Solvent-Free Microwave-Assisted Synthesis of Substituted Pyridines Using NH_4OAc as Nitrogen Source

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Abstract: New 1,5-dicarbonyl compounds were prepared, as versatile precursors to pyridine derivatives, by a tandem *Claisen-Schmidt* condensation/ *Michael* addition reaction, that is condensation between 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde and acetophenones, and the formed adduct then reacts with a second molecule of acetophenone. The preparation of substituted pyridines was achieved using NH_4OAc as nitrogen source under solvent-free microwave irradiation.

Keywords: Chalcone, 1,5-dicarbonyl compounds, cyclocondensation, microwave, NH_4OAc, pyridines, solvent-free procedure.

INTRODUCTION

Pyridine derivatives have attracted considerable attention of organic and medicinal chemists because of their broad spectrum of biological activity; such antitumor [1], antiviral [2], antibacterial, antifungal [3], improvement in MCH1R affinity [4], or potent CDK1 inhibitors [5]. These examples clearly indicate the remarkable potential of pyridine derivatives as a source of valuable drug candidates.

Numerous methods have been reported for the synthesis of pyridine derivatives. The classical method involves dicarbonyl compounds (*The Hantzsch Synthesis*) to give 1,4-dihydropyridine derivatives [6]. Recently, several methods have been reported comprising: i) application of microwave irradiation along with *one-pot* reaction using efficient Lewis acid catalysts such as $InCl_3$ [7]; ii) multicomponent reactions [8], iii) hetero-Diels-Alder reaction from Baylis–Hillman adducts for the preparation of pyridylphosphonates [9] and substituted pyridines [10]. However, those methodologies present a strong limitation, that is the use of high temperatures, expensive and environmentally harmful metal catalysts, and longer reaction times. Therefore, the search for better conditions reaction for the synthesis of substituted pyridine derivatives, have such new catalyst, where the absent solvents or the use of less hazardous solvents is still of prime importance.

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On the other hand, chalcones are well-known precursors to flavones and key intermediates for the combinatorial assembly of different heterocyclic structures [11]. Cyclization of chalcones to afford pyrroles, pyrazoles, pyridines and diazepines has been a developing field within the realm of heterocyclic chemistry for the past several years, because of their ready accessibility and diverse biological activity [12].

Due to our interest in the α,β-unsaturated ketones (chalcones) and their application in the preparation of heterocyclic compounds [13], we have now reported them as precursors of polysubstituted pyridine derivatives bearing a pyrazoles at C-4.

RESULTS AND DISCUSSION

For the preparation of the chalcones we have carried out a Claisen–Schmidt condensation reaction between 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** and acetophenones **2**, so in ethanol with basic catalyst at room temperature during 10-30 minutes, we obtained the respective (*E*)-3-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-arylprop-2-en-1-one **3** [14]. Next, the pyrazole chalcone analogs of **3** are subjected to a base-catalyzed Michael type reaction addition with another equivalent of the acetophenone to produce 1,5-dicarbonyl compounds **4** (Scheme **1**).

The reaction proceeded quite well in moderate yields, both with electron donating and with electron-withdrawing groups at acetophenones.

This process is favored under reactional conditions for two and a half additional hours (*Method A*).

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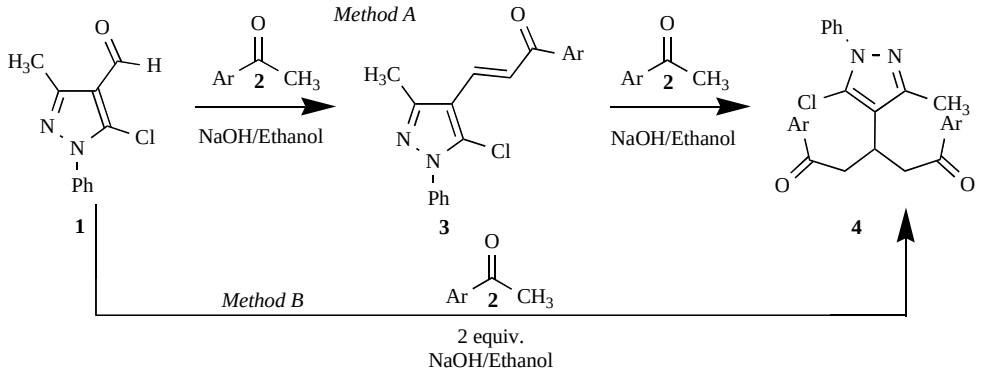


Scheme 1.

Table 1. Heterocyclic Chalcones and 1,5-Dicarbonyl Derivatives by Conventional Method

Entry	Ar	Compound 3		Compound 4*		Compound 6		
		M.p °C	Yield (%)	M.p °C	Yield (%)	M.p °C	Yield (%)	MWI (min.)
a	C_6H_5	116-118	65	120-123	65	163-165	85	2
b	4-$H_3CC_6H_4$	113-115	63	132-136	70	182-185	75	2
c	4-BrC_6H_4	155-157	60	140-145	60	>240 dec.	60	2.5
d	4-ClC_6H_4	153-155	61	>190 dec	50	214-217	85	3
e	4-FC_6H_4	125-127	50	192-196	45	>300	75	2
f	4-$H_3COC_6H_4$	98-100	70	105-107	40	183-185	90	2
g	3,4,5-*tri*-$H_3COC_6H_2$	140-142	70	156-158	65	173-175	90	2
h	Thiophenyl	> 300	60	>180 dec.	45	>300	80	3

* Yields obtained to compounds **4** by Method B.

The direct synthesis of 1,5-dicarbonyl compounds **4** from **1** certainly proceeds through the formation of the corresponding heterocyclic chalcone **3**, which was isolated detected during reaction monitoring. Yields obtained for 1,5-dicarbonyl derivatives were through reaction using two equivalents of acetophenone under similar reaction conditions (*Method B*). These results are given in Table **1**.

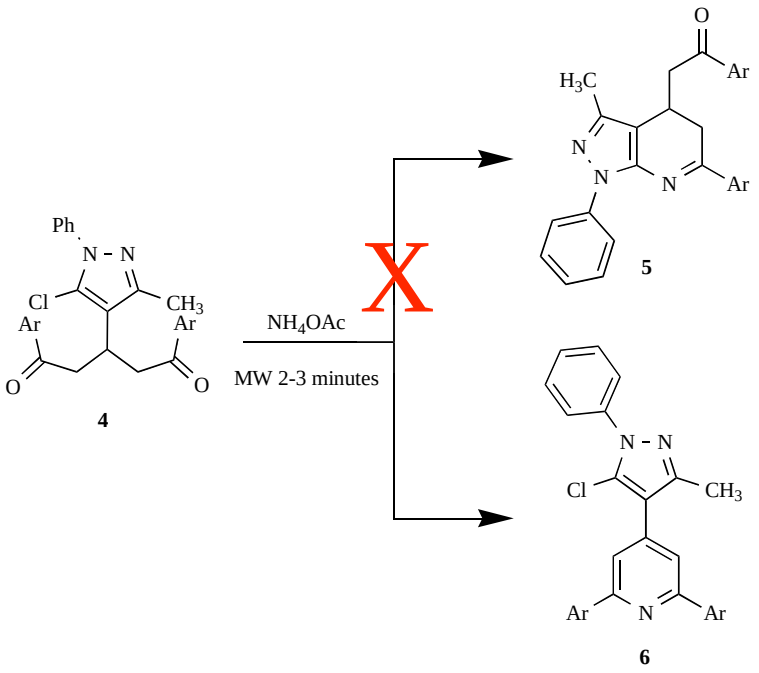
This approach is particularly attractive because of the symmetry presented *via method B*, and the possibility of asymmetric derivatives *via method A*, which pointed towards simple routes to obtained 1,5-dicarbonyl asymmetric derivatives and their corresponding pyridine derivatives. The structures of compounds **4** were elucidated from their analytical and spectroscopic data (IR, ^{1}H and ^{13}C NMR, and MS spectra). Single crystal X-ray diffraction analysis of compound **4a** and **4h** was used to corroborate the postulated structures [15].

Then, we explored the reactivity of the 3-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-diarylpentane-1,5-dione derivatives **4** towards ammonium acetate. Thus, 1,5-dicarbonyl derivatives **4** (1 mmol) with an excess of ammonium acetate (1.3 mmol) were exposed to MWI, using a focused microwave reactor (CEM Discover TM) at 200 °C with a maximum power of 300W during 2-3 minutes, without solvent to get the efficient synthesis of substituted pyridines derivatives **6**, that were isolated in good yields by simple crystallization of the reaction mixture from ethanol (Scheme **2**) [16].

1,5-Dicarbonyl compounds **4** could undergo intramolecular cyclization with the chlorine atom through a SNAr reaction, however, spectral analysis turned up no evidence of the formation of derivative **5** under the reaction conditions (see Scheme **2**). Analytical and spectroscopic data of compounds **6** are all consistent with the proposed structures. All ^{1}H NMR spectra showed a singlet for H_β of pyridine ring at around 7.9 ppm. As depicted from Table **1**, the yields of all products are ranging from good to excellent, and no relationship was found between them and the nature of the substituents at the aryl groups.

CONCLUSION

In this work, we have reported the preparation of 1,5-dicarbonyl compounds, and simple and efficient applications of addition–cyclization reactions for the synthesis assisted by microwave irradiation of substituted pyridines derivatives,. Compared to the reported methods, our method is convenient, safe, and can be performed under ambient conditions with easy isolation procedures. A remarkable achievement is the possibility of incorporating diversity and structural complexity in reaction to yield compounds **4** and so to develop a library of pyridine derivatives. The advantages of this method over existing methods are the short reaction times, solvent-free conditions, low cost, and that the last aromatization step is accomplished under mild conditions without additional dehydration or oxidant



Scheme 2.

reagents. Methodology is addressed towards green and high-throughput chemistry.

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EXPERIMENTAL SECTION

Melting points were determined in a Buchi Melting Point Apparatus and are reported uncorrected. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance 400 spectrometer operating at 400 and 100 MHz, respectively, and using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The mass-spectra were scanned on a Hewlett Packard HP Engine-5989 spectrometer (equipped with a direct inlet probe) which was operating at 70 eV. The elemental analyses have been obtained using a LECO CHNS-900 and Thermo Finnigan FlashEA1112 CHNS-O (STIUJA) elemental analyzers.

General Procedure for the Synthesis of (E)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-arylprop-2-en-1-one 3a-h

A solution of 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** (1.0 mmol) and substituted acetophenones **2** (1.0 mmol) in ethanol (10 mL) with a catalytic amount of NaOH (1 pellet) was stirred during 20–30 minutes at room temperature. The resulting precipitate was filtered, washed with ethanol, and recrystallized from ethanol.

General Procedure for the Synthesis of 3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1,5-diarylpentane-1,5-dione 4a-h

Method B: A solution of (*E*)-3-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-arylprop-2-en-1-one **3** (1.0 mmol) and respectively acetophenone **2** (2.0 mmol) in ethanol (10 mL) with an amount of NaOH (1 pellet) was stirred during two and a half hours at room temperature. The resulting precipitate was filtered, washed with ethanol, and recrystallized from ethanol.

General Procedure for the Synthesis of 4-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2,6-diarylpyridine 6a-h

A mixture of 3-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-diarylpentane-1,5-dione **4** (1 mmol), and an excess of ammonium acetate (1.3 mmol) were subjected to microwave irradiation (maximum power 300W during 2-3 minutes under solvent-free conditions at a controlled temperature of 473 K) using a focused microwave reactor (CEM Discover). The solid products were isolated by simple crystallization of the reaction mixture from ethanol.

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[14] (a) Trilleras, J.; Quiroga, J.; Cobo, J.; Low, J. N.; Glidewell, C. *Acta Cryst*., **2005**, *E61*, 1055; (b) Selective spectral data for **(*E*)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(4-methoxyphenyl)prop-2-en-1-one** (**3f):** White solid, 70%. M.p. 98-100 ºC; IR (KBr cm^{-1}): 3058, 1662. NMR ^{1}H (400 MHz, DMSO-d_6) δ (ppm): 2.47 (3H, s, CH_3), 3.84 (3H, s, OCH_3), 7.08 (2H, d, Hm, aryl, J = 9.0 Hz), 7.56-759 (7H, m, CH phenyl, Hα, Hβ), 8.05 (2H, d, Ho, aryl, J = 9.0 Hz). NMR ^{13}C δ (ppm): 14.0 (CH_3), 55.5 (OCH_3), 113.8 (C4), 114.1 (Cm, aryl), 120.6 (Cα), 125.0 (Cm), 128.9 (Cp), 129.3 (Co), 130.7 (Co, aryl), 131.5 (Cβ), 133.0 (Ci, aryl), 137.2 (Ci), 141.9 (C5), 149.5 (C3), 163.2 (Cp, aryl), 187.0 (C=O). MS IE *m/z*: 317 (M^+ - Cl, 100). Elemental Analysis for $C_{20}H_{17}ClN_2O_2$ C: 68.09, H: 4.86, N: 7.94. Found C: 67.91, H: 4.99, N: 8.23.

[15] (a) Selective spectral data for **3-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-bis(4-methoxyphenyl)pentane-1,5-dione (4f)**: White solid, 40%. M.p. 105-107 °C; IR (KBr cm^{-1}): 3065, 1677. NMR ^{1}H (400 MHz, DMSO-d_6) δ (ppm): 2.22 (3H, s, CH_3), 3.42-3.46 (4H, m, CH_2), 3.82 (6H, s, OCH_3), 3.91-3.95 (1H, m, CH), 7.01 (4H, d, Ho, aryl, *J* = 9.0 Hz), 7.37 (1H, t, Hp, *J* = 7.0 Hz), 7.39 (2H, d, Ho, *J* = 7.0 Hz), 7.45 (2H, t, Hm, *J* = 7.3 Hz), 7.93 (4H, d, Hm, aryl, *J* = 9.0 Hz). NMR ^{13}C δ (ppm): 12.9 (CH_3), 32.1 (CH), 41.7 (CH_2), 55.5 (OCH_3), 113.8 (Co, aryl), 114.9 (Cm, aryl), 118.5 (C4, hetaryl), 123.6 (C5 hetaryl), 124.4 (Co), 127.8 (Cp), 129.0 (Cm), 130.2 (Ci, aryl), 137.7 (Ci), 148.1 (C3 hetaryl), 163.1 (Cp, aryl), 196.8 (C=O). MS: (70 eV) *m/z* = 503/501 (3/7 M^{+2}/M^+), 355/353 (13.45/41.15), 317 (18.1), 135 (100). Elemental Analysis for $C_{29}H_{27}Cl\ N_2O_4$ C: 69.25, H: 5.41, N: 5.57. Found C: 68.90, H: 5.47, N: 5.50; (b) Trilleras, J.; Quiroga, J.; De La Torre, J. M.; Cobo, J.; Low, J.; Glidewell, C. *Acta Crystallogr. Sect. C.*, **2006**, *62*, 518; (c) Trilleras, J.; Quiroga, J.; Cobo, J.; Low, J.; Glidewell, C. *Acta Crystallogr. Sect. C.*, **2005**, *61*, 1892.

[16] Selective spectral data for **4-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2,6-bis(4-methoxyphenyl)pyridine (6f)**: White solid, 90%. M.p. 183-185 ºC; IR (KBr cm^{-1}): 3050, 1596. NMR ^{1}H (400 MHz, DMSO-d_6, 100 °C) δ (ppm): 2.43 (3H, s, CH_3), 3.83 (6H, s, OCH_3), 7.09 (4H, d, Ho, aryl, *J* = 8.8 Hz), 7.52 (1H, t, Hp, *J* = 7.0 Hz), 7.58 – 7.64 (4H, m, phenyl), 7.85 (2H, s, CH, pyridine), 8.19 (4H, d, Hm, aryl, *J* = 8.8 Hz). NMR ^{13}C δ (ppm): 13.2 (CH_3), 55.2 (OCH_3), 114.1 (Co, aryl), 116.9 (C4, hetaryl), 125.1 (C3 pyridine), 128.1 (Cp), 128.6 (Cm), 129.3 (Ci, aryl), 131.1 (Cm, aryl), 137.6; 138.0; 140.6; 147.8 (C3 hetaryl), 156.0 (C4, pyridine), 160.3 (C2, pyridine). MS: (70 eV) *m/z* = 481/482 (34/100, M^{+2}/M^+). Elemental Analysis for $C_{29}H_{24}ClN_3O_2$ C: 72.27, H: 5.02, N: 8.72. Found C: 72.35, H: 4.98, N: 8.68.