HETEROCYCLES, Vol. 55, No. 8, pp. 1443 - 1446, Received, 25th May, 2001

ALUMINA/PHOSPHORUS PENTOXIDE (APP) AS AN EFFICIENT REAGENT FOR THE SYNTHESIS OF 1, 5-BENZODIAZEPINES UNDER MICROWAVE IRRADIATION

Babak Kaboudin* and Kian Navaee

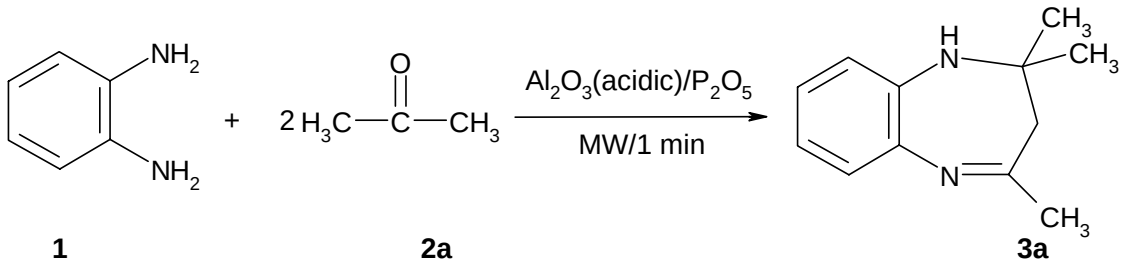
Institute for Advanced Studies in Basic Sciences (IASBS),
Gava Zang, Zanjan 45195-159, Iran
Fax: (+98) 241 4249023
E-mail: kaboudin@iasbs.ac.ir

Abstract- Alumina-supported phosphorus pentoxide was found to be an efficient reagent for the synthesis of 1,5-benzodiazepine derivatives from phenylenediamine and ketones in the solvent-free condition under microwave irradiation. This method is an easy, rapid, and high-yielding reaction for the synthesis of 1, 5-bezodiazepines.

Heterocyclic compounds hold a special place among pharmaceutically important natural and synthetic materials. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and active pharmacophores has largely been contributed to their unique value as traditional key elements of numerous drugs.[1] The benzodiazepine nucleus is a well-studied traditional pharmacophoric scaffold that has emerged as a core structural unit of various sedative hypnotic, muscle relaxant, anxiolytic, antistaminic, and anticonvulsant agents.[2] Although the first benzodiazepine was introduced as a drug nearly 30 years ago the research in this area is still very active and is directed toward the synthesis of compounds of enhanced pharmacological activity. Several methods, not generally applicable, have been reported in the literature for synthesis of 1,5-benzodiazepines.[3-7] Unfortunately, many of these processes suffer limitations, such as drastic reaction conditions, low yields, tedious work-up procedures and co-occurrence of several side reactions. Recently we found that the mixture of magnesium oxide with phosphorus oxychloride is a new reagent for the synthesis of 1,5-benzodiazepines.[8] However, treatment

of the posphorus oxychloride has led to some problems in work-up, and the drastic reaction conditions may promote some severe side-reactions. Surface-mediated solid phase reactions are of growing interest[9] because of their advantages of ease of set up, mild conditions, rapid reactions, selectivity, increased yields of the products and low cost compared with their homogeneous counterpart. As a part of our efforts to explore the utility of surface-mediated reactions,[8, 10-13] in this report, a new method for the synthesis of 1, 5-bezodiazepines on a solid surface under microwave irradiation is described.

It is found that alumina (acidic)-supported phosphorus pentoxide 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 85% yields under microwave irradiation (Scheme 1, Table 1).



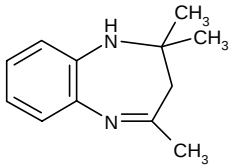
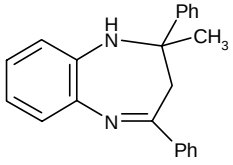
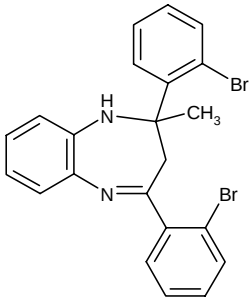
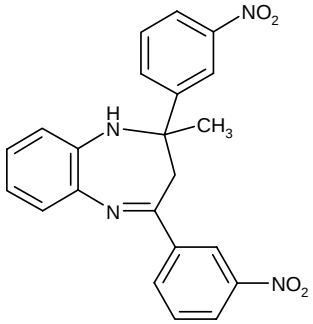
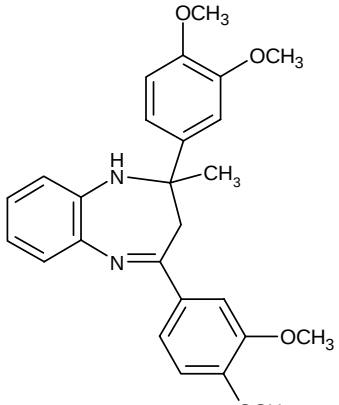
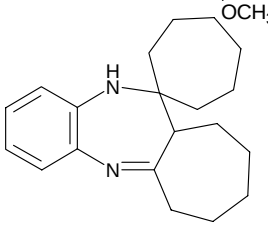
1 **2a** **3a**

Scheme 1

The same process was successfully extended to other 1,5-benzodiazepine derivatives as summarized in Table 1. As shown Table 1, acetophenone in the presence of mixture of acidic alumina/ phosphorus pentoxide with *o*-phenylenediamine (**1**) afforded 2,3-dihydro-2-methyl-2,4-diphenyl-1*H*-1,5-bezodiazepine (**3b**) in 79 % yield. The other derivatives of acetophenones (**2c-2e**) also react with *o*-pheneylenediamine (**1**) in the presence of a mixture of acidic alumina/ phosphorus pentoxide under microwave irradiation, to give the desired compounds (**3c-3e)** in moderate yields. The reaction also proceeds with good yield with cycloheptanone (**2f**) as a cyclic ketone to afford the desired product in moderate yield (**3f**). The condensation of unsymmetrical dialkyl ketones with *o*-phenylenediamine in the presence of this reagent, gave unknown products.

This solvent-free method has operationally simple procedure. A five mmol of the *o*-phenylenediamine (finely ground) was added to a mixture of acidic alumina (Al_2O_3, acidic, 2-3 g, grinded in a mortar and pestle) and phosphorus pentoxide (0.5 g , 35 mmol). The ketone (10 mmol) was added to this mixture and the mixture was irradiated by microwave for 1 min using 720 W (A kitchen-type microwave was used in all experiments). The reaction mixture was grinded in a mortar and pestle until a fine, homogeneous, powder is obtained. Homogeneous mixture was washed with *n*-hexane (200 mL), and the filtrate was dried ($CaCl_2$), and the evaporated to give the crude products. Pure product[13] was obtained by recrystallization from *n*-hexane in 73-85 % yields.

Table 1. The condensation of *o*-phenylenediamine with ketones in the presence of acidic alumina-phosphorus pentoxide under microwave irradiation.

Entry	Ketone **2**	Yield[a] (%)	Product **3**
a	Acetone	85	
b	Acetophenone	79	
c	2-Bromoacetophenone	73	
d	3-Nitroacetophenone	75	
e	3, 4-Dimethoxyacetophenone	79	
f	Cycloheptanone	76	

a) Isolated Yields

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

ACKNOWLEDGMENT

The Institute for Advanced Studies in Basic Sciences (IASBS) is thanked for supporting this work.

REFERENCES AND NOTES

1. H. J. Roth and A. Kleemann, *Pharmaceutical Chemistr*y, Vol. 1, Drug Synthesis, New York, Wiley, 1988.
2. R. N. Castle and S. D. Phillips, *Comprehensive Heterocyclic Chemistry*, Vol 1, ed. by A. R. Katritzky, C. W. Rees, A. J. Boulton and A. McKillop, Pergamon Press, 1984.
3. P. Stahlofen and W. Ried, *Chem. Ber*., 1957, **90**, 815.
4. W. Ried, and E. Torinus, *Chem. Ber*., 1959, **92**, 2902.
5. J. A. L. Herbert and H. Suschitzky, *J. Chem. Soc*., *Perkin Tran*s. *1*, 1974, 2657.
6. H. R. Morales, A. Bulbarela, and R. Contreras, *Heterocycles*, 1986, **24**, 135.
7. D. I. Jung, T. W. Choi, Y. Y. Kim, I. S. Kim, Y. M. Park, Y. G. Lee, and D. H. Jung, *Synth. Commun*., 1999, **29**, 1941.
8. M. S. Balakrishna and B. Kaboudin, *Tetrahedron Lett*., 2001, **42**, 1127.
9. a) A. Fadel, R. Yefash, and J. Saluan, *Synthesis*, 1987, 37; b) G. Rosini, R. Galarini, E. Marotta, and R. Righi, *J. Org. Chem*., 1990, **55**, 781; c) M. Kodomari, T. Sakamoto, and S. Yoshitomi, *J. Chem. Soc., Chem. Commun.*, 1990, 701; d) P. J. Kropp, K. A. Daus, S. D. Crawford, M. W. Tubergren, K. D. Kepler, S. L. Craig, and V. P. Wilson, *J. Am. Chem. Soc*., 1990, **112**, 7433; e) G. Hondrogiannis, R. M. Pagni, G. W. Kabalka, P. Anisoki, and R. Kurt, *Tetrahedron Lett*., 1990, **31**, 5433; d) H. K. Pantney, *Tetrahadron Lett*., 1991, **32**, 2259; f) F. Pauter and M. Daudon, *Tetrahedron Lett*., 1991, **32**, 1457.
10. A. R. Sardarian and B. Kaboudin, *Synth. Commun.*, 1997, **27**, 543.
11. A. R. Sardarian and B. Kaboudin, *Tetrahedron Lett*., 1997, **38**, 2543.
12. B. Kaboudin, *J. Chem. Res. (S)*, 1999, 402.
13. B. Kaboudin, *Tetrahedron Lett*., 2000, **41**, 3169.
14. All products gave satisfactory spectral data in accord with the assigned structures. [E.g. for **3a** ^{1}H NMR ($CDCl_3$, TMS) δ: 1.35(s, 6H, 2-CH_3), 2.25(s, 2H, -CH_2), 2.33 (s, 3H, -CH_3), 3.45(br, 1H, -NH), 6.60-7.25(m, 4H); IR (KBr): ν 3289 (NH), 1637 (C=N), 1597 cm^{-1} (Ar)].