Asian Journal of Chemistry Vol. 19, No. 6 (2007), 4277-4280

Microwave Synthesis of N-Methyl-3-N′-(1-trizolyl)-4-substituted Pyrroles

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A microwave-enhanced synthesis of N-methyl-3-N'-(1-trizolyl)-4-substituted pyrroles, under solvent free conditions is described. The yields and especially the reaction time are noticeably improved in comparison with conventional heating.

Key Words: Microwave irradiation, N-Methyl-3-N′-(1-trizolyl)-4-substituted pyrroles.

INTRODUCTION

1-Methyl pyrrol-3-yl-1,2,4-triazole derivatives are important pharmaceutical compounds[1-3], since its structural frame work have been found to display a wide range of potent biological activities such as cardiotonic[4,5] and antidiuretic[6]. On the other hand, 1-methyl pyrrol-3-yl-1,2,4-triazole framework has been found to be useful building block to construct new fused heterocyclic compounds[7,8].

The literature offers several methods for the synthesis of these compounds in a conventional type, however, these reactions have some drawbacks, since they require either a solvent or an additive compound and/or harsh conditions (high temperatures, longer reaction times) which cause the decomposition of the reagents or/and of the final products. Microwave radiation is becoming an increasingly useful activation technique in synthetic organic chemistry[9-12].

EXPERIMENTAL

All the reactions take place with in the commercially available Panasonic IEC-705 (monomode system 750 W) apparatus. Accelerated microwave synthesis of substituted N-methyl-3-N'-(1-trizolyl)-4-substituted pyrroles by reacting in solvent free conditions and in the absence of any

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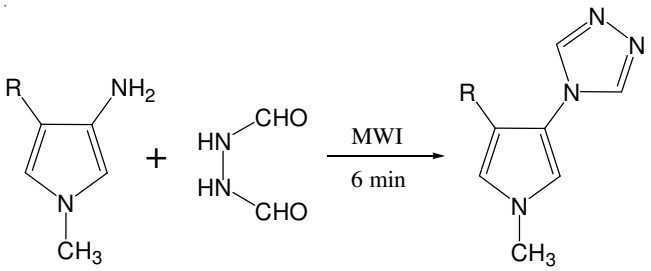
additive compound, 3-amino-1-methyl-4-substituted pyrroles with diformyl hydrazide. In a first operating process the reaction was carried out with 3-amino-1-methyl pyrrole (**1a** 0.01 mol) and diformyl hydrazide (**2** 0.012 mol) irradiated under microwave conditions for 6 min. After cooling, the crude product is poured in dichloromethane and the unreacted diformyl hydrazide is eliminated by filtration, then the organic layer is dried over sodium sulphate and concentrated under reduced pressure. The crude product is precipitated with *n*-hexane:diethylether (1:1), finally, the solid is collected by filtration and washed with a mixture of *n*-hexane and diethyl ether to furnish the pure compound, based on the analytical and spectral data (Table-1) it was further characterized as N-methyl-3-N'-(1'-triazolyl) pyrrole (**3a**) (**Scheme-I**).



1 a-e **2** **3 a-e**

3a: R = H; **3b:** R = CH_3; **3c:** R = OCH_3; **3d:** R = C_6H_5; **3e:** R = NO_2

Scheme-I

RESULTS AND DISCUSSION

Conventional heating and microwave irradiation methods are compared. Different experiments with variable reaction time were performed. The most satisfactory result was obtained after 6 min of irradiation. It is noteworthy that under classical heating a longer time (210 min) was required to achieve comparable yield. In an attempt to optimize the reaction temperature we have also carried out the reaction at lower temperature (150º, 180ºC). Nevertheless, in all cases, the yields decreased dramatically.

These conditions (6 min under MWI) were then applied to various 3-amino-1-methyl 4-substituted pyrroles **1b-e**. As regards to the results depicted in Table-2, all compounds were isolated advantageously within a few minutes and in better yields under microwave irradiation than under conventional heating.

TABLE-1
SPECTRAL AND ANALYTICAL DATA OF N-METHYL-3-N'-(1-TRIZOLYL)-4-SUBSTITUTED PYRROLES

Compd. No	Mass (m/e)	^{1}H NMR (δ ppm, DMSO-d_6)	^{13}C NMR (δ ppm)	m.p. (ºC)	Elemental analyses Calcd. (Found)		
					C	H	N
3a	148	3.51 (*s* 3H, CH_3), 5.77 (*d* 1H, CH) 5.86 (*d* 1H, CH) 7.54 *s* 1H, 9.36 (*s* 2H triazolyl).	42.56, 96.54, 112.55, 114.67, 134.48, 138.66	141	56.74 (56.89)	5.44 (5.56)	37.81 (37.98)
3b	162	2.42 (*s* 1H, CH), 3.48 (*s* 3H, CH_3), 5.87 (*d* 1H, CH), 7.86 (*s* 1H, CH), 9.23 (s 2H, triazolyl).	9.81, 44.32, 114.45, 118.36, 127.91, 130.38, 138.98	163	59.24 (59.41)	6.21 (6.33)	34.54 (34.29)
3c	178	3.55 (*s* 3H, CH_3), 3.94 (*s* 3H, CH_3), 4.91 (*s* 1H, CH), 6.01 *s* 1H, CH), 8.12 (*s* 2H, tiazolyl).	43.56, 57.86, 118.51, 118.64, 126.58, 139.86, 141.33	155	53.92 (53.76)	5.66 (5.59)	31.44 (31.56)
3d	224	3.62 (*s* 3H, CH_3), 6.51 (*s* 1H, CH), 7.11-7.41 (*m* 5H, Ar-H), 8.84 (s 1H, CH) 9.08 (s 2H, triazolyl).	44.61, 115.64, 118.91, 123.62, 128.33, 128.69, 129.81, 135.89, 139.01	182	69.62 (69.44)	5.39 (5.51)	24.98 (24.81)
3e	193	3.59 (*s* 3H CH_3), 6.91 (s 1H, CH) 7.68 (s 1H, CH) 9.92 (s 2H, triazolyl)	41.93, 113.54, 119.67, 124.65, 126.36, 152.09	167	43.53 (43.68)	3.65 (3.77)	36.26 (36.19)

TABLE-2
SYNTHESIS OF N-METHYL-3-N'-(1-TRIZOLYL)-4-SUBSTITUTED PYRROLES (**3a-e**)

Product	Conventional heating yields (%)[a]	Microwave irradiation (b) yields (%)[b]
3a	41	86
3b	48	77
3c	53	95
3d	45	89
3e	56	92

[a]Reaction performed at 180ºC for 210 min in an oil bath.
[b]Reaction performed under MWI for 6 min.

ACKNOWLEDGEMENTS

The authors are highly thankful to Dr. Ch. V. Purushottam Reddy, Secretary & Correspondent, Chaitanya Degree and P.G. College, Hanamkonda, Warangal for providing the facilities and encouragement.

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(*Received*: 7 April 2006; *Accepted*: 2 April 2007) AJC-5550