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Synthesis of Ethyl β-Arylaminocrotonates Catalyzed by Inorganic Solid Support Under Microwave Irradiation

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Abstract: The reactions of arylamine with ethyl acetoacetate catalyzed by a solid support are accelerated by microwave irradiation to result in a rapid and clean production of ethyl β-arylaminocrotonates.

Keywords: β-Arylaminocrotonates, microwave irradiation, solid support.

β-Arylaminocrotonates gain long-standing interests for their potential as important intermediates for the synthesis of 2, 4-disubstituted quinoline and related natural products[1]. The most common method employed for the preparation of β-arylamino-crotonates, which was initiated by Conrad-Limpach, involves the condensation of aryl-amines with ethyl acetoacetate for a prolonged period[2]. Many efforts have been directed to improve the yield and rate of the reaction and recent modifications were mainly focused on the usage of effective catalysts, such as BF_3[3], K-10 Montomorilla[4] and lanthanide[5]. However, these conventional methods usually show weak points such as long reaction time and tedious work-up that resulted from the azeotropic removal of the formed water.

In recent years, microwave irradiation has broken new grounds in synthetic organic chemistry[6], not only in terms of reduction in reaction time, but also simplicity of reaction procedures, as shown in our previous report[7]. The combination with inorganic solid support[8] further extends the application scope of microwave, thus forming a promising candidate for environmentally friendly chemistry.

Here, we wish to report a novel and convenient method for the preparation of β-arylaminocrotonates catalyzed by inorganic solid support under microwave irradiation. Arylamine (1 mmol) and ethyl acetoacetate (1 mmol) were absorbed on a solid support (0.5 g) thoroughly and the resulting fine powder was placed in a beaker and subjected to irradiation inside a microwave oven at 300 W output for a fixed period. The reaction mixture was cooled to room temperature and charged directly on a silica gel column using a mixture of petrol-ether (3:1), the pure β-arylaminocrotonates were obtained

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(**Scheme 1** and **Table 1**), and the spectral data of compounds were listed in **Table 2**.

The results in **Table 1** show that β-arylaminocrotonates substituted with an electron donating group (**3d-3g**) have higher yields than those with an electron withdrawing group (**3b, 3c**). Those because the electron donating groups may strengthen the nucleophilic power of nitrogen atom in the anilines, wheras electron withdrawing substituents weaken it.

The catalytic influence of various inorganic solid supports on the condensation of aniline with ethyl acetoacetate under microwave irradiation were studied and the results are shown in **Table 3**. It can be concluded that the acidity of the inorganic solid support is the dominant factor for the yield. From the reaction mechanism one can see that the hydrogen ion is involved in the condensation reaction, it may strengthen the electrophilic power of the carbonium ion of the ethylacetoacetate. This is in accordance with the condensation carried out by conventional method[9].

Using the reaction of aniline with ethyl acetoacetate, we investigated the effect of the time of irradiation on the reaction. The results are summarized in **Table 4**. The result showed that 5 minutes was the optimum time length of irradiation. Extension of the irradiation time gave essentially the same results.

Scheme 1

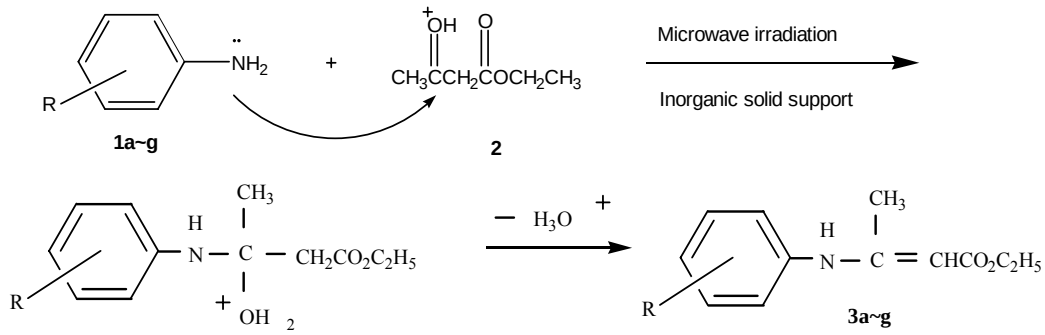

Table 1 β-Arylaminocrotonates prepared under microwave irradiation

Products	R	Mp or Bp		Yield (%)
		Found	Lit	
3a	H	141°C/4 mmHg	142°C/4 mmHg[9]	70
3b	*p*-chloro	55 °C	55 °C[9]	65
3c	*m*-chloro	155 °C/2 mmHg	145-8 °C/1-1.5 mmHg[9]	46
3d	*p*-methoxy	45-6°C	45.5-6°C[10]	78
3e	*o*-amino	85-6°C	85°C[11]	81
3f	*p*-methyl	146-8°C/4 mmHg	146-7°C/4 mmHg[10]	79
3g	*m*-methyl	144-5°C/4 mmHg	144.5-5 °C/4 mmHg [10]	76

a) Using SiO_2 as solid support.

Table 2 The spectral data of compounds **3a~g**

Compunds	^{1}HNMR ($CDCl_3$, δ_{ppm}, J_{Hz})	MS(EI)
3a	1.26 (t, 3H, J=7Hz) 1.96 (s, 3H) 4.12 (q, 2H, J=7Hz) 4.66 (s, 1H) 7.18 (m, 5H) 10.36 (s, 1H)	205(M^+)
3b	1.26 (t, 3H, J=7Hz) 2.01 (s, 3H) 4.14 (q, 2H, J=7Hz) 4.63 (s, 1H) 7.15 (m, 4H) 10.18 (s, 1H)	239(M^+)
3c	1.27 (t, 3H, J=7Hz) 2.01 (s, 3H) 4.14 (q, 2H, J=7Hz) 4.71 (s, 1H) 7.09 (m, 4H) 10.33 (s, 1H)	239(M^+)
3d	1.26 (t, 3H, J=7Hz) 1.86 (s, 3H) 3.77 (s, 3H) 4.12 (q, 2H, J=7Hz) 4.62 (s, 1H) 6.91 (m, 4H) 10.16 (s, 1H)	235(M^+)
3e	1.26 (t, 3H, J=7Hz) 1.79 (s, 3H) 4.11 (m, 4H) 4.70 (s, 1H) 6.86 (m, 4H) 9.68 (s, 1H)	220(M^+)
3f	1.26 (t, 3H, J=7Hz) 1.92 (s, 3H) 2.30 (s, 3H) 4.12 (q, 2H, J=7Hz) 4.64 (s, 1H) 7.02 (m, 4H) 10.29 (s, 1H)	219(M^+)
3g	1.27 (t, 3H, J=7Hz) 1.84 (s, 3H) 2.27 (s, 3H) 4.10 (q, 2H, J=7Hz) 4.69 (s, 1H) 7.12 (m, 4H) 10.13 (s, 1H)	219(M^+)

Table 3 Catalytic effect of various inorganic solid supports

Solid support	SiO_2	Al_2O_3 (acidic)	Al_2O_3 (neutral)	Al_2O_3 (basic)	Molecular Sieve	Diatomite
Yield of **3a** (%)	70	72	60	40	35	~0

Table 4 Effect of irradiation time for the reaction of aniline with ethyl acetoacetate

Time (min.)	2	5	10	15
Yield of **3a** (%)	50	70	71	72

In summary, the condensation of arylamine with ethyl acetoacetate under microwave irradiation with inorganic solid support is rapid and clean for the preparation of β-arylaminocrotonates. This method, compared with the conventional ones, shows ad- ventages of short reaction time, simple work-up, easy isolation and the use of inexpensive catalyst.

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