Nitroalkanes as new, ideal precursors for the synthesis of benzene derivatives

Roberto Ballini,* Alessandro Palmieri and Luciano Barboni

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Nitroalkanes have emerged, in the past few years, as powerful acyclic building blocks to synthesize polyfunctionalized benzene derivatives, avoiding any serious regiochemical ambiguities due to the activating/deactivating and orienting effects of the substituents. Many of these procedures are realized in a one-pot process or a few-step sequence. This *feature article* describes recent results, mainly from our group, in this field.

Introduction

The regiospecific preparation of benzene derivatives has long been a major subject in organic synthesis, owing to their widespread distribution in nature and importance in industrial chemistry. Classical approaches are based on the modification of arenes, and rely heavily on conventional electrophilic or nucleophilic substitutions, catalyzed coupling reactions, and metallation–functionalization reactions. However, these synthetic routes suffer from long multistep reaction sequences, low yields of target products, and, in particular, serious regiochemical ambiguities due to the activating/deactivating and orienting effects of the substituents.[1] Alternatively, aromatization of acyclic precursors is undoubtedly a useful reaction in the synthesis of highly substituted benzenes, and this approach has received growing interest as a promising countermeasure.[2]

In this context, nitroalkanes have emerged, over recent years, as versatile precursors for the synthesis of a collection of polyfunctionalized benzene derivatives. In fact, the nitronate anion that can be generated by basic treatment[3–7] acts as nucleophile, leading to carbon–carbon bond formation[3,5,8] and cyclization, under appropriate conditions.[8] Moreover, as the nitro group can be both eliminated or turned into an array of functional groups,[5,9–11] the cyclic nitro derivatives are good precursors for functionalized aromatic compounds.

Thus, after our first work on the synthesis of 1-acyl-2,5-dialkylbenzenes,[12] nitroalkanes appeared as ideal precursors for the synthesis of a variety of polysubstituted benzene derivatives, difficult to obtain by alkylation of aromatic structures. This article reports a variety of applications, mainly from our group, of nitro- and dinitroalkanes to the syntheses of benzene derivatives, discovered in the past few years.

Dipartimento di Scienze Chimiche dell'Università, Via S. Agostino 1, 62032 Camerino (MC), Italy. E-mail: roberto.ballini@unicam.it; Fax: +39 0737 402297; Tel: +39 0737 442270

Results and discussion

Our group has long been interested in the chemistry of nitroalkanes to access complex carbon frameworks. Our long term goal is to use these compounds to fabricate the skeletal structures of important fine chemicals and/or of various natural products,[13] culminating in their total synthesis. Just in the past few years, primary 1-nitro- and 1,3-dinitroalkanes have been discovered as convenient key building blocks in the preparation of a variety of polyfunctionalized aromatics, avoiding any serious regiochemical problem. In addition, many of these procedures can be realized in one-pot or in a reduced number of steps.

Roberto Ballini

Roberto Ballini is full Professor of Organic Chemistry at the University of Camerino. His research interests include a large area of the chemistry of aliphatic nitro compounds, with particular interest in the generation of new carbon–carbon single and double bonds. Other special fields of interest concern the development of new eco-sustainable processes in organic synthesis.

Alessandro Palmieri obtained his Laurea degree cum laude in Chemistry in 2002 at the University of Camerino. After a scholarship in the laboratory of Prof. Ballini, in February 2007 he obtained his PhD degree in Chemical Sciences. His research interests include the chemistry of nitro compounds and the development of new eco-friendly processes.

Luciano Barboni is Associate Professor in organic chemistry at the University of Camerino. In 1995 he joined Prof. Ballini's group and in 2000 he worked with G. Georg at the University of Kansas on the synthesis of taxol derivatives. His current research interests include a green approach to the chemistry of nitro compounds and the isolation and structural elucidation of bioactive natural products.

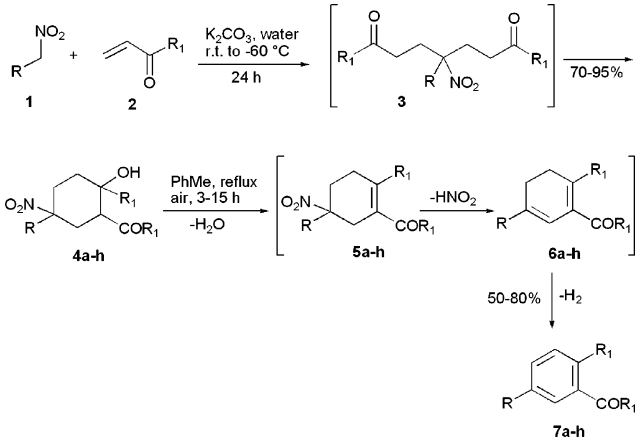
1. Synthesis of benzene derivatives from primary nitroalkanes

Primary nitroalkanes can be employed in the preparation of arenes mainly because the nitro group can act both as a carbanion stabilizer, giving rise to the generation of a new carbon–carbon bond, and as a good leaving group, favouring nitrous acid elimination.

1.1 Two-step synthesis of 1-acyl-2,5-dialkylbenzene derivatives

The first foray into investigating the use of nitroalkanes for arene synthesis was centered on the two-step preparation of 1-acyl-2,5-dialkylbenzene derivatives.[12] The first step of the procedure was the double Michael addition, in aqueous medium, of primary nitroalkanes **1** to enones **2**, followed by *in situ* intramolecular aldol reaction of the adducts **3** (Scheme 1). Cyclohexanols **4** were obtained in 70–95% yields as a diastereomeric mixture. After work up, the compounds **4** and a stoichiometric amount of *p*-TsOH were dissolved in toluene and refluxed with a Dean–Stark apparatus, with the simultaneous injection of air. Thus, the aromatic compounds **7** were obtained directly in 50–80% yields. The conversion of **4** to **7** proceeds initially through the elimination of both water (compound **5**) and nitrous acid, leading to dienes **6** which convert, by air oxidation, to the aromatic systems **7**. It is important to point out the key role of the nitro group that firstly favours the generation of two C–C bonds, then acts as good leaving group, yielding the diene intermediate **6**. The target acetyl derivatives **7** (R_1 = Me) are of great interest since they can be easily converted into phenols (Baeyer–Villiger rearrangements)[14] or carboxylic acids (haloform reaction),[15] giving rise to 2,5-dialkylphenols and 2,5-dialkylbenzoic acids, both important targets widely used for industrial[16] and pharmaceutical applications.[17,18]

The procedure allows the preparation of aromatic systems in satisfactory to good yields (Table 1) and the appropriate choice of the starting nitroalkane and/or of the alkyl vinyl ketone offers the opportunity to predict the relative positions of the substituents.



Scheme 1 Two-step synthesis of 1-acyl-2,5-dialkylbenzene derivatives.

Table 1 Synthesis of aromatic derivatives **7**

Compound	R	R_1	Yield (%) of **4** from **1**	Yield (%) of **7** from **4**
7a	Me	Me	90	53
7b	Et	Me	85	55
7c	*n*-Pr	Me	93	65
7d	*n*-Bu	Me	95	72
7e	*n*-C_5H_{11}	Me	95	61
7f	*i*-Pr	Me	75	50
7g	Ph	Me	70	80
7h	Me	Et	77	50

1.2 Synthesis of highly substituted phenols by [5 + 1] annulation

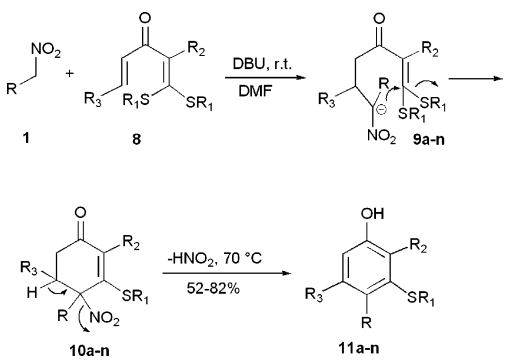
α-Alkenoylketenedithioacetals **8** show promising structural features as novel organic intermediates because of their (i) five-carbon 1,5-bielectrophilic nature, (ii) dense and flexible substitution patterns, and (iii) good leaving group (alkylthio) that can be subjected to a nucleophilic vinylic substitution (S_NV) reaction.[19] These prompted Dong *et al.*[20] to explore the feasibility of the construction of a substituted phenolic ring **11** relying upon utilization of **8**, as the 1,5-bielectrophilic component, in a [5 + 1] annulation with nitroalkanes **1**, which are well-known carbon nucleophiles (Scheme 2).

After several trials 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) proved to be the most efficient base and DMF the most efficient solvent, in order to produce **11** in good yields and in a one-pot manner.

Thus, the best reaction conditions, as reported in Scheme 2, need 1.5 equivalents of DBU at rt followed by heating at ~70 °C (after consumption of **1**, monitored by TLC). Under these conditions a range of reactions was carried out with systematically varied substrates **8** and nitroalkanes **1**. It was observed that all the reactions proceeded smoothly under the essentially mild basic conditions to afford the corresponding substituted phenols **11a**–**11n** in moderate to good yields (Table 2).

The results exhibit the generality of the benzannulation reaction with respect to a range of aliphatic and aromatic substrates. Indeed the protocol provides a straightforward pathway to construct highly substituted phenols.

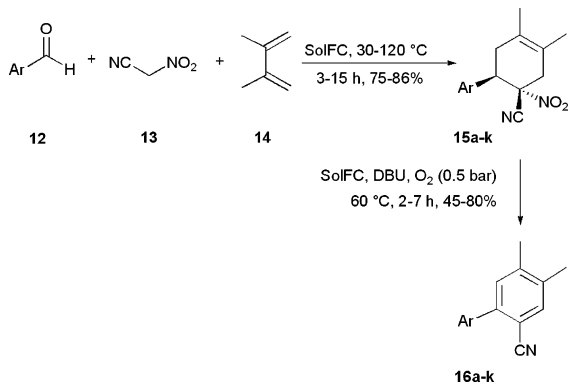
A possible mechanism for the [5 + 1] annulation of **1** and **8** is the addition of the stabilized carbanions, derived from nitroalkanes, to the double bond bearing an aryl group,



Scheme 2 Synthesis of highly-substituted phenols by [5 + 1] annulation.

Table 2 Preparation of highly substituted phenols **11**

Compound	R	R_1	R_2	R_3	Yield (%) of **11** from **8**
11a	Me	Et	4-ClC_6H_4NHCO	4-$CH_3C_6H_4$	67
11b	Me	Et	4-ClC_6H_4NHCO	3,4-$(O_2CH_2)C_6H_3$	72
11c	Me	Et	4-ClC_6H_4NHCO	4-ClC_6H_4	80
11d	Me	Et	4-ClC_6H_4NHCO	4-FC_6H_4	76
11e	Me	Et	4-ClC_6H_4NHCO	2-Thienyl	82
11f	Me	Et	4-ClC_6H_4NHCO	2-Furyl	75
11g	Me	Et	4-ClC_6H_4NHCO	PhCH=CH	64
11h	Me	Et	2-MeC_6H_4NHCO	4-MeC_6H_4	72
11i	Me	Et	PhCO	4-MeC_6H_4	79
11j	Me	Et	PhCO	PhCH=CH	56
11k	Me	Me	4-ClC_6H_4NHCO	4-MeC_6H_4	77
11l	Me	*n*-Bu	4-ClC_6H_4NHCO	4-MeC_6H_4	65
11m	Et	Et	4-ClC_6H_4NHCO	4-MeC_6H_4	78
11n	COOEt	Et	4-ClC_6H_4NHCO	4-MeC_6H_4	52



Scheme 3 Multicomponent synthesis of biphenyl-2-carbonitrile derivatives.

followed by an intramolecular addition–elimination (S_NV) reaction. The resulting cyclohexenones **10** shed HNO_2 and then aromatize to **11**.

1.3 Uncatalyzed, solvent-free, multicomponent process for the synthesis of biphenyl-2-carbonitrile derivatives

Biphenyls represent a key structural motif in a large number of compounds used as pharmaceuticals, agrochemicals, dyes, chiral ligands for metal catalysis, liquid crystals, organic semiconductors, and materials for molecular recognition devices; furthermore, the biaryl subunit is present in an extensive range of natural products.[21]

Thus, considering the importance of this class of compounds, an eco-friendly approach for their synthesis has been developed under solvent-free conditions (SolFC), *via* a metal-free multicomponent strategy, starting from aryl aldehydes **12**, nitroacetonitrile **13** and 2,3-dimethylbutadiene **14** (Scheme 3).[22]

The synthesis is based on the construction of the second aryl ring by two processes: (i) nitroaldol condensation, and Diels–Alder cycloaddition of the formed electron-poor alkene (conjugate nitroalkene) *via* a multicomponent procedure, and (ii) final aromatization, strongly favoured by nitrous acid elimination under basic conditions.

All the experiments have been performed by using **12** : **13** : **14** in 1 : 1.5 : 2 ratio, with a variety of aldehydes **12**, affording the cyclohexene derivatives **15**, in a one-pot way and in high yields (75–86%, Table 3).

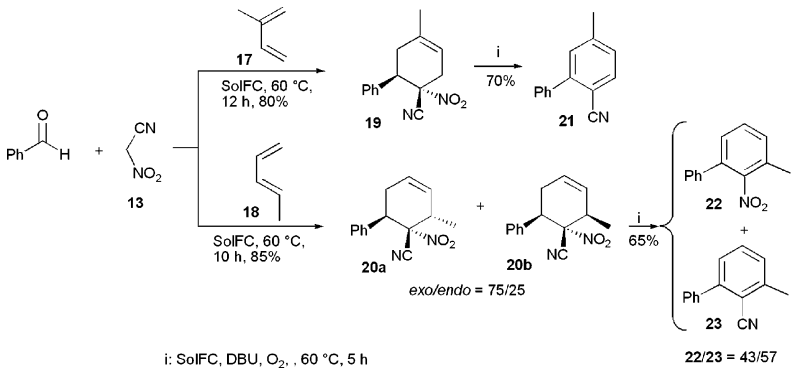
To convert **15** into biphenyls **16**, the nitrocyclohexenes were treated with 2.0 molar equivalents of DBU under SolFC in the presence of O_2 (0.5 bar) at 60 °C for 2–7 h. Satisfactory to good yields (45–80%, Table 3) were observed in the aromatization.

In addition, the reactions among benzaldehyde, nitro compound **13** and isoprene **17** or (*E*)-piperylene **18** have also been performed to evaluate the regio- and stereoselectivity of the process (Scheme 4).

In the first case, adduct **19** was exclusively formed and isolated in 80% yield, whereas with **18** the *exo*/*endo* adducts **20** were formed in a 75 : 25 ratio and isolated in 85% yield. The aromatization of the latter adducts gave a mixture of

Table 3 Synthesis of biphenyl-2-carbonitrile derivatives **16a**–**16k**

Compound	Ar	Temperature/°C to yield **15**	Time/h to yield **15**	Yield (%) of **15** from **12**	Time/h to yield **16**	Yield (%) of **16** from **15**
16a	Ph	60	5	86	3	75
16b	2-MeC_6H_4	60	6	85	6	57
16c	2-$MeOC_6H_4$	60	20	88	3	60
16d	2-$NO_2C_6H_4$	30	12	78	6	57
16e	2-$CF_3C_6H_4$	30	12	77	2.5	70
16f	2,4-$(MeO)_2C_6H_3$	30	12	80	5	45
16g	2-Cl-6-FC_6H_3	30	12	82	2	70
16h	2,4-$Cl_2C_6H_3$	60	6	84	5	70
16i	2,4,6-$Me_3C_6H_2$	30	12	78	3	62
16j	2,5-$(Br)_2$-4-$(OH)C_6H_2$	30	15	75	7	80
16k	4-$(CN)C_6H_4$	30	10	85	6	77



Scheme 4 Multicomponent process using isoprene or (*E*)-piperylene.

aromatic derivatives **22** and **23** due to the competitive elimination of nitrous acid to give **23** or hydrogen cyanide acid.

The authors planned to (i) operate on a large scale that would enable the use of the more efficient mechanical stirrer, allowing operation with equimolar amounts of **13** and **14**, (ii) perform the aromatization of cycloadducts **15** in the same pot on the crude products, and (iii) isolate **16** by recrystallization to reduce the use of costly organic solvents.

Thus, 4-cyanobenzaldehyde (40 mmol) was charged in a metallic reactor equipped with a mechanical stirrer, and at 30 °C, nitroacetonitrile **13** (40 mmol) and diene **14** (40 mmol) were subsequently added. After 10 h, the formation of cycloadduct **15k** was complete and DBU (80 mmol) was added *in situ*. The reactor was then sealed and left under mechanical stirring for 12 h at 30 °C under O_2 atmosphere (0.5 bar). The final biphenyl **16k** was isolated as a pure compound after filtration of the reaction mixture through a silica gel pad (sample : silica gel = 1 : 1 ratio) and recrystallization from acetone, in a satisfactory 72% overall yield.

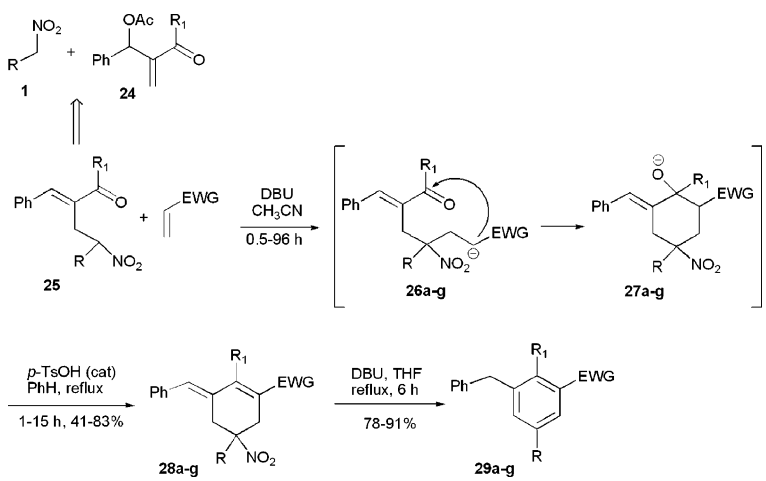
1.4 Tetra- and pentasubstituted benzene derivatives from Baylis–Hillman adducts *via* a [4 + 2] annulation strategy

Polysubstituted benzenes are highly useful entities, which are widely used in industry as well as in the laboratory and their regioselective preparation is one of the challenging problems in organic synthesis.[23]

During studies on the chemical transformations of Baylis–Hillman adducts, Kim *et al.*[24] envisaged that the they might be used as a four-carbon unit for the construction of tetrasubstituted benzene rings in a regiocontrolled manner. A Michael acceptor can serve as the remaining two-carbon unit as depicted in Scheme 5.

The synthesis of substrate **25** (four-carbon unit) was carried out by the addition–elimination protocol, starting from the acetate of the Baylis–Hillman adduct of methyl (or ethyl) vinyl ketone **24** and primary nitroalkane **1** in the presence of K_2CO_3.[25] The next step was the construction of six-membered ring intermediate **27** *via* the consecutive Michael addition of **25** to electron poor alkenes and aldol-type cyclization, which occurred in good yields, with the aid of DBU in MeCN. The crude diastereomeric mixture **27** was subjected, after usual work-up, to dehydration conditions (*p*-TsOH, benzene, reflux), giving **28** in good overall yields. The final step was the elimination of HNO_2 and isomerization of the *exo*-double bond to the desired benzene ring **29**. Due to the favourable aromatization effect, nitrous acid elimination and isomerization can occur simultaneously after treatment with DBU. Both the transformations were performed in one-pot and in good yields (Table 4).

As shown in Table 4, variation of the substituents of the Baylis–Hillman adducts or of the nitroalkanes did not alter the reactivity, which was instead affected by the nature of the Michael acceptor. The reaction rates of the addition of **25** to



Scheme 5 Synthesis of tetrasubstituted benzenes from Baylis–Hillman adducts.

Table 4 Synthesis of tetrasubstituted benzene derivatives **29a**–**29g**

Compound	R	R_1	EWG	Yield (%) of **28** from **25**	Yield (%) of **29** from **28**
29a	Me	Me	COMe	83	86
29b	Et	Me	COMe	75	78
29c	*n*-Bu	Me	COMe	71	80
29d	Me	Me	COEt	78	85
29e	Me	Et	COMe	73	89
29f	Me	Me	COOMe	65	80
29g	Me	Me	CN	41	91

the electron-poor alkenes were similar, but the reactivities in the aldol cyclization reaction were found to be different, much depending on the nature of the electron-withdrawing group of the Michael acceptors. This is presumably due to the different acidities of the α-protons near the EWG groups. However, the subsequent dehydration, nitrous acid elimination, and aromatization reactions from **27** to the final product **29** were all straightforward in these cases also.

Based on the importance and difficulties of regioselective synthesis of polysubstituted benzene derivatives, the same research group (Kim *et al.*) extended the above protocol to the synthesis of pentasubstituted benzene derivatives by using β-substituted Michael acceptors.[26] The authors reasoned that, if the sequential Michael addition–intramolecular aldolization steps could occur successfully with β-substituted Michael acceptors, pentasubstituted benzenes could be easily synthesized (Scheme 6). After several trials, the best reaction conditions found for the cyclization of **25** with **30** are the use of TBAF (tetra-*n*-butylammonium fluoride) as the catalyst in refluxing THF.

The crude mixtures of **31** under the influence of *p*-TsOH (10 mol%) in benzene, at refluxing temperature, afforded **32** as a mixture of isomers (*syn*/*anti*) in 27–71% yield. The reaction of **32** and K_2CO_3 (3 equiv.) in DMF at around 120–130 °C (3–7 h) gave the desired final pentasubstituted benzenes **33** in good yields (71–86%, Table 5). The elevated temperature is needed in order to aromatize both the isomers (*syn*/*anti*) of **32** into the final products.

In some cases, traces of the oxidized compounds **34b**–**34d** were observed in small amounts.

When ethyl 4,4,4-trifluorocrotonate (R_2 = OEt, R_3 = CF_3) is used as Michael acceptor, the *cis* and *trans* isomers of **32f** can be separated in 26% and 31% yield, respectively (Scheme 7). The elimination of nitrous acid was fast from *cis*-**32f** (rt, <1.5 h), but relatively slow for *trans*-**32f** (heating, 5 h). The elimination of HNO_2 for *cis*-**32f** must occur *via* the facile antiperiplanar pathway.[27] The elimination of HNO_2 from *trans*-**32f** must occur by the difficult *syn*-elimination mode.

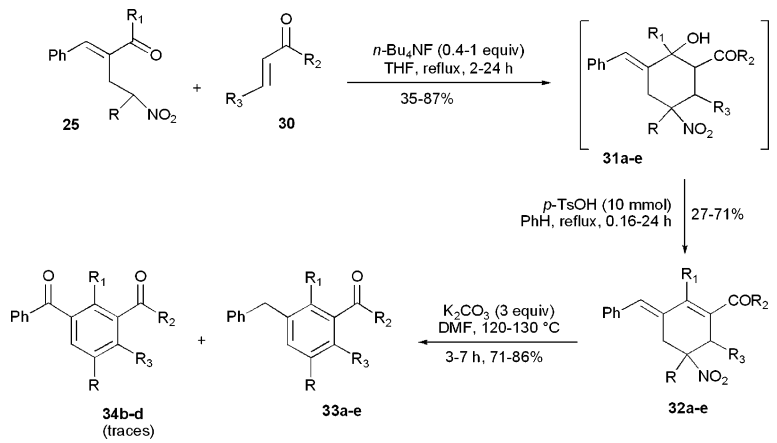
In addition, following the same procedure as above, the reaction of **25** with 2-cyclohexen-1-one offers the opportunity to prepare tetralone derivatives **36** in moderate yields (Scheme 8).

1.5 One-pot synthesis of benzene 1,2,3,5-tetracarboxylates

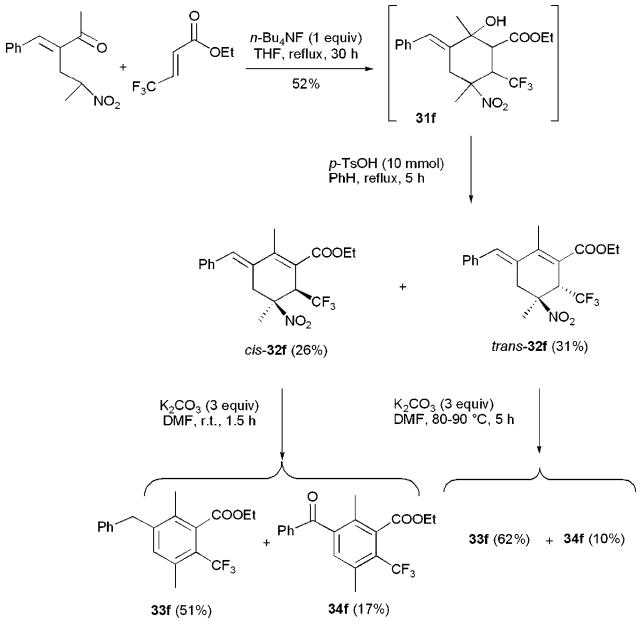
The chemistry of aromatic polycarboxylates is of great importance owing to the variety of bridging abilities of these compounds in the formation of inorganic–organic frameworks. In particular, multiple benzenecarboxylate ligands have been shown to be good building blocks in the design of metal–organic materials with desired topologies, owing to their rich coordination modes.[28] These compounds can be easily produced, in a one-pot way, by the reaction of alkyl propiolates **37** (2 equiv.) with alkyl 2-nitroethanoates **38**

Table 5 Pentasubstituted benzene derivatives **33a**–**33e**

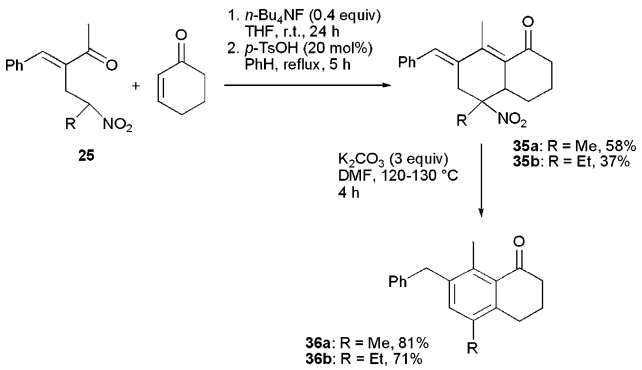
Compound	R	R_1	R_2	R_3	Yield (%) of **33** from **32**
33a	Me	Me	Ph	Ph	86
33b	Me	Me	Me	Ph	71
33c	Me	Et	Me	Ph	74
33d	Et	Me	Et	Ph	75
33e	Me	Me	OEt	Ph	71



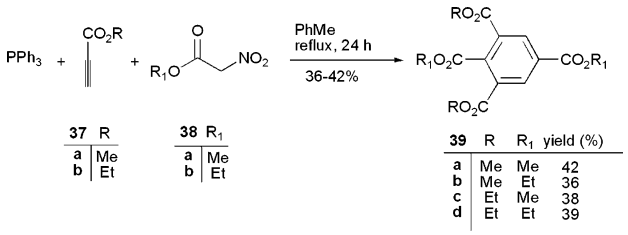
Scheme 6 Synthesis of pentasubstituted benzenes from Baylis–Hillman adducts.



Scheme 7 Synthesis of pentasubstituted benzenes from ethyl 4,4,4-trifluorocrotonate.



Scheme 8 Synthesis of tetralone derivatives.



Scheme 9 One-pot synthesis of benzene tetracarboxylates.

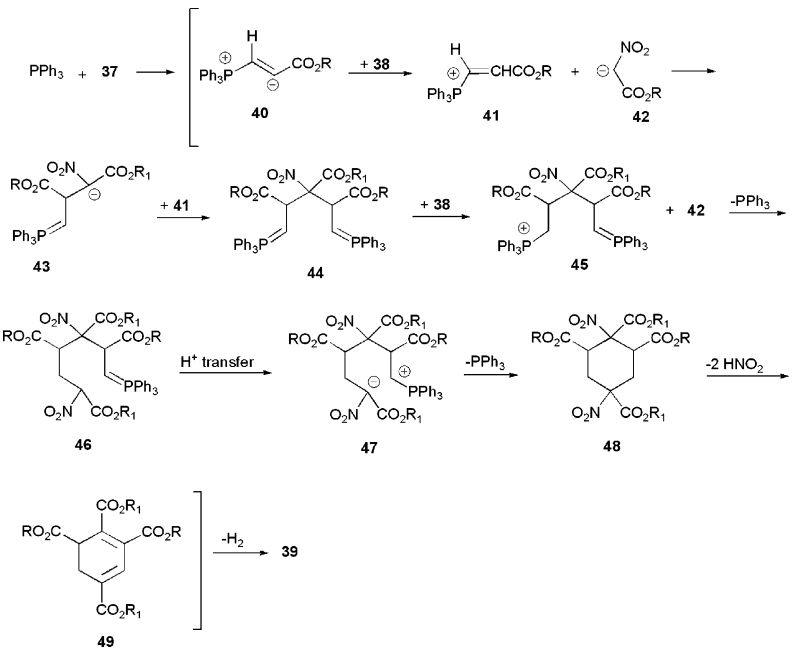
(2 equiv.), in the presence of triphenylphosphine (Ph_3P, 1.1 equiv.), under reflux in toluene (Scheme 9).[29]

The overall yields can be considered of great interest (36–42%, overall) since, on the basis of the proposed mechanism (Scheme 10), the one-pot process results as the sum of several steps.

Thus, a zwitterionic intermediate of type **40**, formed from Ph_3P and alkyl propiolate, is protonated by **38** to furnish **41**, which is attacked by the carbanion **42** to produce the ylide **43**. Further reaction of the latter with **41** leads to the bis-ylide **44**, which could undergo stepwise cyclization with **38** to produce the cyclohexane derivative **48** by elimination of PPh_3. The cyclohexadiene **49**, produced by elimination of HNO_2, is finally converted into **39** by aromatization.

2. Synthesis of benzene derivatives from 1,3-dinitropropanes

1,3-Dinitropropanes are an interesting class of difunctionalized derivatives that can be easily obtained from aldehydes and nitromethane.[30] The potential of these intermediates is due to the presence of two primary nitro groups that makes them valuable 1,3-dinucleophilic compounds, provided with good leaving groups. These characteristics have been found



Scheme 10 Presumable mechanism to furnish **39**.

useful for the preparation of a variety of polyfunctionalized benzene derivatives.

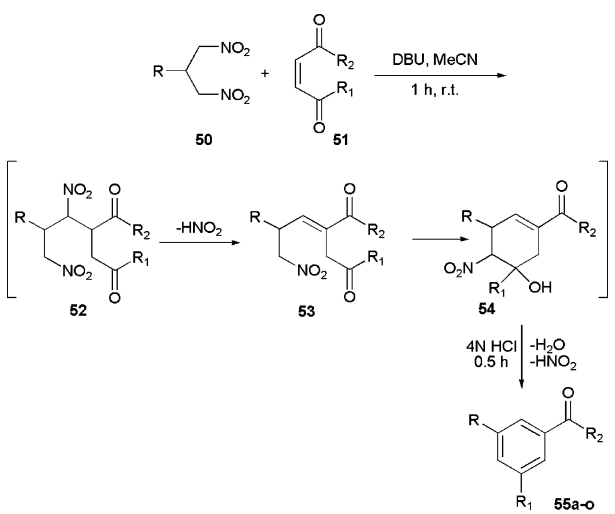
2.1 One-pot synthesis of 3,5-alkylated acetophenone and benzoate derivatives *via* an anionic domino process

3,5-Alkylated acetophenones and methyl benzoate derivatives are key building blocks for the preparation of a variety of important targets such as retinoic acids, which have potent antiproliferative activity in cervical cancer cells,[31a] HIV-protease activity inhibitors,[31b] tyrosine kinase inhibitors,[31c] HIV-1 integrase inhibitors,[31d] NMDA receptor antagonists,[31e] and a variety of other important targets.[31f,g]

In the past few years our group reported the direct formation of carbon–carbon double bonds under basic conditions (1,8-diazabicyclo[5.4.0]undec-7-ene, DBU) through the conjugate addition of primary or secondary nitroalkanes to electron-poor alkenes bearing two electron withdrawing groups in the α- and β-positions.[32] The application of this strategy to the reaction of 1,3-dinitroalkanes **50**,[30,33] with conjugate enediones **51**, allows the one-pot preparation of 3,5-alkylated acetophenones and methyl benzoate derivatives **55** (Scheme 11).[34] In fact, the reaction in acetonitrile of **50** with **51** using DBU as base, proceeds as an anionic domino process in which a regioselective Michael addition (yielding **52**) is presumably followed by the elimination of nitrous acid, to give the corresponding nitro-enone derivatives **53**.

The latter compounds are prone to an intramolecular nitroaldol (Henry) reaction, yielding the nitrocyclohexenols **54** in less than 1 h. The formation of **54** can be easily observed *in situ* by TLC. Treatment of **54** with 4 N hydrochloric acid favours the elimination of water and a further molecule of nitrous acid, thus allowing the one-pot synthesis of the target molecules **55** in 42–77% yield (Table 6).

This one-pot procedure formally includes five different transformations: (i) Michael addition, (ii) nitrous acid elimination, (iii) intramolecular nitroaldol reaction, (iv) water elimination, and (v) elimination of a further molecule of nitrous acid.



Scheme 11 One-pot syntheses of 3,5-alkylated acetophenones and methyl benzoates.

Table 6 Disubstituted acetophenone and benzoate derivatives **55a–55o**

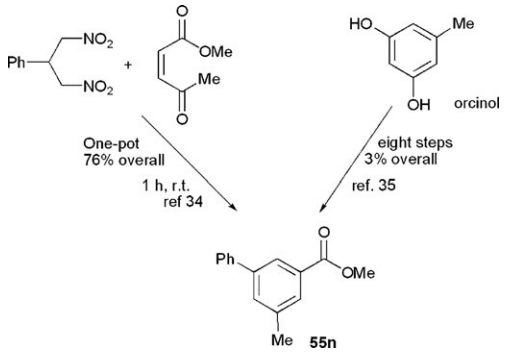
Compound	R	R_1	R_2	Yield (%) of **55** from **51**
55a	n-C_5H_{11}	Me	Me	55
55b	n-C_5H_{11}	Ph	Me	62
55c	n-C_8H_{17}	Me	Me	58
55d	$Ph(CH_2)_2$	Me	Me	57
55e	n-C_8H_{17}	Ph	Me	61
55f	n-C_5H_{11}	Me	OMe	60
55g	$Ph(CH_2)_2$	Me	OMe	59
55h	m-$CF_3C_6H_4$	Me	Me	58
55i	p-$MeOC_6H_4$	Ph	Me	61
55j	m-$CF_3C_6H_4$	Me	OMe	60
55k	p-$MeOC_6H_4$	Me	OMe	77
55l	p-$MeOC_6H_4$	Me	Me	66
55m	m-$NO_2C_6H_4$	Me	OMe	42
55n	Ph	Me	OMe	76
55o	2-Py	Me	OMe	43

It is important to note the key role of the dinitro compounds **50**, whereby their nitro functionalities act both as good electron withdrawing groups and excellent leaving groups. This makes it possible to generate two carbon–carbon double bonds, and so strongly promote the drive to aromatize the ring system.

A significant applicative example of this regiodefined procedure is the synthesis of the compound **55n**, a key building block in the preparation of a farnesyl-protein transferase inhibitor. This has previously been prepared in eight steps from orcinol in only 3% overall yield (Scheme 12),[35] while, following the above procedure, the same compound has been obtained in a one-pot way and in 76% overall yield.

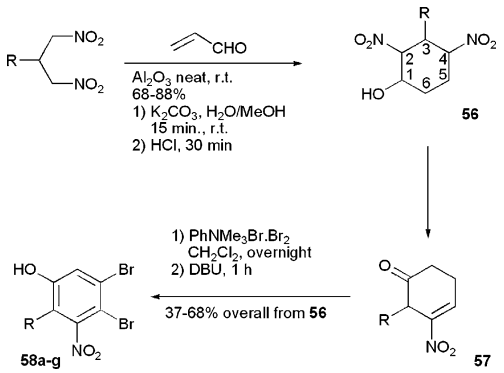
2.2 Three-step synthesis of brominated phenols

Phenols are of great interest in organic synthesis since they are found in a large number of biologically active compounds and/or are employed as key building blocks for the preparation of important targets.[36] Of particular interest are polyfunctionalized compounds such as nitrophenol derivatives and bromophenols. The former possess a range of versatile applications as dyes[37] and pharmaceutical agents or their intermediates.[38] Bromophenols are present in algae, such as *Polysiphonia lanosa*, where they are thought to be responsible for the cytotoxic activity against human colon adenocarcinoma.[39] However, the synthesis of these classes of compounds suffers, in general, from low regioselectivity and/or rearrangements



Scheme 12 Comparative synthesis of **55n**.

Table 7 Synthesis of brominated phenols **58**



Compound	R	Yield (%) of **56** (reaction time/h)	Yield (%) of **58** from **56**
58a	n-C_5H_{11}	88 (8)	44
58b	$Ph(CH_2)_2$	74 (6)	46
58c	Ph	71 (4)	51
58d	p-$MeOC_6H_4$	76 (18)	37
58e	p-CNC_6H_4	70 (20)	68
58f	m-$NO_2C_6H_4$	68 (48)	54
58g	2-Py	71 (6)	47

that make the introduction of alkyl groups, longer than an ethyl group, difficult.[40]

An efficient preparation of these molecules has been pointed out starting from the reaction of 2-alkylated 1,3-dinitropropanes with acrolein under basic conditions (basic Al_2O_3, neat).[41] Thus, as reported in Table 7, the reaction proceeds firstly trough a tandem Michael–nitroaldol (Henry) reaction, allowing the one-pot formation of a diastereomeric mixture of the cyclohexanols **56** (68–88% yields). Treatment of compounds **56** with potassium carbonate, followed by acidic work up, transforms them to nitrocyclohexenones **57**, *via* water elimination from C1–C2 and nitro to carbonyl conversion (Nef reaction)[10] at C4. Reaction of the crude **57** with phenyltrimethylammonium tribromide (a well-known α-keto brominating agent[42]) allows the direct synthesis of nitro dibromophenols **58**. All the reactions proceeded smoothly to afford the corresponding substituted phenols **58** in satisfactory yields (37–68% overall, from **56**).

Although mechanistic evidence for the conversion of **57** to **58**, is not available a possible hypothesis could be that reported in Scheme 13.

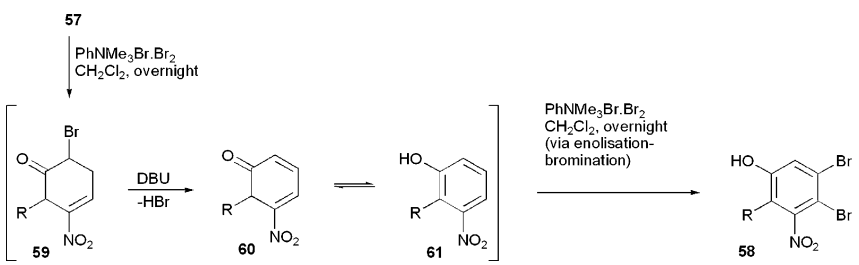
Nitrocyclohexenone **57**, after both bromination and HBr elimination, is converted into the structure **60** in equilibrium with its enol form **61**. Subsequent bromination of the latter allows the one-pot synthesis (from **57**) of the target phenols **58**.

Whatever the details of the mechanism, the reaction represents a reproducible method for the preparation of a variety of brominated phenols from acyclic precursors. It should be noted that the synthesis of substituted biphenyls (compounds **58c**–**58f**) can also be accomplished, and the reaction conditions allow the survival of other functionalities such as methoxy and nitrile.

2.3 Two-step synthesis of symmetrical diarylamines

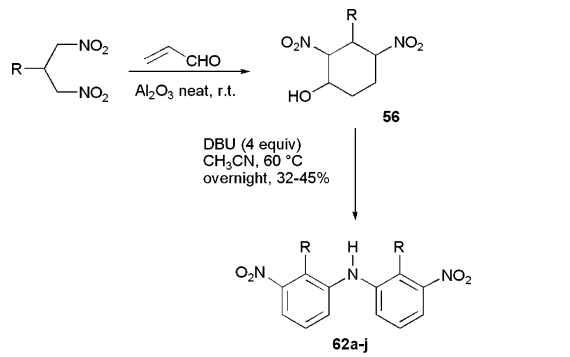
Arylamines are found in pharmaceuticals, materials with important electronic properties, and ligands for early metal catalysts.[43] Usually, their preparation needs the presence of a preformed aromatic system. However, 1,3-dinitroalkanes have recently been demonstrated to be key acyclic precursors for the preparation of symmetrical diarylamines.[43]

The synthetic strategy is similar, at the beginning, to those reported for the preparation of brominated phenols **58** (Table 7). In fact, reaction of dinitro derivatives with acrolein (Table 8), under basic conditions (neat basic alumina) affords **56** in a one-pot sequence. After extraction, treatment of the crude **56** with 4 equivalents of DBU, in acetonitrile as solvent, and warming overnight at 60 °C, directly produces the



Scheme 13 Hypothesis of the mechanism for the conversion of **57** to **58**.

Table 8 Synthesis of diarylamines **62**



Compound	R	Yield (%) of **62** from dinitroalkanes
62a	Ph	42
62b	*p*-$CF_3C_6H_4$	36
62c	*p*-$MeOC_6H_4$	37
62d	$Ph(CH_2)_2$	36
62e	$Me(CH_2)_4CH{=}CH(CH_2)_2$	35
62f	*i*-Pr	32
62g	*n*-Pr	36
62h	*n*-C_5H_{11}	38
62i	*n*-C_8H_{17}	36
62j	*c*-C_6H_{11}	45

diarylamines **62** in satisfactory overall yields (32–45%) from dinitroalkanes.

The mechanism of the conversion of **56** to **62** is not clear and the formation of **62** is an unexpected behaviour of compounds **56** under the reported conditions. A possible pathway could be firstly, (i) the conversion of the intermediate **56** into a 2-alkyl-1,3-dinitroaromatic system (in the same way as for mononitrocyclohexanols),[12,34] followed by (ii) a reductive coupling reaction (with loss of NO_2),[44] that leads to the diamine derivatives **62**.

Anyway, independently of the mechanism, the reaction constitutes a new, reproducible, useful method for the preparation of a range of symmetrical diarylamines from acyclic precursors.

2.4 Synthesis of polysubstituted nitrobenzene derivatives from Baylis–Hillman adducts

Recently, Kim *et al.* reported the preparation of polysubstituted phenols starting from the Baylis–Hillman adducts **63** and dimethyl acetone-1,3-dicarboxylate.[45] In the synthesis, the Baylis–Hillman adducts served as a 1,3-dielectrophilic three-carbon component and dimethyl acetone-1,3-dicarboxylate as the 1,3-dinucleophilic three-carbon unit. During the investigations, the same authors presumed that also 1,3-dinitroalkane derivatives could act the role of an effective 1,3-dinucleophilic component in the reaction providing polysubstituted nitrobenzene derivatives as shown in Table 9.[46]

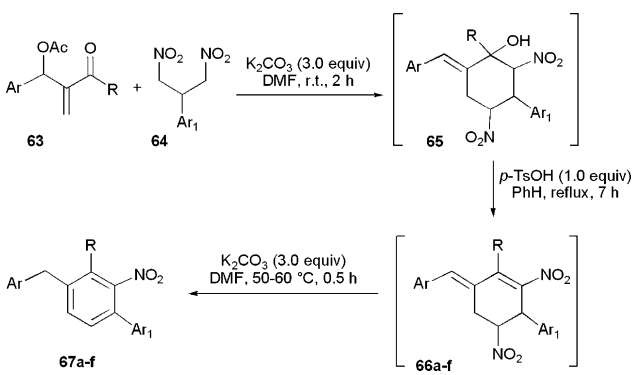
In fact, the reaction of the Baylis–Hillman acetates **63** and 1,3-dinitroalkanes **64** in the presence of K_2CO_3 in DMF at room temperature allows the formation of a diastereomeric mixture of the nitrocyclohexanols **65**. The latter were then converted into the nitroalkenes **66**, as a *syn*/*anti* mixture, by treatment with *p*-TsOH under refluxing benzene.[47]

After the column separation of **66** as a mixture, the aromatization was completed by treatment with K_2CO_3–DMF, at 50–60 °C.

The mechanism for the formation of nitroarenes **67** could be thought of as follows: (i) S_N2' type substitution of **64** at the primary position of **63**, (ii) intramolecular nitroaldol reaction to form the diastereomeric mixture **65**, (iii) *p*-TsOH-catalyzed dehydration to afford **66**, (iv) elimination of HNO_2 and concomitant isomerization of the double bond to **67**.

Several substrates can be aromatized by this [3 + 3] annulation strategy and a variety of polysubstituted nitrobenzene derivatives can be obtained in 19–28% overall yields that,

Table 9 Synthesis of polysubstituted nitrobenzenes **67**



Compound	Ar	Ar_1	R	Yield (%) of **66** from **63**	Yield (%) of **67** from **66**
67a	Ph	Ph	Me	38	64
67b	*p*-ClC_6H_4	*p*-$MeOC_6H_4$	Me	48	58
67c	*p*-MeC_6H_4	Ph	Me	34	56
67d	*p*-ClC_6H_4	*p*-$NO_2C_6H_4$	Me	41	58
67e	Ph	Ph	Et	38	60
67f	Ph	2-Naphthyl	Me	40	61

considering the conversion of the starting materials to the final products as a multistep sequence, can be judged of interest.

Conclusions

Nitroalkanes are firmly established as pivotal intermediates in many synthetic processes resulting in the preparation of aromatic derivatives. As reactive nucleophiles, nitroalkanes are deeply involved in the nucleophilic addition to electrophiles such as carbonyl derivatives (nitroaldol–Henry reaction) or electron-poor alkenes (conjugate addition).

Moreover, the nitro group is a good leaving group, favouring the formation of carbon–carbon double bonds *via* nitrous acid-elimination.

Thus, the availability of a variety of nitroalkanes, and their chemical versatility and reactivity make these compounds emerging, ideal acyclic precursors for the preparation of a collection of benzene derivatives.

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