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Microwave Promoted Alkylation of Halonitrobenzene with Malonates in Solvent-free Medium

Venkat Narsaiah Akkirala

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Abstract The alkylations on different substituted halonitro benzenes have been demonstrated with various malonates under the influence of microwaves irradiation. The reactions were catalyzed by potassium carbonate and benzyltriethylammoniumchloride. The salient features of this methodology are mild reaction conditions, high regioselectivity, rapid conversions, solvent-free medium and easy isolation of products

Keywords Microwave-irradiation · Alkylation · Malonates · Halonitrobenzenes · TEBA

1 Introduction

Therapeutically active compounds of the α-aryl propionic acids (profens), such as Flurbiprofen (**1**), Ibuprofen, Naproxen and Tenidap (**2**) have emerged as an important class of non-steroidal anti-inflammatory drugs (NSAID), analgesics and antipyretics [1, 2]. Due to the commercial importance of this group of drugs, several methods have been developed for their production (Fig. 1).

Among the various methods reported so far to prepare α-aryl propionic acids involves the arylation of dialkyl malonates with halonitrobenzenes to obtain the alkylated products. In general, these reactions have been carried out, using strong bases [3, 4] at high reaction temperature for a long time [5–8] and which leads to a mixture of isomers containing ortho and para products and most of the information available for the synthesis of these drugs is in the form of patents.

V. N. Akkirala (✉)
Organic Chemistry Division-III, Fine Chemicals Laboratory, Indian Institute of Chemical Technology, Hyderabad 500007, India
e-mail: vnakkirala2001@yahoo.com

2 Experimental Section

2.1 General Information

IR (KBr) spectra were recorded on a Shimadzu 470 IR Spectrometer. Silica gel (60–120 mesh) was used for column chromatography. ^{1}H NMR-Spectra was recorded in $CDCl_3$ on Varian FT-200 spectrophotometer (200 MHz) Machine using TMS as internal standard. Mass spectra were taken on a Finnigan Mat-1210 double focusing spectrometer. Microwave irradiation was performed using 450 W (2,450 MHz), BPL, BMP-800T domestic microwave oven.

2.2 General Experimental Procedure

A mixture of halonitro benzene (5 mmol), malonate ester (6 mmol), potassium carbonate (10 mmol) and benzyltriethyl ammonium chloride (0.5 mmol) were mixed with neutral alumina and taken in a small beaker and irradiated to microwave for 3–5 min (Table 1). The progress of the reaction was monitored by thin layer chromatography (TLC). To the reaction mixture was added ethyl acetate (50 mL) and stirred well for some time and then it was filtered. The cake was washed with ethyl acetate (2 × 25 mL). The filtrate was washed with water, brine and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude products were purified by column chromatography to give the pure products.

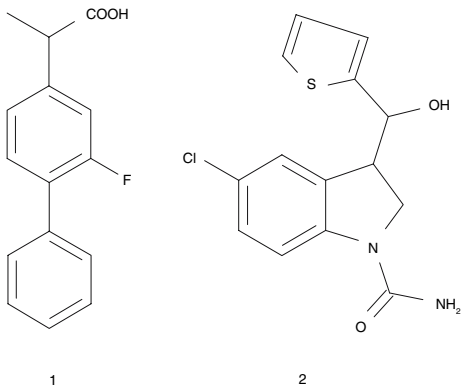


Fig. 1

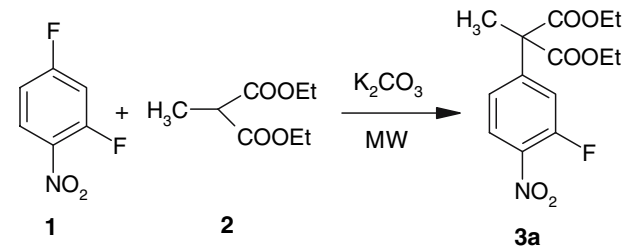
2.3 Spectral Data for Selected Compounds

(**3a**) Pale yellow liquid IR (neat): *v* 3,097, 2,963, 2,871, 1,721, 1,608, 1,579, 1,506, 1,437, 1,352, 1,218, 1,106, 1,059, 953, 841, 752 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.26 (t, 6H, J = 6.8 Hz), 1.85 (s, 3H), 4.24 (q, 4H, J = 6.8 Hz), 7.26–7.44 (m, 2H), 8.07 (t, 1H, J = 8.0 Hz). EIMS *m/z* (%): 313 (m^+ 29), 255 (12), 167 (43), 140 (100), 121 (61), 94 (10), 75 (32), 50 (25). (**3b**) Light colored liquid IR (neat): *v* 3,095, 2,964, 2,847, 1,722, 1,605, 1,546, 1,506, 1,463, 1,327, 1,284, 1,107, 1,053, 1,015, 950, 923, 836, 751 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.28 (t, 6H, J = 6.8 Hz), 4.22 (q, 4H, J = 6.8 Hz), 4.50 (s, 1H), 6.98–7.10 (m, 2H), 7.98–8.10 (m, 1H). EIMS *m/z* (%). 299 (m^+ 25), 270 (20), 226 (45), 197 (15), 153 (100), 134 (18), 107 (18), 88 (32), 70 (12), 51 (26).

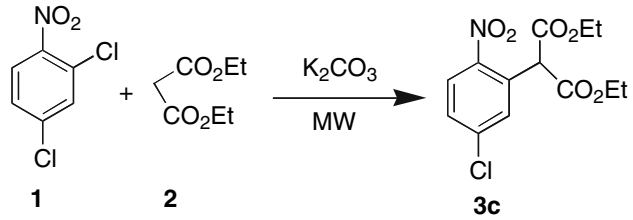
3 Results and Discussion

Because of the increasing pharmaceutical demand, it became necessary to develop a convenient method for the synthesis of the crucial intermediates (**3a**) diethyl-2–methyl-2-(3-fluoro-4-nitrophenyl) malonate for Flurbiprofen and (**3c**) dimethyl-2-(3-chloro-2-nitrophenyl) malonate for Tenidap [9, 10] (Scheme 1).

Recently, there has been a growing interest in the application of microwave irradiation in chemical transformations [11–18]. The salient features are improved reaction rates and formation of cleaner products. The solvent-free reactions are especially appealing as they provide an opportunity to work with open vessels, so it avoids the risk of high-pressure development. In continuation of our research program on developing new synthetic methodologies in solvent-free conditions [19–24], herein we wish to report, an efficient, procedure for the alkylation of different malonates with various substituted halonitro benzenes using K_2CO_3-neutral alumina (Scheme 2).



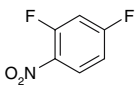
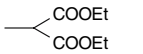
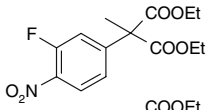
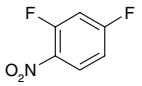
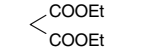
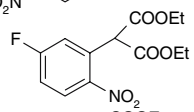
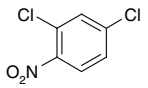
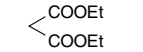
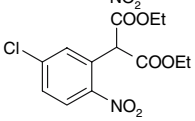
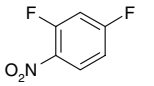
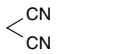
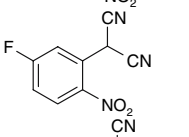
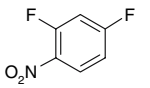
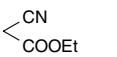
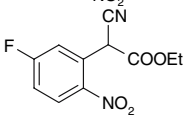
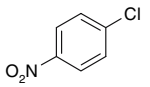
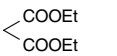
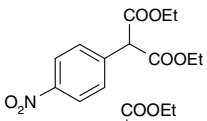
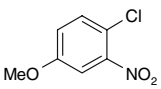
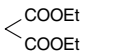
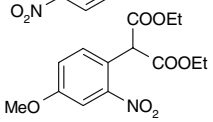
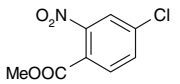
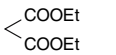
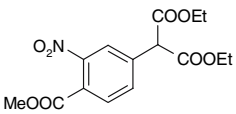
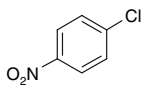
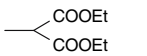
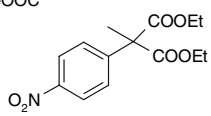
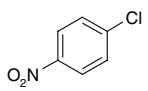
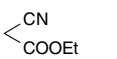
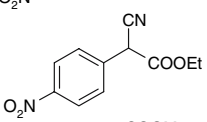
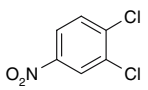
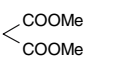
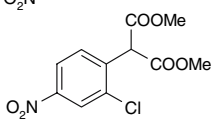
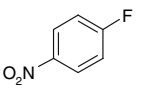
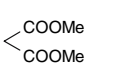
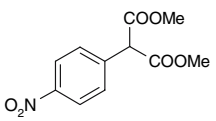
Scheme 1



Scheme 2

In our investigation, the competitive displacement of halogen from 2,4-dichloro nitro benzene and 2,4-difluoronitrobenzene, by a variety of carbon nucleophiles have been carried out as shown in the Table 1. For instance, a mixture of 2,4-difluoronitro benzene (5 mmol), methyl diethyl malonate (6 mmol), K_2CO_3 (10 mmol) and a catalytic amount of benzyltriethyl ammonium chloride (TEBA, 0.5 mmol) was treated to microwave on neutral alumina for 3 min. The resulted mixture was cooled to room temperature and extracted with ethyl acetate to obtain the crude products containing *para*-substituted product (entry **a**) as major (95%) and *ortho*-substituted product as minor (5%). The same reaction was required 18 h in conventional method at 70 °C in acetonitrile solvent. Encouraged by the result obtained with microwave irradiation, we have carried out the reactions with various malonates such as diethyl, dimethyl, dicyano and ethylcyano malonates with halonitrobenzenes under similar reaction conditions to obtain the corresponding alkylated products in very good yields. The regio-selectivity in the case of methyl diethyl malonate is due to the steric hindrance of methyl group at nucleophilic carbon (entry **a**) to *para*-substituted product (entry **a**) as major. In the case of diethyl malonate, the obtained product containing the *ortho*-isomer as major (90%) and the *para*-isomer as minor (10%), because no steric hindrance at nucleophilic carbon (entry **b**). The similar observation was found in the case of dicyanomalonate (entry **d**) and ethylcyanomalo nates (entry **e**). In the case of monohalonitrobenzene, the substituted products were obtained in very good yields without any side products. The mildness of this procedure is the tolerance of ether and ester functional groups without hydrolysis (entry **g**, **h**). We have observed that the

Table 1 Aromatic nucleophilic substitution—assisted by microwave irradiation

Entry	Substrate	Melonate	Product[a]	Time (min)	Yield[b] (%)	ortho : para[c]
a				3	85	05 :95
b				5	80	90 :10
c				4	80	88 :12
d				4	87	85 :15
e				3	80	86 :14
f				5	90	—
g				4	85	—
h				4	82	—
i				4	92	—
j				3	89	—
k				3	80	—
l				4	84	—

[a] All the products were characterized of their m.p. IR and ^{1}H NMR spectra with those of the authentic samples

[b] Isolated yields and unoptimized

[c] Ratio of isomers

phase-transfer catalyst benzyltriethyl ammonium chloride (TEBA) played a vital role in enhancing the rate of reaction. This observation was confirmed by conducting the reactions with 2,4-difluoronitrobenzene and diethyl malonate using K_2CO_3 in various equivalents and with and without TEBA. Table 2 shows the conversions of the reactants at different conditions in 5 min of reaction time. The base K_2CO_3 in two equivalents and the phase-transfer catalyst TEBA in 10 mol% is the more ideal ratio for this alkylation reaction. In the case of entry **a**–**e**, the *ortho* and *para* isomers were separated by column chromatography using silica gel 60–120 mesh, while eluting with ethyl acetate and petroleum ether mixture. In a similar fashion, the aryl halides having different substituents reacted smoothly with a wide range of malonates under these reaction conditions to give the corresponding alkylated derivatives in very good yields within 3–5 min of reaction time. Whereas it requires, more than 15 h of reaction time

Table 2 A study on alkylation of 2,4-difluoronitrobenzene with diethylmalonate under various conditions

S.No.	K_2CO_3	TEBA	Reaction time (min)	Conversion (%)
1	1.0	0	5.0	25
2	2.0	0	5.0	40
3	3.0	0	5.0	40
4	1.0	0.10	5.0	80
5	2.0	0.10	5.0	100
6	2.0	0.20	5.0	100

in conventional methods for complete conversion of substrates. The experimental procedure is very simple, convenient and also does not require any special precautions for the isolation of products. The alkylated products were converted to their corresponding Flurbiprofen and Oxindole by known methods in the literature [25–28].

The reaction proceeded rapidly under microwave irradiation and solvent-free conditions. The reaction was carried out both under microwave irradiation as well as thermal conditions. Microwave irradiations were carried out using BPL, BMO-800T domestic microwave oven operated at 2,450 MHz (450 W). The reaction temperature was controlled using a pulsed irradiation technique (1 min with 20 s intervals). The temperature was measured after each pulse. The lowest observed temperature was 80 °C after irradiation for 1 min at 450 W and the highest temperature was 110 °C after 3 min irradiation at the same power. The reaction rates and yields were dramatically enhanced by microwave irradiation. The rate enhancement under microwave irradiation may be attributed to the absorption of more microwave energy by the polar media (neutral alumina), which generates sufficient heat energy to promote the reaction. The same reaction, under thermal conditions at 85–90 °C took 15 h for completion. Among the solid supports (silica gel and neutral alumina) tested, the neutral alumina was found to be more efficient in promoting the reactions.

4 Conclusion

In conclusion, the present methodology describes a simple, convenient and efficient procedure for the alkylation of halonitrobenzenes with different malonates under microwave irradiation. The notable features of this procedure are mild reaction conditions, cleaner reaction profiles, improved yields, enhanced reaction rates and simplicity in operation, which makes it a useful process for aromatic alkylation. All the reactions were carried out using neutral alumina as a solid support.

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