—H), 3(s, 2H, N=C—CH_2), 2.5 (m, 3H, N=C—CH_3), 1.50–1.75 (s, 6H, $2CH_3$).

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