Synthesis of 1,3,4-oxadiazoles derivatives from α-amino acids and acyl hydrazides using microwave irradiation

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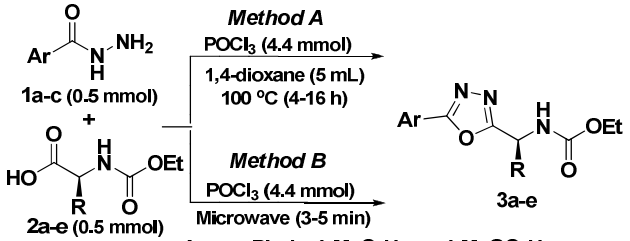
INTRODUCTION

The 1,3,4-oxadiazoles constitute an important family of heterocyclic compounds as they have attracted significant interest in medicinal chemistry, pesticide chemistry and polymer science. These compounds derivatives have been found to exhibit diverse biological activities such as analgesic,[1] anti-inflammatory,[2] antimicrobial,[3] anti-HIV[4] and other biological properties. Consequently, the synthesis of compounds containing this heterocycle core has attracted considerable attention and a wide variety of methods have been used for its assembly. By far the most common synthetically protocol involves the dehydrative cyclization of diacylhydrazides, usually with strongly acidic reagents such as $SOCl_2$,[5] P_2O_5,[6] $POCl_3$ [7] and H_2SO_4.[8]

RESULTS AND DISCUSSION

We now describe herein an improved procedure for the preparation of 1,3,4-oxadiazoles **3a-e** (Scheme 1), using microwave irradiation. The oxadiazoles were obtained in good yields (54-75%), from acyl hydrazides **1a-c** and N-protected α-amino acids **2a-e** in presence of $POCl_3$.

Scheme 1



Ar = a: Ph; b: 4-MeC$_6$H$_4$; c: 4-MeOC$_6$H$_4$
R = a: Me; b: Bn; c: *i*-Bu; d: CH$_2$SBn; e: CH$_2$CH$_2$SMe

The reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 100 ± 5 °C, power 200-250 W. The products were isolated and characterized by spectroscopic methods (^{1}H NMR and ^{13}C NMR). The respective compounds **3** were also obtained using conventional heating in an oil bath 100°C temperature, but requires an extended period of time, 4–16 h. Table 1 shows comparison of eleven conventionally prepared oxadiazoles **3a-e** with the ones obtained by microwave procedure.

Table 1. Comparison of conventional heating and microwave irradiation in the synthesis of 1,3,4-oxadiazoles **3**.

Entry	Conventional method		Microwave method	
Compounds	Time (h)	Yield (%)	Time (min)	Yield (%)
3aa	7	51	4	62
3ab	4	57	3	65
3ac	7	41	4	70
3ad	7	40	4	54
3ae	4	58	3	72
3ba	16	45	4	63
3bb	16	40	4	75
3bc	16	41	4	60
3ca	4	40	4	56
3cc	16	40	4	54
3ce	16	42	5	60

CONCLUSION

In conclusion we have developed a one-pot synthesis of 2,5-disubstituted-1,3,4-oxadiazoles under microwave irradiation using phosphorous oxychloride as an efficient promoter. Good yields, short reaction times, simple operation and easy work-up procedure are some advantages of this protocol compared to their synthesis under conventional thermal heating conditions.

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REFERENCES

[1] Akhter, M.; Husain,A.; Azad,B.; Ajmal,M. Eur. *J. Med. Chem.*, 2009,*44*, 2.
[2] Jayashankar, B.; Lokanath Rai, K.M.; Baskaran, N.; Sathish, H.S. *Eur. J. Med. Chem.*, **2009**, *44*, 3898.
[3] Gupta, V.; Kashaw, S.K.; Jatav, V.; Mishra, P. *Med. Chem. Res.*, **2008**, *17*, 205.
[4] El-Emam, A.A.; Al-Deeb, O.A.; Al-Omar, M.; Lehmann, J. *Bioorg. Med. Chem.*, 2004, *12*, 5107.
[5] Brog, S.; Vollinga, R. C.; Labarre, M.; Payza, K.; Luthman L.; Terenius, K. *J. Med. Chem.*, **1999,** *42*, 4331.
[6] Shafiee, A.; Naimi, E.; Mansobi, P.; Foroumadi A.; Shekari, M. *J. Heterocycl. Chem.*, **1995.** *32*, 1235.
[7] He, D.-H.; Zhu, Y.-C.; Yang, Z.-R.; Hu A.-X.; Cao, G. *Turk. J. Chem.*, **2009**, *33*, 1.
[8] Sharma,S.; Srivastava,V.K; Kumar, A. *Eur. J. Med. Chem.*, **2002,** *37*, 689.