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# A simple and new method for the synthesis of 1,5-benzodiazepine derivatives on a solid surface

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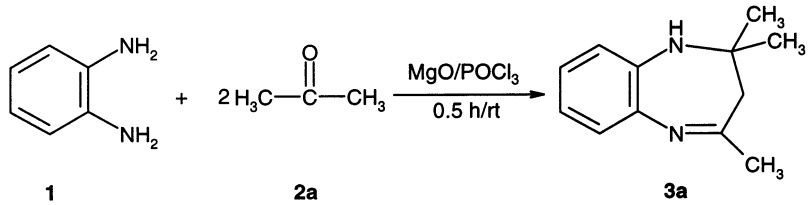
**Abstract**—Magnesium oxide/phosphorus oxychloride (MOPO) was found to be an efficient reagent for the preparation of 1,5-benzodiazepine derivatives of *o*-phenylenediamine and ketones. This method is an easy, rapid, and high yielding reaction for the synthesis of 1,5-benzodiazepine derivatives. 

Benzodiazepines are interesting compounds because of their pharmacological properties.[1] Many members of this family are, in fact, nowadays widely used as tranquilizing and anticonvulsant agents. Although the first benzodiazepine was introduced as a drug nearly 30 years ago,[2] the research in this area is still very active and is directed towards the synthesis of compounds of enhanced pharmacological activity. Some benzodiazepine derivatives are also used in industry, such as in photography (as dyes for acrylic fibers),[3] and also as anti-inflammatory agents.[4] 1,5-Benzodiazepines are also used as starting materials for the preparation of some fused ring benzodiazepine derivatives, such as triaxol,[5] and oxadiazol.[6] Despite their wide range of pharmacological activity, industrial and synthetic applications, the synthesis of 1,5-benzodiazepines has received little attention. The following methods, not generally applicable, have been reported in the literature: (i) condensation of α,β-unsaturated compounds with *o*-phenylenediamines,[7] (ii) reaction of β-haloketones with *o*-phenylenediamine,[8] and (iii) the recently reported condensation of methyl ketones with *o*-phenylenediamines in the presence of PPA at high temperature.[9] However, all of these methods have problems, including drastic reaction conditions and also severe side-reactions. Surface-mediated solid phase reactions are of growing interest[10] because of their ease of execution and work-up, mild reaction conditions, rate of reaction, selectivity, high yields, lack of solvent and low cost in comparison with their homogeneous counterparts. As a part of our efforts to explore the utility of surface-mediated reactions,[11–13] we report here a new method for the preparation of 1,5-benzodiazepine derivatives by condensation of *o*-p1henylenediamine with ketones. It was found that a mixture of magnesia/phosphorus oxychloride under solvent-free conditions was capable of producing high yields of 2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine **3a** by condensation of *o*-phenylenediamine with acetone under mild reaction conditions in 90% yield (Scheme 1; Table 1).




**1** **2a** **3a**

**Scheme 1.**

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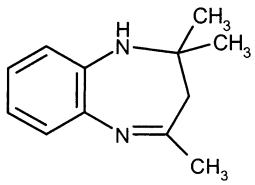
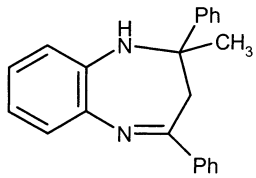
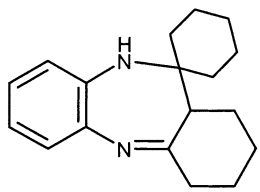
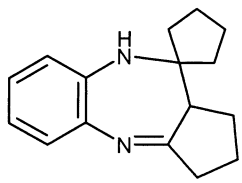
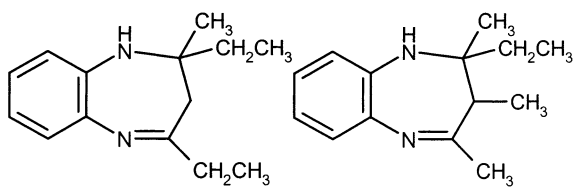
The same process was successfully extended to other 1,5-benzodiazepine derivatives as summarized in Table 1. As shown in Table 1, acetophenone in the presence of a mixture of magnesia/phosphorus oxychloride with *o*-phenylenediamine **1** afforded 2,3-dihydro-2-methyl-2,4-diphenyl-1*H*-1,5-bezodiazepine **3b** in 87% yield. The reaction of cyclic ketones (**2c** and **2d**) with *o*-phenylenediamine **1**, in the presence of magnesia/phosphorus oxychloride, gave fused ring 1,5-benzodiazepine derivatives (**3c** and **3d**) in good yields. The condensation of 2-butanone **2e** with *o*-phenylenediamine, in the presence of this reagent, gave two products (**3e** and **3e′**).

This solvent-free method has an operationally simple procedure. A mixture of the *o*-phenylenediamine (0.504 g, 5 mmol, finely ground) and magnesia (MgO, 1.5 g) was prepared in a mortar and pestle by grinding them together until a fine, homogeneous mixture was obtained (5–10 min). Phosphorus oxychloride (0.8 ml) was added to this mixture. After 10 min of vigorous stirring, the ketone (10 mmol) was added to this mixture, which was stirred for 0.5 h. The reaction mixture was washed with *n*-hexane (200 mL), dried ($CaCl_2$), and the solvent evaporated to give the crude products. Pure product[14] was obtained by crystallization from *n*-hexane in 65–90% yields.

In summary, a simple work-up, low consumption of solvent, fast reaction rates, mild reaction condition, good yields, and selectivity of the reaction make this method an attractive and a useful contribution to present methodologies.

**Table 1.** The condensation of *o*-phenylenediamine with ketones in the presence of $MgO/POCl_3$

| Entry | Ketone (2) | Yield[a] (%) | Product(s) (3) |
|---|---|---|---|
| **a** | Acetone | 90 |  |
| **b** | Aetophenone | 87 |  |
| **c** | Cyclohexanone | 80 |  |
| **d** | Cyclopentanone | 65 |  |
| **e** | 2-Butanone | 80 |  30% 70% (diastereoisomers not separated) |

a: Isolated Yields

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14. All products gave satisfactory spectral data in accord with the assigned structures [e.g. for **3a** $^1$H NMR ($CDCl_3$, TMS) $\delta$: 1.35 (s, 6H, 2-$CH_3$), 2.25 (s, 2H, -$CH_2$), 2.33 (s, 3H, -$CH_3$), 3.45 (br, $^1$H, -NH), 6.60–7.25 (m, 4H); IR (KBr): $\nu$ 3289 (NH), 1637 (C=N), 1597 cm$^{-1}$ (Ar)].