Pergamon

Tetrahedron Letters, Vol. 37, No. 42, pp. 7591-7594, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01668-1

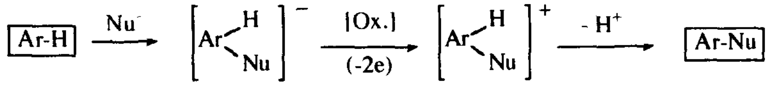
Direct Coupling of Carbon Nucleophiles with *m*-Dinitrobenzene: A Novel Fluoride Promoted Nucleophilic Aromatic Photosubstitution for Hydrogen

Maria Cervera and Jordi Marquet*

[a]*Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain.*

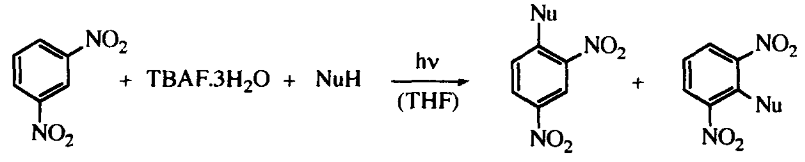
Abstract : Useful yields are achieved in the C-arylation of ketones, nitriles and esters through direct hydrogen nucleophilic aromatic photosubstitution of *m*-dinitrobenzene, promoted by fluoride anion.

Nucleophilic aromatic substitution is one of the more widely used approaches for the functionalization of aromatics and forms the backbone of numerous important syntheses of pharmaceuticals and potential drugs.[1] The majority of reactions between nucleophiles and electron-deficient aromatic compounds can be separated into two classes. The most common is nucleophilic aromatic substitution of halide and, in particular, the reaction of nucleophiles with halogenated nitroaromatics.[2] These reactions are believed to proceed via attack of a nucleophile on the nitroarene generating an anionic σ-complex, followed by departure of the leaving group and rearomatization.[3] The second is nucleophilic aromatic substitution for hydrogen, which formally requires the replacement of a hydride ion. These reactions happen "spontaneously", consuming part of the starting material (the nitroaromatic is reduced) in the oxidation of the anionic σ-complex, or they are promoted by the addition of external oxidants (Scheme 1).[4] The need of halogenated aromatics (with their associated environmental concern) in the first class reactions, and the low yields[5] (with very few exceptions)[6] and the lack of generality[7] observed in the second class reactions, can be cited as main drawbacks of these synthetic procedures. In addition, some of the substances used as oxidants, such as permanganate, are hazardous in their own right, negating any environmental advantages gained by eliminating halogen derivatization. More recently, the removal of a proton and two electrons from σ-complexes has been shown to be facilitated in a new class of reaction referred to as vicarious nucleophilic substitution (VNS).[8] These reactions require a good leaving group[9], mostly halide[10], in a position α to the nucleophile such that decomposition of the corresponding σ-complex results in β-elimination of HX. While this class of reaction has provided useful mechanistic insight and a significant synthetic utility, the requirement for an auxiliary leaving group still persists.



Scheme 1

Typical nucleophilic aromatic substitutions of hydrogen with "spontaneous" oxidation of the intermediate σ-complex give very poor yields probably due to two main reasons: 1) the single electron transfer from the σ-complex to the starting nitroaromatic, that triggers the process, is an endergonic step and therefore it must be rather slow; 2) the efficiency of an electron transfer nitroaromatic reduction is very dependent on the steps that follow the ET,[11] in this case a proton transfer[12] is inefficient in the usual strong basic media. Therefore, we decided to test the use of irradiation (the excited states are more easily oxidised and reduced than the



1 **2**

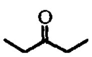
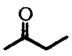
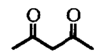
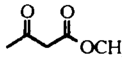
Scheme 2

Table 1.- Phototoreactions of m-DNB with carbon nucleophiles in the presence of TBAF in the absence of solvent.

Exp.	Nucleophile	Conditions[a]	Recovered *m*-DNB (%)	**1** Yield (%)[b]	**2** Yield (%)[b]	Global yield (%)[b]
1	CH_3COCH_3	3.5 h, r.t., **hv UV**	---	**67**	---	**67**
2		3.5 h, r.t., hv VIS	8	21	---	21
3		3.5 h, r.t., dark	10	10	---	10
4	CH_3CN	1.5 h, r.t., **hv UV**	---	**65**	**22**	**87**
5		1.5 h, r.t., hv VIS	---	traces	---	traces
6		3.5 h, r.t., dark	42	---	---	---
7	CH_3CO_2Et	4 h, r.t., **hv UV**	37	**64**	**20**	**84**
8		4 h, r.t., hv VIS	37	5	traces	5
9		3.5 h, r.t., dark	32	9	traces	9

[a] Nucleophile as a solvent. 3 eq. of $FTBA.3H_2O$ Inert atmosphere. 125W Medium pressure Hg lamp with pyrex filter in the UV photoreactions. Daylight in the VIS reactions. [b] Products of C-arylation. Preparative yields based on non recovered starting material.

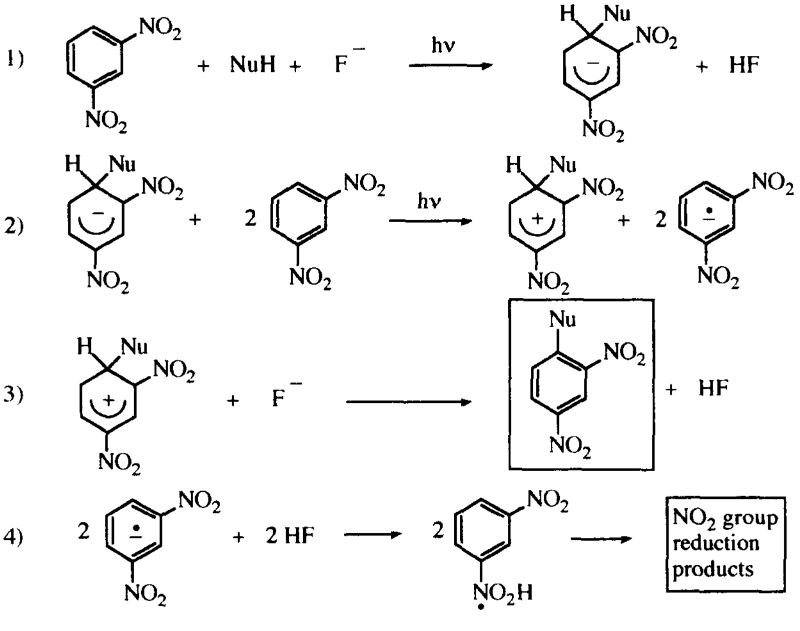
Table 2.- Photoreactions of m-DNB with carbon nucleophiles in the presence of TBAF in THF as a solvent.

Exp.	Nucleophile[a]	Conditions[b]	Recovered *m*-DNB (%)	**1** Yield (%)[c]	**2** Yield (%)[c]	Global yield (%)[c]
1	$PhCH_2CN$	4 h, THF, r.t., hv UV	24	48	8	56
2		3 h, THF, r.t., hv UV	29	49	---	49
3		3 h, THF, r.t., hv UV	33	57[d] 26[e]	---	83
4		3 h, THF, r.t., hv UV	quant.	---	---	---
5		3 h, THF, r.t., hv UV	56	79[f]	---	79

[a] Excess of nucleophile (10 eq.). [b] 3 eq. of $FTBA.3H_2O$. Inert atmosphere. 125W Medium pressure Hg lamp, pyrex filter. [c] Products of C-arylation. Preparative yields based on non recovered starting material. [d] 1-(2,4-dinitrophenyl)butan-2-one. [e] 3-(2,4-dinitrophenyl)butan-2-one. [f] Methyl 2-(2,4-dinitrophenyl)acetylacetate.

corresponding ground states) to overcome the first obstacle, and the use of tetrabutylammonium fluoride (TBAF) as activating agent to overcome the second. It is well known that fluoride anion activate nucleophiles with acidic hydrogens (through formation of strong hydrogen bonds), but a TBAF solution is essentially neutral.[13] In addition, HF is an acid strong enough ($pK_a \approx 15$ in DMSO)[14] to be able to quench by protonation the nitroaromatic radical anion precluding the back electron transfer and leading to the photoreduction of the starting nitroaromatic and to the oxidation of the σ-complex and to the final substitution of hydrogen. Complete reduction of a nitro group (6 electrons)[11] would correspond to the oxidation of three σ-complexes (2 electrons each). Only a few reports of hydrogen photosubstitution exist in the literature,[15] and all of them include weakly basic nucleophiles as cyanide anion.[16]

In Table 1 (Scheme 2), the photoreactions (UV light, pyrex filter, exp. 1, 4, 7) of *m*-dinitrobenzene (*m*-DNB) with different nucleophiles, in the presence of TBAF, and in inert atmosphere are described. Thus, in experiments 1 and 4 the photoreaction of *m*-DNB in the presence of TBAF and using acetone or acetonitrile as nucleophile-solvent led to excellent yields of hydrogen photosubstitution. The yields obtained of the C-arylated products are of the same order or higher than the reported ones for the corresponding VNS reactions of *m*-DNB with chloroacetone (68%)[17] and chloroacetonitrile (30%)[18]. A similar result was obtained using ethyl acetate (exp. 7). The influence of the irradiation was investigated by carrying out blank experiments in the dark. Less than 10% yield of the condensation products (1 + 2) was obtained in each case. Curiously enough, in all the cases, consumption of the starting *m*-DNB occurred to a significant extent. Visible light had no appreciable effect except in the case of the reaction carried out in acetone where a 21% yield of 2,4-dinitrophenylpropanone was obtained. In any case, UV irradiation was necessary to obtain good preparative yields. Attempted photoreactions carried out without taking any precaution to exclude oxygen led only to the recovery of the starting *m*-DNB. The particular properties of TBAF as a promoter of the photoreaction were demonstrated by performing exp. 1 (Table 1) using potassium *t*-butoxide instead of TBAF. No hydrogen substitution product could be detected.



Scheme 3

In Table 2, related photoreactions carried out using THF as a solvent are described. The yields (C-arylated products) range from fair to good, making this photoreaction the method of choice for preparing these substituted aromatics without using auxiliary leaving groups. Results of experiments 3, 4, and 5, suggest that contrary to previous interpretations found in the literature for fluoride promoted alkylations of ketones,[13] the fluoride anion in our case seems to directly activate the hydrogens bonded to carbon in the keto tautomer. Thus, exp. 3 (Table 2) shows predominant formation of the product of kinetic control (attack through the carbon that has the more acidic hydrogens). This result is difficult to rationalise as occurring via the intermediacy of a fluoride activated enol. In addition, the yields of the photoreactions seem to be inversely dependant on the enol ratio in the tautomeric equilibrium. Thus, the photoreaction fails using a nucleophile with a high enol content such as acetylacetone (exp. 4, Table 2), but it gives good results for compounds having a lower enol content in the equilibrium as methyl acetylacetonate (exp. 5, Table 2).

In Scheme 3, a mechanistic hypothesis that can justify the reported results is advanced. Thus, the success of the process seem to be due to the joint action of UV irradiation (improvement of the steps 1 and especially 2) and the fluoride anion (activation of the nucleophile in essentially neutral conditions, step 1, and protonation of the *m*-DNB radical anion by the conjugate acid, step 4). The deleterious effect of oxygen is probably related to the quenching of the excited states involved in the photoreaction.

Acknowledgements. Financial support from "M.E.C." of Spain through the project DGICYT PB93-0895 and from "Generalitat de Catalunya" through the projects GRQ93-2070 and 1995SGR00469 are gratefully acknowledged.

REFERENCES

1. Buncel, E.; Dust, J.M.; Terrier, F. *Chem. Rev.* **1995**, *95*, 2261.
2. a) Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* **1951**, *49*, 273.
3. Miller, J. "Aromatic Nucleophilic Substitution", Elsevier: Amsterdam, **1968**.
4. Terrier, F. "Nucleophilic Aromatic Displacement. The Influence of the Nitro Group" Chapter 5. VCH Publishers, Inc. New York, **1991**.
5. a) Zimmermann, W.Z. *Physiol. Chem.* **1935**, *233*, 257. b) King, T.J.; Newall, C.E. *J. Chem. Soc.* **1962**, 367. c) Foster, R.; Mackie, R.K. *Tetrahedron*, **1962**, *18*, 1131.
6. a) Hamana, M.; Iwasaki, G.; Saeki, S. *Heterocycles*, **1982**, *17*, 177. b) Iwasaki, G.; Hamana, M.; Saeki, S. *ibid.* **1982**, *19*, 162. c) Iwasaki, G.; Wada, K.; Saeki, S.; Hamana, M. *ibid.* **1984**, *22*, 1811. d) Stern, M.K.; Hileman, F.D.; Bashkin, J.K. *J. Am. Chem. Soc.* **1992**, *114*, 9237.
7. a) Rajanbabu, T.V.; Fukunaga, T. *J. Org. Chem.* **1984**, *49*, 4571. b) Rajanbabu, T.V.; Reddy, G.S.; Fukunaga, T. *J. Am. Chem. Soc.* **1985**, *107*, 5473. c) Rajanbabu, T.V.; Chenard, B.L.; Petti, M.A. *J. Org. Chem.* **1986**, *51*, 1704.
8. Makosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282, and references therein.
9. a) Traynelis, V.J.; McSweeney, J.V. *J. Org. Chem.* **1966**, *31*, 243. b) Katritzky, A.R.; Laurenzo, K.S. *J. Org. Chem.* **1988**, *53*, 3978. c) Ayyangar, N.R.; Naik, S.N.; Srinivasan, K.V. *Tetrahedron Lett.* **1990**, *31*, 3217.
10. a) Makosza, M.; Wojciechowski, K. *Tetrahedron Lett.* **1984**, *25*, 4791. b) Makosza, M.; Golinski, J.; Baran, J. *J. Org. Chem.* **1984**, *49*, 1488.
11. a) Mir, M.; Marquet, J.; Cayon, E. *Tetrahedron Lett.* **1992**, *33*, 7053. b) Dopp, D. *Topics in Current Chem. 1975*, **55**, 49.
12. a) Sundararajan, K.; Ramakrishnan, V.; Kuriacose, J.C. *Indian J. Chem., Sect B* **1983**, *22B*, 257. b) Ibid. *J. Photochem.* **1984**, *27*, 61.
13. Clark, J.H. *Chem Rev.* **1980**, *80*, 429.
14. Bordwell, F.G. *Acc. Chem. Res.* **1988**, *21*, 456.
15. Cornelisse, J.; Havinga, E. *Chem. Rev.* **1975**, *75*, 353.
16. a) Letsinger, R.L.; McCain, J.H. *J. Am. Chem. Soc.* **1966**, *88*, 2884. b) Letsinger, R.L.; McCain, J.H. *J. Am. Chem. Soc.* **1969**, *91*, 6425.
17. Wrobel, Z.; Makosza, M. Pol. J. Chem. 1992, 66, 2005.
18. Makosza, M.; Wenäll, M.; Golinski, M.; Kinowski, A. *Bull. Acad. Pol. Sci. Ser. Sci. Chim.* **1985**, *33*, 9.

(*Received in UK* 15 *July* 1996; *revised* 16 *August* 1996; *accepted* 23 *August* 1996)