New synthesis of 1,3-diaryl-4-nitro-1-butanones by microwave-promoted Michael addition of nitromethane to chalcones without solvent

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The Michael addition of nitromethane to chalcones promoted by microwave irradiation without solvent afforded 1,3-diaryl-4-nitro-1-butanones in good yield. The products were characterised by IR, ^{1}H NMR and elemental analysis.

Keywords: 1,3-diaryl- 4-nitro-1-butanone, Michael addition, chalcone; microwave irradiation, synthesis

1,3-Diaryl-4-nitro-1-butanones are versatile synthetic intermediates. For example, 3-p-chlorophenyl-1-phenyl- 4-nitro-1-butanone was used to synthesise the therapeutically useful $GABA_B$ receptor agonist (*R*)-baclofen hydrochloride[1] that is used to treat spasms caused by spinal cord injury or disease. The reductive cyclisation of 4-nitro-1-butanones is a standard method for the preparation of pyrrolidine derivatives.[2]

The enantioselective reduction of prochiral 1-aryl-4-nitro-1-butanones to the corresponding nitroalcohols leads to a class of chiral building blocks that are useful for the synthesis of a variety of heterocyclic compounds.[3]

The Michael reaction of nitromethane to chalcones is the most commonly used method for the preparation of 1,3-diaryl-4-nitro-1-butanones. Usually, the Michael reaction is promoted with acids, bases and metal complexes. Solid supported reagents and micelles catalyse the process.[4-7] Recently there has been a growing interest in the use of conventional microwave heating in organic synthesis,[8] and it has been proved to be of particular benefit in promoting reactions on solid supports with a catalyst and without a solvent.[9-11] Although recent advances have made this reaction more attractive, some of these methods are limited by long reaction times and expensive catalysts.[12] We now report a remarkably rapid Michael addition of chalcones nitromethane to chalcones under microwave irradiation without solvent leading to 1,3-diaryl- 4-nitro-1- butanones (Scheme 1).

Results and discussion

The Michael reaction was carried out by simple mixing the chalcone, nitromethane and K_2CO_3 adsorbed in Al_2O_3, and then irradiating in an open beaker in a domestic microwave oven for 5-8 minutes. The reaction proceeded smoothly and yields reached 62–90%.

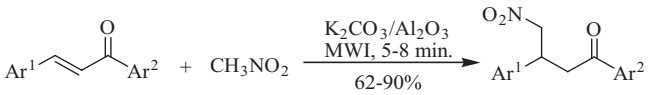
After the reaction, the 1,3-diaryl-4-nitro-1-butanones were isolated by silica gel column chromatography, using petroleum ether (60–90°C)-ethyl acetate as eluent.

In our search for an economical, environmentally friendly reaction to 1,3-diaryl-4-nitro-1-butanones, we used cheap, readily available, and nontoxic bases. In the Michael addition of nitromethane to chalcones, it was found that the yield depended largely on the base (Table 1). Comparing the yields of entries 1–6, it can be seen that the reactions in the presence of the bases K_2CO_3, or Na_2CO_3 gave better yields than those in the presence of KF, CsF or piperidine. Amongst these bases, KF/Al_2O_3 was quite effective for Michael reactions of α,β-unsaturated compounds with nucleophiles.[13] However, it readily promoted the double Michael additions of nitromethane to chalcones, and cyclic compounds were formed from chalcones and nitromethane under microwave irradiation.[14] Under our conditions we found that the double addition can be avoided and chalcone was converted into compound **3e** in 70% yield using 4 times the equivalent amount of nitromethane. A negligible amount of the cyclic compound was formed. K_2CO_3/Al_2O_3, Na_2CO_3/Al_2O_3 are moderate basic reagents and are widely used in organic reactions.

Table 1 The effect of base in the Michael reaction of chalcones with nitromethane

Entry	Base	Yield of compound **3e**/%
1	K_2CO_3	90
2	Na_2CO_3	86
3	KF	72
4	Et_3N	70
5	piperidine	78
6	CsF	60

Microwave power, 200 W; reaction time, 7 min.



1a-j **2** **3a-j**

Entry	Ar^1	Ar^2	Irrad.Time(min)	3 yield(%)
a	C_6H_5	C_6H_5	7	68
b	C_6H_5	p-ClC_6H_4	7	74
c	C_6H_5	p-$O_2NC_6H_4$	5	72
d	C_6H_5	p-$MeOC_6H_4$	6	66
e	C_6H_5	2,4-$Cl_2C_6H_3$	7	90
f	C_6H_5	p-HOC_6H_4	8	70
g	p-$MeOC_6H_4$	p-ClC_6H_4	5	69
h	p-$MeOC_6H_4$	p-$O_2NC_6H_4$	8	82
i	p-$MeOC_6H_4$	2,4-Cl_2C_6H	8	80
j	p-$MeOC_6H_4$	C_6H_5	7	62

Scheme 1

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Table 2 Effect of the time of microwave irradiation on the synthesis of **3e**

Reaction time/min	4.0	5.0	6.0	7.0	8.0
Compd **3e** yield/%	62	78	86	90	83

Microwave power, 200 W; base: K_2CO_3/Al_2O_3.

Table 3 Effect of the power of microwave irradiation on the synthesis of **3e**

MW power/W	100	150	200	250	300
Compd **3e** yield/%	42	75	90	82	53

Reaction time, 7 min; base: K_2CO_3/Al_2O_3.

To optimise the reaction conditions, the effect of the time of microwave irradiation and the power of the microwave irradiation on the synthesis of **3e** were studied. As shown in Tables 2 and 3, the reaction gave a satisfactory yield of **3e** for 6-7 min. and a longer reaction time was not necessary. The reaction was quite microwave power dependent, and 200W is recommended. Normally, reaction occurred slowly below 200W and the low boiling-point nitromethane quickly evaporated when the microwave power was above 200W (Table 3).

Under very similar conditions, the other chalcones and nitromethane underwent the Micheal addition to yield corresponding 1,3-diaryl- 4-nitro-1-butanones in 62–90%. As illustrated in Scheme 1, this method is quite general and the yields of **3a**–**j** were not significantly affected by substituents at aromatic ring.

In conclusion, we have developed a microwave-promoted procedure for the Michael addition of nitromethane to chalcones in the presence of K_2CO_3/Al_2O_3 without solvent to prepare 1,3-diaryl-4-nitro-1-butanones (**3**). The yields of the reaction are excellent and much higher than the results obtained by using the conventional method. The structures of compounds **3** were identified on the basis of their IR, ^{1}H NMR data and elemental analyses.

Experimental

Chalcones were prepared according to known literature procedure.[15-16] Elemental analyses were obtained using a model 240 analyser, IR spectra were measured with a model 408 infrared spectrometer, ^{1}H NMR spectra were recorded on a JNM-90Q Spectrometer by using TMS as an internal standard ($CDCl_3$ as solvent).

General procedure for the Michael addition of nitromethane to chalcones under microwave irradiation

A mixture of chalcones (5 mmol), nitromethane (1.22 g, 20 mmol) and K_2CO_3 (0.69 g, 5 mmol) adsorbed on 5 g Al_2O_3 (300 mesh) was introduced into a Galanz WP 750A domestic microwave oven in a 25 ml beaker. Microwave irradiation was performed at the microwave power 200 W for the appropriate time. After the reaction, the mixture was cooled to ambient temperature, the product **3** was isolated directly by silica gel column chromatography, using petroleum ether (60–90°C)–ethyl acetate as eluent.

1,3-diphenyl-4-nitro-1-butanone (**3a**): M.p. 81–83°C (PE/EtOAc); IR: 1690, 1600, 1580, 1500, 1390 cm^{-1}; ^{1}H NMR: 3.38 (d, J = 18 Hz, 2H), 3.98–4.51 (m, 1H), 4.66–4.83 (m, 2H), 7.01–8.00 (m, 10H); Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.39; H, 5.58; N, 5.20; Found C, 71.80; H, 5.70; N, 5.10%.

1-phenyl-3-p-chlorophenyl-4-nitro-1-butanone (**3b**): M.p. 81–82°C (PE/EtOAc); IR: 1700, 1600, 1590, 1510, 1390 cm^{-1}; ^{1}H NMR: 3.40 (d, J = 20.1 Hz, 2H), 4.30–4.52 (m, 1H), 4.68–4.86 (m, 2H), 7.02–8.00 (m, 9H); Anal. Calcd. for $C_{16}H_{14}NO_3Cl$: C, 63.26; H, 4.61; N, 4.61; Found C, 63.10; H, 4.61; N, 4.58%.

1-phenyl-3-p-nitrophenyl-4-nitro-1-butanone (**3c**): M.p. 93–95°C (PE/EtOAc); IR: 1700, 1600, 1592, 1500, 1400 cm^{-1}; ^{1}H NMR: 3.38 (d, J = 18 Hz, 2H), 4.30–4.56 (m, 1H), 4.68–4.90 (m, 2H), 7.05–8.06 (m, 9H); Anal. Calcd. for $C_{16}H_{14}N_2O_5$: C, 61.15; H, 4.46; N, 8.92; Found C, 61.10; H, 4.40; N, 8.82%.

1-phenyl-3-p-methoxyphenyl-4-nitro-1-butanone (**3d**): M.p. 66–68°C (PE/EtOAc); IR: 1695, 1600, 1590, 1540, 1502, 1400 cm^{-1}; ^{1}H NMR: 3.39 (d, J = 18 Hz, 2H), 3.60 (s, 3H), 4.00–4.10 (m, 1H), 4.46–4.80 (m, 2H), 6.70–7.90 (m, 9H); Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.23; H, 5.70; N, 4.68; Found C, 68.20; H, 5.60; N, 4.67%.

1-phenyl-3-(2,4-dichloro)phenyl-4-nitro-1-butanone (**3e**): M.p. 108–110°C (PE/EtOAc); IR: 1698, 1595, 1540, 1500, 1390 cm^{-1}; ^{1}H NMR: 3.42 (d, J = 17.7 Hz, 2H), 4.10–4.52 (m, 1H), 4.68–4.90 (m, 2H), 7.00–8.20 (m, 8H); Anal. Calcd. for $C_{16}H_{13}NO_3Cl_2$: C, 56.80; H, 3.85; N, 4.14; Found C, 56.80; H, 3.76; N, 4.00%.

1-phenyl-3-p-hydroxyphenyl-4-nitro-1-butanone (**3f**): M.p. 124–126°C (PE/EtOAc); IR: 3500–3300, 1710, 1600, 1580, 1490, 1390 cm^{-1}; ^{1}H NMR: 3.42 (d, J = 1.8 Hz, 2H), 4.20–4.50 (m, 1H), 4.68–4.86 (m, 2H), 7.00–8.02 (m, 9H), 9.80 (s, 1H); Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.37; H, 5.26; N, 4.91; Found C, 67.56; H, 5.18; N, 4.86%.

1-p-methoxyphenyl-3-p-chlorophenyl-4-nitro-1-butanone (**3g**): M.p. 126–128°C (PE/EtOAc); IR: 1690, 1600, 1590, 1500, 1390 cm^{-1}; ^{1}H NMR: 3.41 (d, J = 18 Hz, 2H), 3.60 (s, 3H), 4.20–4.58 (m, 1H), 4.66–4.90 (m, 2H), 7.02–7.98 (m, 8H); Anal. Calcd.for $C_{17}H_{16}NO_4Cl$: C, 61.17; H, 4.80; N, 4.20; Found C, 61.10; H, 4.62; N, 4.10%.

1-p-methoxyphenyl-3-p-nitrophenyl-4-nitro-1-butanone (**3h**): M.p. 162–164°C (EtOH); IR: 1700, 1606, 1592, 1500, 1455, 1392 cm^{-1}; ^{1}H NMR: 3.42 (d, J = 18 Hz, 2H), 3.62 (s, 3H), 4.20–4.66 (m, 1H), 4.70–4.90 (m, 2H), 7.00–8.02 (m, 8H); Anal. Calcd. for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.65; N, 8.12; Found C, 59.20; H, 4.60; N, 8.06%.

1-p-methoxyphenyl-3-(2,4-dichloro)phenyl-4-nitro-1-butanone (**3i**): M.p. 129–131°C (PE/EtOAc); IR: 1700, 1600, 1588, 1500, 1450, 1390 cm^{-1}; ^{1}H NMR: 3.40 (d, J = 18 Hz, 2H), 3.60 (s, 3H), 4.20–4.60 (m, 1H), 4.70–4.86 (m, 2H), 7.02–8.00 (m, 7H); Anal. Calcd. for $C_{17}H_{15}NO_4Cl_2$: C, 55.43; H, 4.08; N, 3.80; Found C, 55.30; H, 4.06; N, 3.72%.

1-p-methoxyphenyl-3-phenyl-4-nitro-1-butanone (**3j**): M.p. 101–103°C (PE/EtOAc); IR: 1700, 1608, 1590, 1480, 1450, 1395 cm^{-1}; ^{1}H NMR: 3.35 (d, J = 18 Hz, 2H), 3.60 (s, 3H), 4.10–4.60 (m, 1H), 4.70–4.86 (m, 2H), 7.00–8.02 (m, 9H); Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.23; H, 5.69; N, 4.68; Found C, 68.17; H, 5.62; N, 4.70%.

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