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Dimethyl malonate as a one-carbon source: a novel method of introducing carbon substituents onto aromatic nitro compounds†

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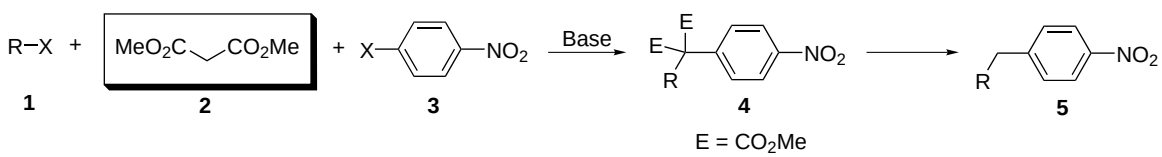
Abstract—A number of carbon substituents possessing various functional groups could be introduced onto aromatic nitro compounds using dimethyl malonate as a one-carbon source and linker. Decarboxylation of both the ester groups originating from dimethyl malonate in this methodology is particularly significant.

Alkylation of aromatic rings is one of the important transformations in organic synthesis. While the Friedel–Crafts alkylation procedure continues to occupy center stage for the alkylation of numerous aromatic rings, it does not proceed successfully with aromatic substrates having electron withdrawing groups.[1] In addition, the Friedel–Crafts method has the disadvantage of rearrangement of the alkyl group being used and it often leads to alkylation at more than one site.[2] The other possibility for the alkylation of electron deficient aromatics is to introduce carbon nucleophiles onto such aromatics possessing leaving groups such as halides. Even though introducing 'N' and 'O' nucleophiles to such aromatics is a standard aromatic nucleophilic substitution reaction in organic synthesis, there are not many successful examples of arylation of carbanions by nucleophilic aromatic substitution. The major limitation for this addition–elimination process is that the nitro aromatics often react with carbanions by electron-transfer processes.[3]

In this communication, we present the use of dimethyl malonate as a one-carbon source and linking agent for attaching a variety of carbon substituents possessing reactive functional groups such as esters, nitriles, olefins, ketones, etc. to aromatic nitro compounds. Thus, the reaction of dimethyl malonate **2** with an aromatic compound **3** under basic conditions, followed by alkylation with an alkyl halide **1**, produces a product **4** (Scheme 1). After introducing the carbon substituents onto the aromatic nitro compound using dimethyl malonate, both the ester functionalities can be removed under suitable conditions leading to the alkylated compound **5**. The overall protocol of preparing compound **5** from a nitro compound **3** constitutes an indirect method of alkylating the aromatic nitro compounds.

For example, the treatment of dimethyl malonate **2** with 3,4-dichloronitrobenzene **6** under basic conditions afforded the nitro-diester **7** in good yield (Scheme 2).[4,7] The stabilized anion obtained by the treatment of the resultant diester **7** with NaH underwent alkylation with benzyl bromide to give the alkylated compound **8** in 72% yield.[7] Having introduced two fragments onto dimethyl malonate, both the ester functionalities were removed under Kraphcho's decarboxylation conditions leading to the nitro compound **10** in high yield.[5,7] The overall transformation of 3,4-dichloronitrobenzene **6**



Scheme 1.

Keywords: decarboxylation; alkylation; Friedel–Crafts reaction; rearrangement; Michael addition.

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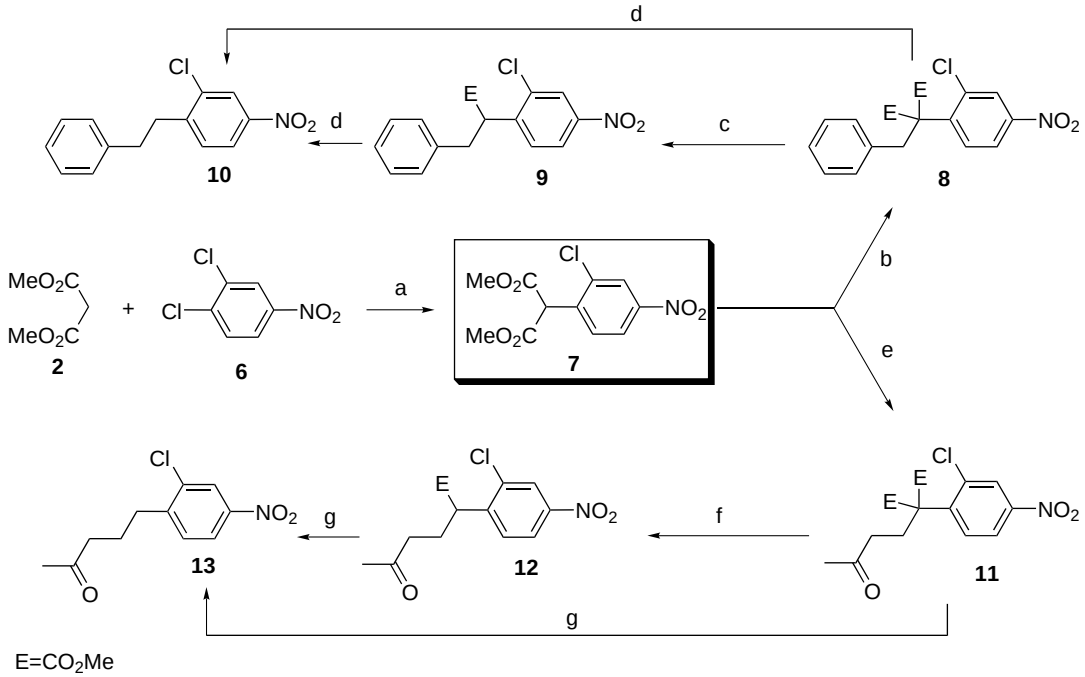


Scheme 2. (a) NaH, THF, 0→60°C, 75%; (b) NaH, DMF, BnBr, rt, 72%; (c) NaCl, DMSO, 110°C, 73%; (d) NaCl, DMSO, 155°C, 85%; (e) NaOMe, methyl vinyl ketone, MeOH, rt, 100%; (f) NaCl, DMSO, 110°C, 70%; (g) NaCl, DMSO, 155°C, 56%.

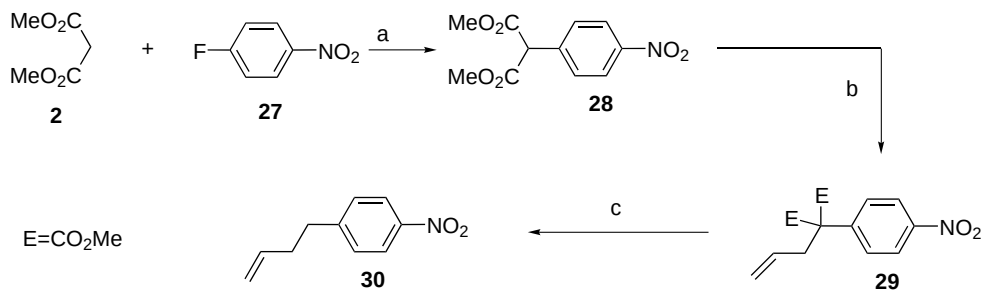
into the ester **10** constitutes a novel method of alkylation of aromatic nitro compounds. Even though the monodecarboxylation of malonates to esters is a conventional transformation, the decarboxylation of the second ester group is interesting and is realized probably because it is situated on a benzylic carbon of an electron deficient aromatic ring. The experiment could also be performed under controlled conditions so as to stop the reaction at monodecarboxylation product **9** at will. This option offers an opportunity to have an access for further functionalization whenever necessary.

In addition, the nitro-diester **7** also underwent a Michael addition with methyl vinyl ketone leading to the keto-diester **11** in quantitative yield (Scheme 2).[6,7] As expected, the decarboxylation of the compound **11** resulted in the nitro compound **13** in 56% yield. The monodecarboxylated product **12** could also be obtained from the nitro-diester **11** at a slightly lower temperature. In a similar fashion, methyl acrylate and acrylonitrile gave alkylated compounds **24** and **26**, respectively (entries 6 and 7, Table 1).

Having established a protocol for the alkylation of aromatic nitro compounds, we further pursued the generality of the method. A summary of several nitro-diesters, obtained by treatment of a number of alkyl halides and Michael acceptors with compound **7**, and the corresponding decarboxylation products, is given in Table 1. This method is flexible for the alkylation of diester **7** with allyl halides, benzyl halides and halides having a α-carbonyl functionality (entries 1 to 4, Table 1). However, the alkylated compound **22** obtained from an unsubstituted alkyl halide did not undergo the decarboxylation as expected (entry 5, Table 1).

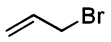
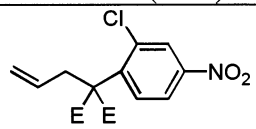
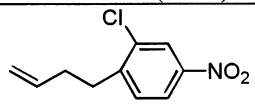
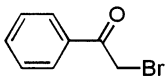
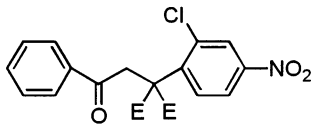
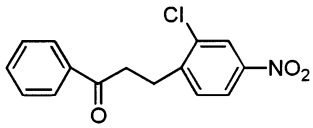
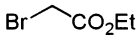
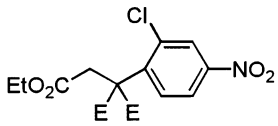
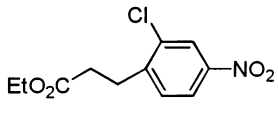
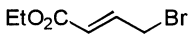
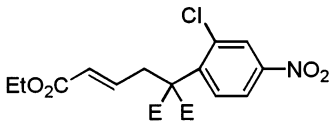
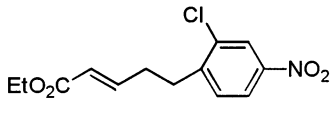
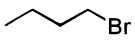
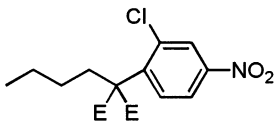
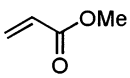
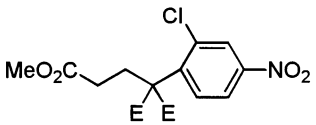
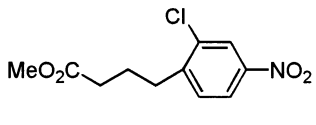
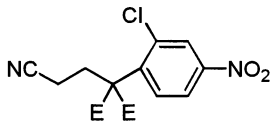
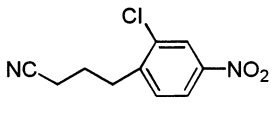
In order to establish the generality of this approach with other aromatic rings, the nitro-diester **28** which was prepared from 4-fluoronitrobenzene **27** and dimethyl malonate, was found to undergo alkylation with allyl bromide to give the compound **29** (Scheme 3). The nitro-diester **29** was in turn decarboxylated, giving the alkylated nitro compound **30** in 61% yield.

The alkylated compounds prepared in this communication have potential as intermediates or starting materials in organic chemistry. For instance, the nitro-diester **32** obtained by the reaction of 2-fluoronitrobenzene **31**



Scheme 3. (a) NaH, THF, 60°C, 65%; (b) NaH, allyl bromide, rt, 55%; (c) NaCl, DMSO, 155°C, 61%.

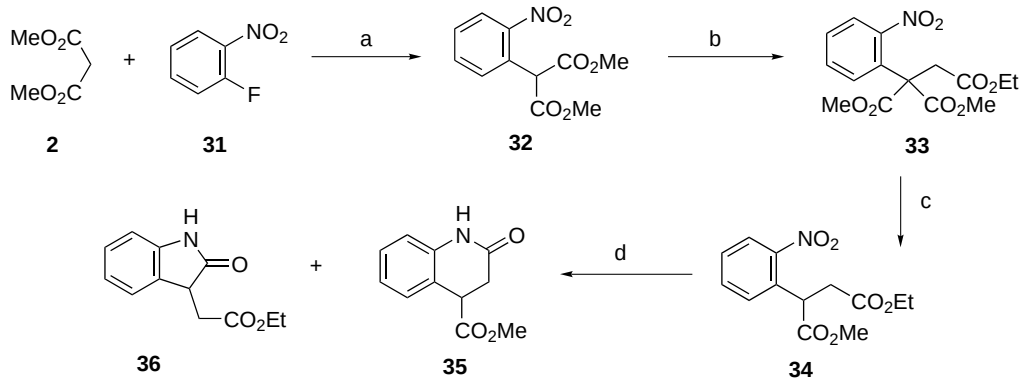
Table 1. Examples of the preparation of various alkylated nitrobenzenes[a]

Entry	Alkyl halide or Michael acceptor	**Compounds Analogous to 8 or 11** (Yield)	**Compounds Analogous to 10 or 13** (Yield)
1		 **14** (86%)	 **15** (74%)
2		 **16** (70%)	 **17** (56%)
3		 **18** (76%)	 **19** (61%)
4		 **20** (85%)[c]	 **21** (44%)[d]
5		 **22** (82%)	No Product[b]
6		 **23** (80%)	 **24** (48%)[d]
7		 **25** (72%)[c]	 **26** (70%)

[a] E represents CO_2Me.
[b] Only starting material was recovered.
[c] Yields based on recovered starting materials which ranges between 10 and 15%.
[d] The corresponding monodecarboxylated product of ca. 10% was also isolated.

with dimethyl malonate underwent alkylation with ethyl bromoacetate to afford the nitro-triester **33** in 58% yield over the two steps (Scheme 4). The hydrogenation of nitro-diester **34**, obtained by the controlled decarboxylation of compound **33**, resulted in the bicyclic lactams **35** and **36** in the ratio of 4:1 in four steps and in good yields. This would constitute a short synthesis of substituted 3,4-dihydro-2(1*H*)quinolinones of type **35**.

In conclusion, we have developed a methodology to introduce alkyl substituents possessing various functional groups onto aromatic nitro compounds. In addition, compounds **17** and **10** could be potential intermediates in the preparation of chalcones and stilbenes, respectively, with one of the aromatic rings containing a nitro group. The preparation of chalcones, stilbenes and further work to utilize the compounds prepared above in organic chemistry is currently underway in our laboratory.



Scheme 4. (a) NaH, THF, rt, 80%; (b) NaH, DMF, ethyl bromoacetate, rt, 72%; (c) NaCl, DMSO, 110°C, 58%; (d) H_2, Pd on C, THF, 73% (4:1 ratio of **35** to **36**).

Acknowledgements

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References

1. *Friedel–Crafts and Related Reactions*, *Vols. I–IV*; Olah, G. A., Ed.; Wiley-Interscience: New York, 1962–1964.
2. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, *Part B*; Plenum Press: New York, 1991.
3. *Comprehensive Carbanion Chemistry*, *Part A*; Durst, T., Ed.; Elsevier: Amsterdam, 1980; Chapter 5.
4. Snyder, H. R.; Merica, E. P.; Force, C. G.; White, E. G. *J. Am. Chem. Soc.* **1958**, *80*, 4622.
5. Kraphcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, *14*, 957.
6. Kaiser, E. W.; Mao, C. L.; Hauser, C. F.; Hauser, C. R. *J. Org. Chem.* **1970**, *35*, 410.
7. **Selected experimental procedures**:

Preparation of compound 7: To a suspension of NaH (60%, 5.49 g, 137.5 mmol) in dry DMF (80 mL) under ice cooling was added dimethyl malonate (16.5 g, 125 mmol) dropwise over a period of 10 min followed by a solution of 3,4-dichloronitrobenzene (12.0 g, 62.5 mmol) in dry DMF (15 mL) under an Ar atmosphere. The resultant mixture was stirred at 70°C overnight and then allowed to cool to rt. The reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate (4×200 mL). The combined organic extracts were washed with water, brine and dried (Na_2SO_4). The residue obtained upon evaporation of the solvents was purified on a column of silica gel to afford the nitro-diester **7** as a light yellow solid (13.5 g, 75%). Mp 109°C; IR (neat, ν cm^{-1}): 1748 (br), 1523, 1349, 1230, 1155, 738; δ_H (200 MHz, $CDCl_3$): 3.81 (s, 6H), 5.32 (s, 1H), 7.74 (d, J=8.3 Hz, 1H), 8.17 (dd, J=2.4 and 8.3 Hz, 1H), 8.31 (d, J=2.4 Hz, 1H); Mass (CI method): 288 $(M+H)^+$; Anal. calcd for $C_{11}H_{10}ClNO_6$: C, 45.94; H, 3.50; N, 4.87. Found: C, 46.12; H, 3.44; N, 4.80.

Preparation of compound 8: To a suspension of NaH (60%, 390 mg, 9.75 mmol) in dry DMF (15 mL) under ice cooling was added a solution of the compound **7** (2 g, 6.96 mmol) in dry DMF (5 mL) dropwise over a period of 5 min under an Ar atmosphere followed by benzyl bromide (1.76 g, 10.4 mmol). After stirring the resultant mixture at rt overnight, it was quenched with saturated NH_4Cl and extracted with ethyl acetate (4×60 mL). The combined organic extracts were washed with water, brine and dried. The residue obtained upon evaporation of the solvents was purified on a column of silica gel to afford compound **8** as a colorless oil (1.89 g, 72%). IR (neat, ν cm^{-1}): 1744, 1527, 1352, 1211, 767; δ_H (200 MHz, $CDCl_3$): 3.82 (s, 8H), 6.85–7.31 (m, 6H), 7.88 (dd, J=2.4 and 8.8 Hz, 1H), 8.26 (d, J=2.4 Hz, 1H); δ_C (50 MHz, $CDCl_3$): 39.47, 53.42 (2C), 64.77, 120.70, 125.45, 127.00, 127.81 (2C), 130.23 (2C), 132.14, 134.44, 135.13, 142.23, 146.91, 168.68 (2C); Mass (CI method): 378 $(M+H)^+$, 348, 288, 91.

Preparation of compound 10: A solution of compound **8** (500 mg, 1.32 mmol), NaCl (232 mg, 3.97 mmol) and H_2O (0.3 mL) in distilled DMSO (8 mL) was heated to 155°C overnight. The reaction mixture was allowed to cool to rt and then worked up by adding water and extracting with ethyl acetate (4×60 mL). The combined organic extracts were washed with water, brine and dried. The residue obtained upon evaporation of the solvents was purified on a column of silica gel to afford compound **10** as an orange colored solid (294 mg, 85%). Mp 60°C; IR (neat, ν cm^{-1}): 1521, 1350, 909, 734; δ_H (200 MHz, $CDCl_3$): 2.95–3.20 (m, 4H), 7.18–7.46 (m, 6H), 8.04 (dd, J=2.4 and 8.3 Hz, 1H), 8.29 (d, J=2.4 Hz, 1H); δ_C (50 MHz, $CDCl_3$): 35.19, 35.70, 121.53, 124.51, 126.30, 128.31 (2C), 128.42 (2C), 130.88, 134.64, 140.17 (2C), 146.67; Mass (CI method): 262 $(M+H)^+$, 91. Anal. calcd for $C_{14}H_{12}ClNO_2$: C, 64.26; H, 4.62; N, 13.55. Found: C, 64.06; H, 4.68; N, 13.38.

Preparation of compound 11: To a solution of the nitro-diester **7** (1.0 g, 3.5 mmol) and methyl vinyl ketone (0.714 g, 10.2 mmol) in absolute MeOH (10 mL) was added a catalytic amount of sodium methoxide at rt under Ar. The reaction mixture was stirred for 40 h at the same temperature and then diluted with CH_2Cl_2 (200 mL). The resultant mixture was washed with water, brine and dried. The residue obtained upon evaporation of the solvents was purified on a column of silica gel to give compound **11** as a colorless oil (1.18 g, 95%). IR (neat, ν cm^{-1}): 1737 (br), 1628, 1352, 1257, 893; δ_H (200 MHz, $CDCl_3$): 2.10 (s, 3H), 2.47–2.76 (2t, 4H), 3.78 (s, 6H), 7.51 (d, J=8.8 Hz, 1H), 8.12 (dd, J=2.4 and 8.8 Hz, 1H), 8.26 (d, J=2.4 Hz, 1H); δ_C (50 MHz, $CDCl_3$): 27.93, 29.77, 39.13, 53.24 (2C), 61.85, 121.56, 125.88, 129.99, 135.11, 142.54, 147.31, 169.00 (2C), 206.43; Mass (CI method): 358 $(M+H)^+$, 326, 111.