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

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The reaction of primary 1,3-dinitroalkanes with 2-ene-1,4-dione or 2-ene-4-oxo ester derivatives in acetonitrile with DBU as base, allow the one pot synthesis of 3,5-alkylated acetophenones and methyl benzoate derivatives respectively *via* an anionic domino process.

The synthesis of complex molecules is traditionally performed by a chain of separate steps, each of which requires its own conditions, reagents, solvent and catalyst. After each reaction is complete, the solvent and the waste products are removed and discarded, and the intermediate product is separated and purified. Environmental and economic pressures are now forcing the chemical community to search for more efficient ways of performing chemical transformations.[1] These issues can be addressed by the development of new synthetic methods that, by bringing together simple components, can generate complex structures in one pot, in much the same way as occurs in nature. In this context the anionic domino transformations are of great interest.[2]

Aromatic compounds are important reagents in organic synthesis.[3,4] In particular, 3,5-alkylated acetophenones and methyl benzoate derivatives are key building blocks in the synthesis of retinoic acids, which have potent anti-proliferative activity in cervical cancer cells,[4a] HIV-protease activity inhibitors,[4b] tyrosine kinase inhibitors,[4c] HIV-1 integrase inhibitors,[4d] NMDA receptor antagonists,[4e] and a variety of other important targets.[4f,g] Aromatization of acyclic precursors is undoubtedly a useful reaction in the synthesis of highly substituted aromatic rings,[5] and several methods are known for this purpose.[6] We now wish to report an unprecedented, one pot aromatization of 1,3-dinitroalkanes through their reaction with enediones. In fact, the nucleophilicity of nitroalkanes and the ability of the nitro functionality to act as a leaving group[7] makes it possible to usefully synthesise a variety of acetophenone and methyl benzoate derivatives using an anionic domino process.

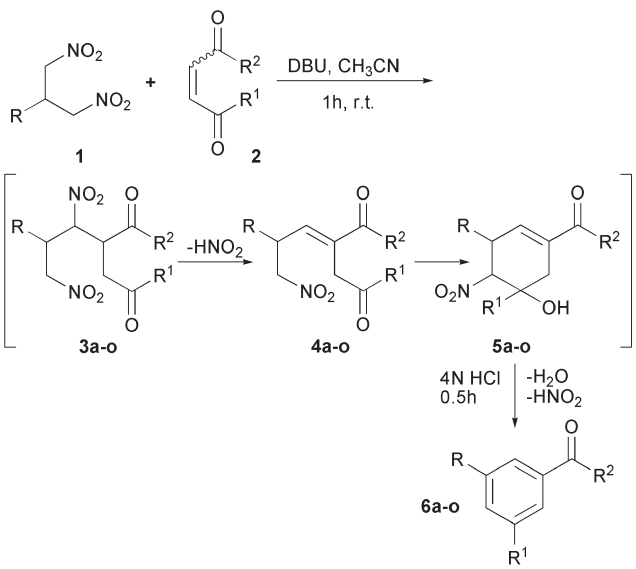
In the last few years we have reported the direct formation of carbon–carbon double bonds under basic conditions (1,8-diazabicyclo[5.4.0]undec-7-ene, DBU) through the conjugate addition of primary or secondary nitroalkanes leading to electron-poor alkenes bearing two electron withdrawing groups in the α- and β-positions.[8] The application of this strategy to the reaction of 1,3-dinitroalkanes **1**,[9] with conjugate enediones **2**, allows the one pot preparation of the title compounds. In fact, the reaction in acetonitrile of **1** with **2** (Scheme 1) using DBU as base, proceeds as a tandem process in which a regioselective Michael addition (yielding **3**) is presumably followed by the elimination of nitrous acid, to give the corresponding nitro-enone derivatives **4**.

The latter compounds are prone to an intramolecular nitroaldol (Henry) reaction, yielding the nitrocyclohexenols **5** in less than 1 h.

The formation of **5** can be easily observed *in situ* by TLC. Treatment of **5** with 4M hydrochloric acid favours the elimination of water and a further molecule of nitrous acid, thus allowing the one pot synthesis of target molecules **6** in 42–77% yield (Table 1). When 1-phenyl-2-penten-1,4-dione was used as the Michael acceptor (Table 1, Entries b, e and i), only the listed regioisomers were formed, the structures of which were determined from their MS spectra (CH_3CO^+ at m/z = 43).

Our procedure for the one pot preparation of aromatic systems from open chain compounds therefore 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.

It is important to note the key role of the dinitro compounds **1**, whereby their nitro functionalities act both as good electron-withdrawing groups and good leaving groups. This makes it possible to generate two carbon–carbon double bonds, and so strongly promote the drive to aromatize the ring system. Several



Scheme 1

† Electronic Supplementary Information (ESI) available: General procedure for the preparation of type **6** compounds, analytical data of compounds **6a–o** and their ^{13}C NMR spectra as criterion of purity. See http://www.rsc.org/suppdata/cc/b5/b500846h/

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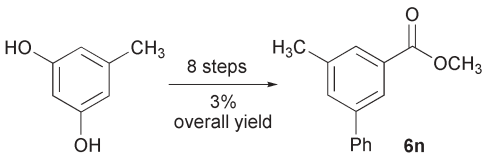
Table 1 A summary of compounds of type **6** prepared

Entry	R	R^1	R^2	Yield of **6** (%)[a]
a	$CH_3(CH_2)_4$	CH_3	CH_3	55
b	$CH_3(CH_2)_4$	Ph	CH_3	62
c	$CH_3(CH_2)_7$	CH_3	CH_3	58
d	$PhCH_2CH_2$	CH_3	CH_3	57
e	$CH_3(CH_2)_7$	Ph	CH_3	61
f	$CH_3(CH_2)_4$	CH_3	CH_3O	60
g	$PhCH_2CH_2$	CH_3	CH_3O	59
h	*m*-$CF_3C_6H_4$	CH_3	CH_3	58
i	*p*-$MeOC_6H_4$	Ph	CH_3	61
j	*m*-$CF_3C_6H_4$	CH_3	CH_3O	60
k	*p*-$MeOC_6H_4$	CH_3	CH_3O	77
l	*p*-$MeOC_6H_4$	CH_3	CH_3	66
m	*m*-$NO_2C_6H_4$	CH_3	CH_3O	42
n	Ph	CH_3	CH_3O	76
o	2-Py	CH_3	CH_3O	43

[a] Yield of pure, isolated product.



Scheme 2

advantages can be seen in our approach, such as the avoidance of *ortho–meta–para* mixture formation, common in conventional aromatic synthesis. In fact, our regiodefined preparation method for acetophenone and benzoate derivatives is very difficult to undertake by the electrophilic substitution of benzenes. In this context, a significant example is our synthesis of compound **6n** (*i.e.* Table 1, Entry n), a key building block in the preparation of a farnesyl-protein tranferase inhibitor. This has previously been prepared in eight steps from orcinol in only 3% overall yield (Scheme 2),[10] while we obtained the same compound *via* our one pot method in 76% isolated yield, starting from **1** (R = Ph) and **2** (R^1 = CH_3, R^2 = CH_3O).

Moreover, in our method, by making an appropriate choice of starting 1,3-dinitroalkane and/or the enedione, the opportunity is offered to predict the relative nature and positions of the substituents in the products. It also consents to the insertion of several *n*-alkyl groups without the isomerization problems typical of classical Friedel–Crafts alkylation. Finally, the possibility of one pot introduction of aromatic (compounds **6h–n**) and heteroaromatic (compound **6o**) substituents avoids the need for the cross-coupling reactions that are usually employed in the preparation of biphenyl systems.[11]

In conclusion, we have developed the first one pot synthesis of the title compounds with satisfactory to good yields by the aromatization of simple, low cost starting materials through an anionic domino process, promoted by highly versatile nitroalkanes.

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