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Modified Biginelli reaction: Synthesis of fused Dihydropyrimidones

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Abstract

A base catalysed, three-component one pot synthesis of quinoline fused dihydropyrimidines by the Biginelli reaction of 4-hydroxyquinolin-2(1H)-ones with aromatic aldehydes and thiourea is reported. The reaction has been carried out in solvent-free condition at microwave irradiation.

Keywords: Thiourea, quinoline, dihydropyrimidine, microwave, synthesis.

Introduction

Microwave irradiation is a new tool for conducting chemical reactions. Organic reactions are induced by microwaves is largely proved elsewhere, and in many cases, microwave techniques were became more effective and advantages than conventional method[1-5]. Microwave (MW) activation as a non-conventional energy source has become a very popular and useful technology in organic chemistry[6-10]. Recent years, most of the publications describe important accelerations for a wide range of organic reactions especially when carried out under solvent-free conditions. The microwave irradiation coupled with solvent-free reaction conditions which lead to large reductions in reaction times, enhancement in conversions and green approach[11].

Dihydropyrimidines have recently emerged as important target molecules due to their biologicalproperties[12-15] such as antiviral, antimitotic, anticarcinogenic, calcium channel blockers, antihypertensive agents, alpha-antagonists. Biginelli first reported a conventional synthesis of dihydropyrimidines (DHPM) by multi-component reaction of ethyl acetoacetate, aromataic aldehyde and urea under strongly acidic conditions[16]. These reactions are commonly performed in ethanol or tetrahydrofuran under strong protic acid catalyst[17-20].

In recent years, Biginelli reaction have been modified by varying acyclic β-ketone, aldehyes of initial multi-component scheme and changing catalyst, reaction conditions. Some Researcher reported[21,22] synthesis of dihydropyrimidines via modified Biginelli reaction by using 1,3-cyclic ketones like dimedone, indane-1,3-dione instead of acyclic ketone. In this aspect, we studied the modified Biginelli reaction by using heterocyclic 1,3-di ketone such as 4-hydroxyquinolin-2(1*H*)-one (**1**) under basic condition.

Material and Methods

Experimental: Melting points (mp) were determined using Boetieus micro heating table and are uncorrected. IR (KBr, cm-1) spectra were obtained on Shimadzu–8201 spectrophotometer. 1H-NMR spectra were recorded on Bruker AMX-400 (400 MHz) spectrometer using TMS as an internal reference (Chemical shifts in d, ppm). Elemental analyses were performed on Perkin Elmer CHN-analyzer. Mass spectrawere recorded on Shimadzu GCMS-QP5050A (70 ev) mass spectrometer. Reactions were monitored using thin layer chromatography (TLC) carried out on Merck silica gel 60 F254 precoated glass plates. The visualization was achieved under staining with iodine. All reactions were performed in a microwave reactor modified for synthesis.

Preparation of 4-phenyl-1,4-dihydropyrimido[5,4-c]quinolin-2-thio-5-(3H,6H)-ones (**2a-g**): **General procedure***:* 4-Hydroxyquinolin-2(1*H*)-one, aryl aldehydes, thiourea and few drops of triethylamine were mixed well and irradiated at 180 W under microwave condition for the specified time. The reaction was monitored 30 seconds interval by the TLC. After the irradiation, the reaction mixture was poured into ice water. The yellow solid obtained was filtered, dried and purified by column chromatography using the solvents petroleum ether and ethyl acetate (6:2).

Results and Discussion

In recent years there has been an increasing interest in synthesis of dihyrdopyrimidine via modified Biginelli reaction. We herein report a one-pot synthesis of DHPMs using triethylamine as a catalyst under solvent-free microwave irradiations through modified Biginelli reaction. As a continuation of our interest on the Biginelli reaction[23] and the intention of extending the scope of the multi-component Biginelli reaction to the heterocyclic diketones instead of acyclic ketones.

In our initial studies to bring about modified Biginelli reaction, we attempted reaction of 4-hydroxyquinolin-2(1*H*)ones, various aldehydes thiourea and triethylamine in a single mode microwave power (CEM, Discover Benchmate, 120ºC) and the product yield was thoroughly investigated scheme 1. The whole reaction was completed in less than ten minutes and led to high, reproducible yields of pure product [81-92%]. The same procedure was successfully extended to range of various pyrimidoquinoline derivatives (table 1). All the synthesized compounds are characterized by spectral (IR, ^{1}H NMR, and Mass spectrum) and elemental analysis data[24,25]. The IR spectrum of compound 2a showed prominent peaks at 1211 cm^{-1}(>C=S), 1642 cm^{-1} (>C=O), 3200-2800 (NH). The proton NMR spectrum assessing the success of the cyclisation was the appearance of deshielded pyrimidone C_4 signal at δ 6.08-6.35 and two singlets at δ 10.73 and 10.10 for NH group and a mulplet in region δ 6.89-8.11 for aromatic protons. The melting point, time required for preparation and yield percentage of all the products have been summarised in table-1.

We proposed the mechanism of modified Biginelli reaction (Scheme 2), initial step formation of Schiff base (3) by condensation of aldehyde and thiourea. Second step, Schiff base (3) undergoes addition reaction with 4-hydroxy quinolin-2(1*H*)-one (1) followed by dehydration to give pyrimido[5,4-*c*]quinolin-2-thione (2).

Spectral data of compound 2a: IR (KBr, ν_{max}): 3200-2800 (NH), 1642 cm^{-1} (>C=O), 1211 cm^{-1} (>C=S); ^{1}H-NMR (DMSO-d_6, 400MHz) [δ/ppm]: δ 10.73 (s, 2H, 2xNH), 10.10 (s, 1H, NH), 6.89-8.11 (m, 9H, Ar-H), 6.31 (s, 1H, C_4-H); ^{13}C-NMR (DMSO-d_6, 100 MHz) [δ/ppm]: δ 195.9, 170.5, 153.3, 148.5, 144.5, 141.7, 134.7, 133.4, 133.3, 132.9, 131.9, 130.9, 129.3, 128.2, 127.7, 126.5 and 101.9; EI-MS (70 eV, m/e, $M^{+\cdot}$): 307; Anal. Calcd. For ($C_{17}H_{13}N_3OS$): C, 66.45; H, 4.27; N, 13.68. Found: C, 66.42; H, 4.23; N, 13.65.

Spectral data of compound 2b: IR (KBr, ν_{max}): 3276-2813 (NH), 1641 cm^{-1} (>C=O), 1216 cm^{-1} (>C=S); ^{1}H-NMR (DMSO-d_6, 400MHz) [δ/ppm]: δ 10.65 (s, 2H, 2xNH), 10.00 (s, 1H, NH), 6.97-7.94 (m, 8H, Ar-H), 6.17(s, 1H, C_4-H); ^{13}C-NMR (DMSO-d_6, 100 MHz) [δ/ppm]: δ 196.6, 170.5, 153.3, 148.5, 144.5, 141.2, 134.7, 133.4, 133.3, 132.9, 131.9, 130.1, 129.8, 128.2, 127.7, 127.5 and 101.9; EI-MS (70 eV, m/e, $M^{+\cdot}$): 341; Anal. Calcd. For ($C_{17}H_{12}N_3OSCl$): C, 59.82; H, 3.55; N, 12.32; Found: C, 59.79; H, 3.51; N, 12.30.

Conclusion

In conclusion, we have illustrated a new efficient procedure for the modified Biginelli reaction by heterocylic 1,3-diketones, aldehydes and thiourea within 9 minutes. The reaction proceeds briskly under solvent- free condition coupled with microwave irradiation and work up is equally rapid and green approaches. The application of this method provides a simple powerful tool for the synthesis of a large number of ring fused pyrimidine derivatives.

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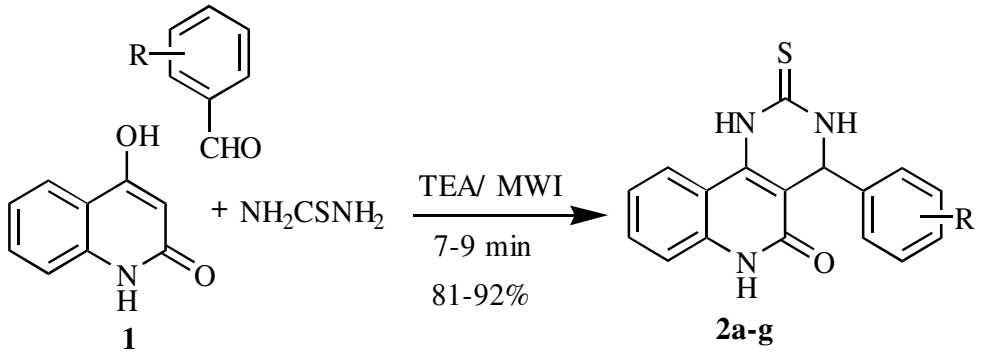
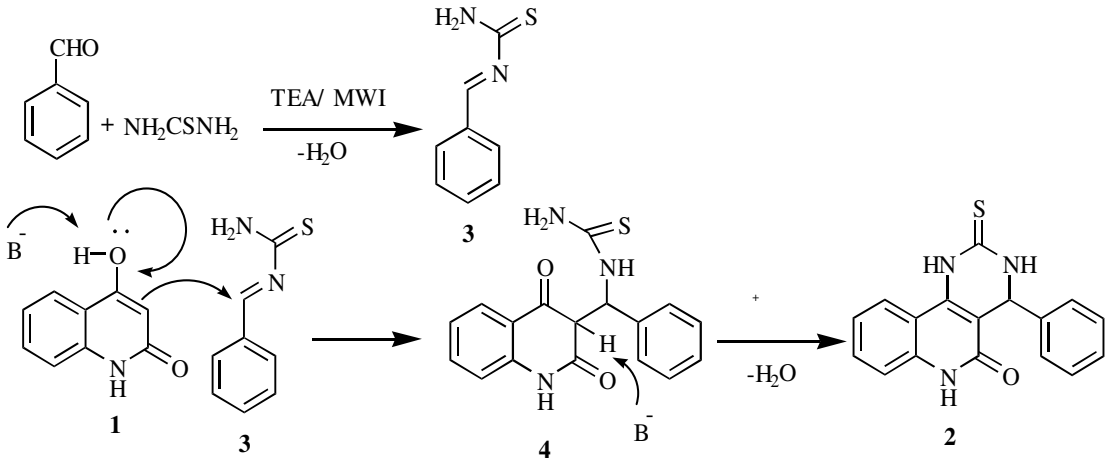
Table-1
Physical data of synthesised pyrimido[5,4-c]quinolines 2a-g

Compound	R	Reaction Time (min)	Yield (%)	mp^o C
2a	H	7	90	240
2b	*o*-Cl	7	89	205
2c	*p*-Cl	8	91	238
2d	*m*-Cl	9	92	245
2e	*o*-OH	7	85	215
2f	*p*-OH	7	81	207
2g	*m*-NO_2	9	90	218



R = H, *o*-Cl, *p*-Cl, *m*-Cl, *o*-OH, *p*-OH, *m*-NO_2

Scheme-1
Synthesis of pyrimido[5,4-c]quinolies 2a-g



Scheme-2
Proposed mechanism for the modified Biginelli reaction

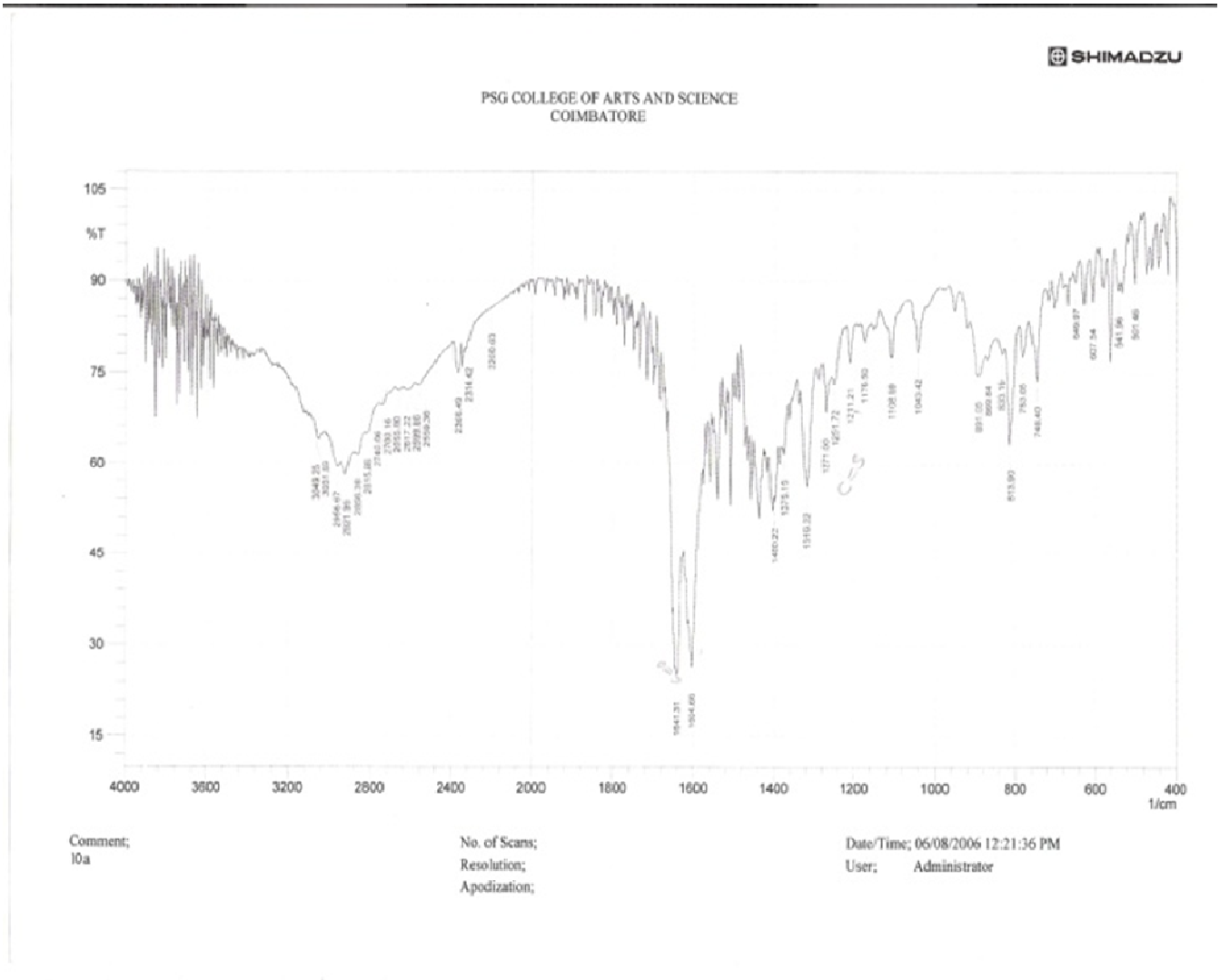


Figure-1
IR Spectrum of 2a

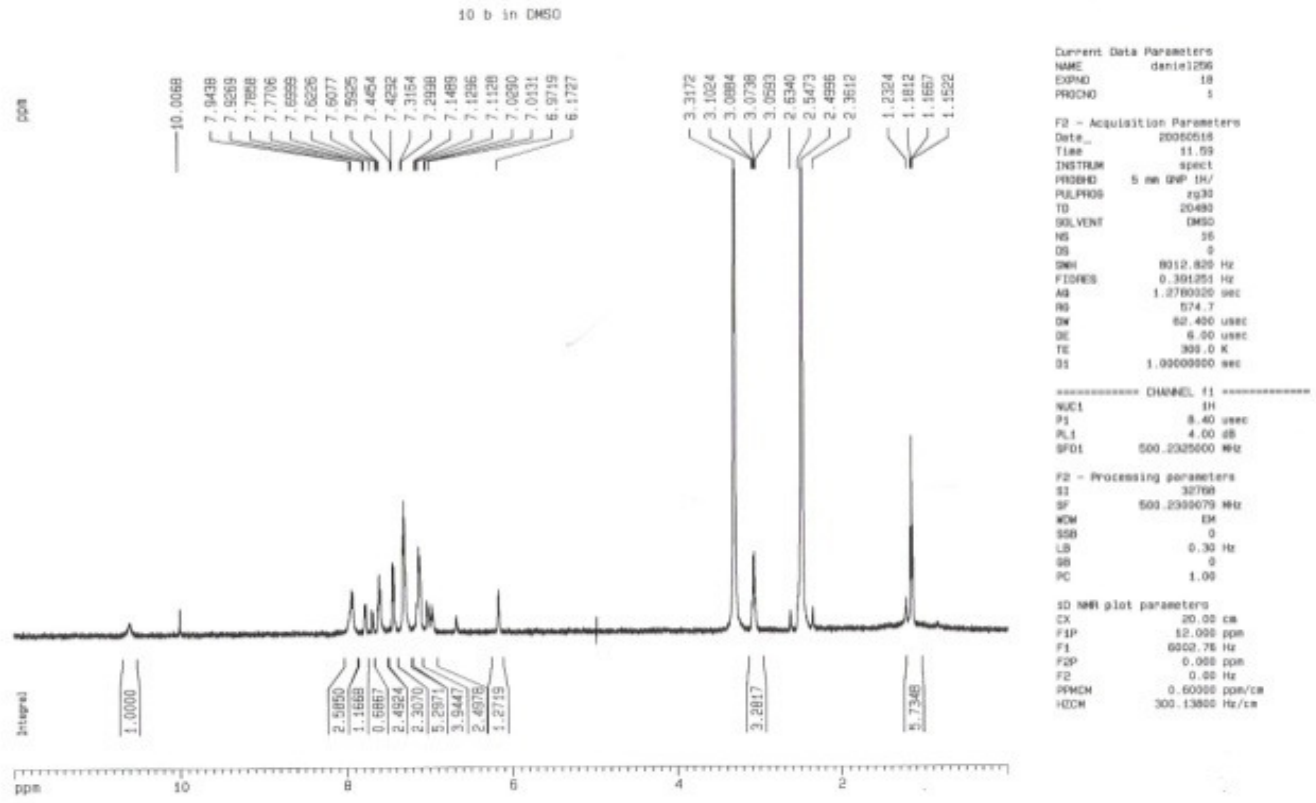


Figure-2
1HNMR Spectrum of 2a

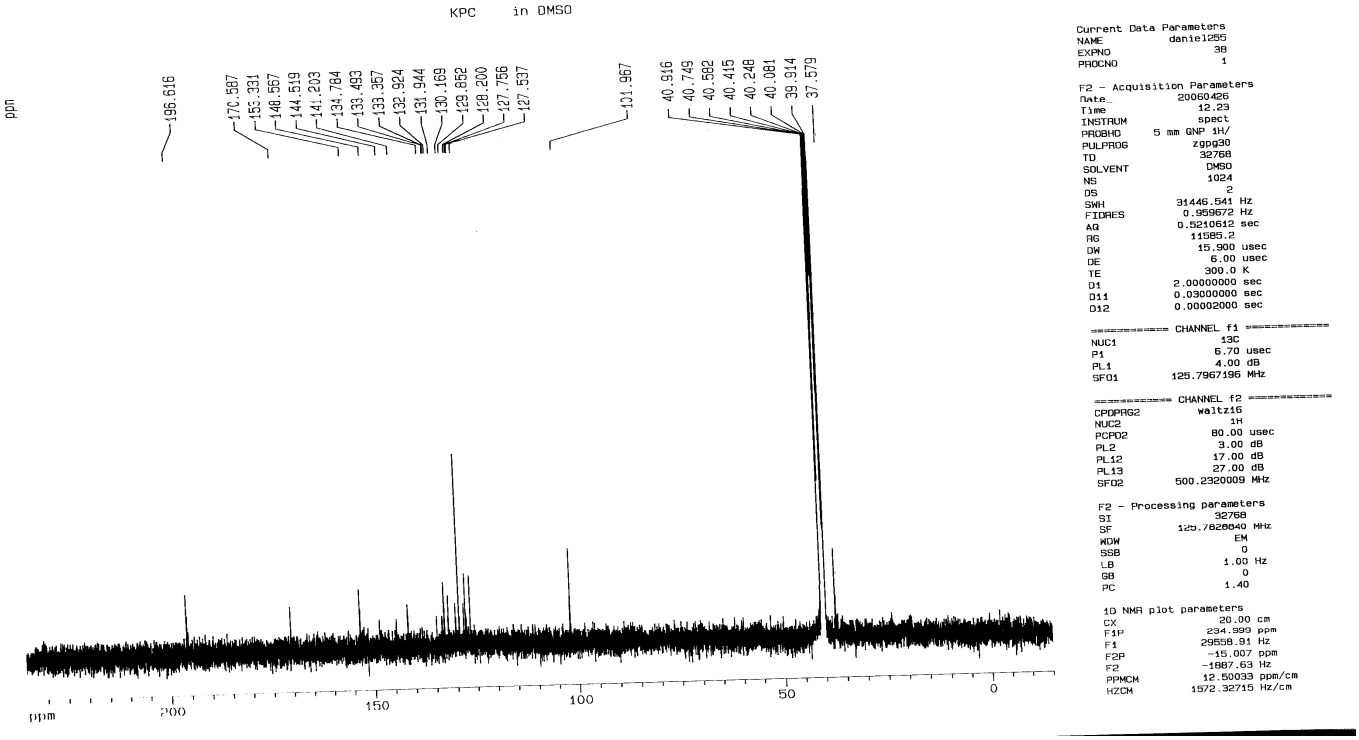


Figure-3
13CMR Spectrum of 2a

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