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A novel and efficient arylation of malononitrile catalyzed by nickel(0) complexes

Henri Jean Cristau,[a,*] Rachel Vogel,[a] Marc Taillefer*[a] and Alain Gadras[b]

[a]*Laboratoire de chimie organique, ENSCM (UMR 5076), 8 rue de l'Ecole Normale, 34296 Montpellier cedex 05, France*

[b]*CRIT DECINES, Rhône-Poulenc Industrialisation, 24 rue Jean Jaures, 691920 Decines, France*

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Abstract

We report the first use of a nickel catalyst for the direct arylation of a β-difunctionalized compound, the malononitrile, from halogenated aromatic substrates. The catalytic system is quite simple: $Ni(PPh_3)_3$, generated in situ from $NiBr_2(PPh_3)_2$, PPh_3 and zinc. Good yields and excellent selectivities have been obtained in α-arylmalononitriles from iodobenzene, but also from bromo- or chloro-aromatic substrates.
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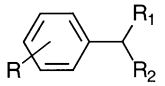
α-Arylmalononitriles, α-arylmalonates and α-aryl-β-cyanoacetates are important intermediates in the synthesis of useful organic compounds such as bioactive materials[1] and heterocyclic compounds.[2] Moreover, *p*-phenylene dimalononitrile and analogues are key reagents in the synthesis of TCNQ and the analogues, which are attractive materials as components of organic electric conductors.[3]



R_1, R_2 = CN, CO_2Et

These molecules are often synthesized by arylation of the corresponding β-difunctionalized compounds (malononitrile, malonate, cyanoacetate). The known methods require the synthesis of precursors (diaryliodonium salts,[4] organobismuth reagents,[5] aryllead triacetate[6]), particular conditions (electrochemistry; $S_{RN}1$[7]), or a metal in stoichiometric amount (arenes activated by cyclopentadienyl ruthenium[8] or the use of copper[9]). These methods, often specific to a particular substrate, lack generality.

In comparison, the direct arylation of β-difunctionalized compounds by aryl halides, catalyzed by a metal, seems to be an interesting synthetic route. The copper[10] and palladium[11] complexes

* Corresponding authors. E-mail: cristau@cit.enscm.fr; taillefe@cit.enscm.fr

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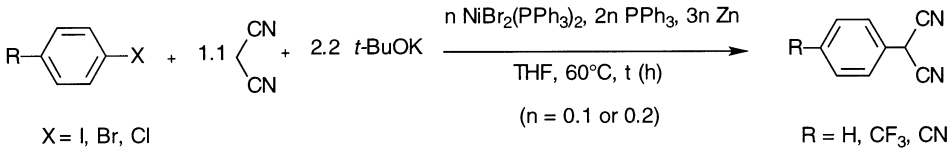
have already been shown to catalyze this reaction. Thus, the literature reports some examples of palladium catalysis for the arylation of malononitrile and cyanoacetate by aryl iodides or bromides.[11a–d] When mentioned, the arylation by aryl chlorides is presented as impossible,[11b] except in one case concerning the arylation of the ditertiobutyl malonate by chlorobenzene.[11e]

However, in these last examples the reaction requires the use of an electron rich and bulky phosphine ligand on the palladium catalyst (D^{t}BPF: ditertiobutyl phosphinoferrocene), which limits interest in the method from an economical point of view.

To the best of our knowledge, no arylation of β-difunctionalized compounds mediated by nickel complexes in stoichiometric or catalytic amount, has been described until now. Moreover, Uno and co-workers[11a,b] have mentioned the almost total inactivity of the nickel complexes in this type of reaction. Furthermore, it must be pointed out that few methods of direct arylation of monofunctionalized enolates of ketones or esters have been described with nickel complexes, otherwise these methods require a stoichiometric amount of metal.[12]

However, as part of our research on new and economical methods to synthesize α-aryl-β-difunctionalized compounds, we have found a new way to synthesize α-arylmalononitriles from malononitrile and the corresponding aryl halides, using a simple and inexpensive nickel catalysis.

Our first experiments were performed starting from iodobenzene as a model. This arylating agent, in the presence of triphenylphosphine, zinc and nickel complexe in catalytic amounts (Scheme 1: $n = 0.1$ or 0.2), was reacted with malononitrile anion as a nucleophile (1.1 equiv.) in THF at 60°C. The reaction, carried out in the presence of one equivalent of a base (sodium hydride, potassium or sodium *t*-butoxide) in order to generate in situ the malononitrile carbanion, allowed the synthesis of the corresponding phenylmalononitrile, but in a low yield (10%) and a low selectivity. However, we could increase the yield to 30% ($n = 0.1$) or 70% ($n = 0.2$), and the selectivity to 100%, using 2 equiv. of base. This result could be explained by the fact that the excess of base can avoid a transmetallation reaction between the malononitrile anion and the phenylmalononitrile. It should be noted that for similar reactions catalyzed by palladium, the use of 2 equiv. of base, reported by Buchwald and co-workers[11d] is not always necessary to obtain good results.[11e]



Scheme 1. Arylation of malononitriles by aryl halides

In the same experimental conditions, but starting from bromobenzene, we observed only a very small amount of phenylmalononitrile (<5%).

On the basis of these results, we have tried to extend the application field of our nickel system to the synthesis of electron-withdrawing substituted arylmalononitrile (R = CN, CF_3). These target molecules have been chosen according to their interest in agrochemistry and pharmaceutical chemistry. We have also chosen to start from the corresponding aryl bromides and chlorides, even if they are potentially less reactive than the iodo derivatives, because of their availability and their interest from an economical point of view (Table 1).

A mixture of the aryl halide with the malononitrile anion, generated in situ from malononitrile and potassium tertiobutoxide, was then heated to 60°C under nitrogen in the presence of a catalytic amount of nickel(0) complex (generated in situ by the reduction of $NiBr_2(PPh_3)_2$ with Zn).[13]

We could thus synthesize α-(*p*-trifluoromethylphenyl)malononitrile from the corresponding *p*-trifluoromethylbromobenzene in a yield of 45% and a good selectivity (96%). It is important to notice that in the absence of nickel complex, the reaction mixture leads only to the formation of trace amounts of product, thus demonstrating the catalytic effect of the nickel. By this method we have also obtained α-(*p*-cyanophenyl)malononitrile from the *p*-cyanobromobenzene with a better yield (65%) and the same excellent selectivity. This interesting reactivity of bromoarenes was also encountered with a chloroarene, the *p*-trifluoromethylchlorobenzene, which affords the corresponding α-(*p*-trifluoromethylphenyl)malononitrile with a yield of 46% and an excellent selectivity (98%), using 0.1 equiv. of nickel catalyst. As for iodobenzene, the use of twice as much catalyst (0.2 equiv.), permits a strong increase in the yield of product (85%), while keeping an excellent selectivity (93%).

These preliminary results will be soon developed by studying various parameters (experimental conditions, nature of the phosphine and of the nickel catalyst…), and will be extended to the reaction of heteroaromatic and vinylic halides as well as to other nucleophiles (ethyl cyanoacetate, diethyl malonate). This catalytic system will also be tested for the arylation of monofunctionalized anions.

This method is the first to use a nickel catalyst for the arylation of a β-difunctionalized anion. Moreover, the reaction, simple and inexpensive, works with a catalytic amount of nickel and with brominated or chlorinated aromatic derivatives without use of electron rich and bulky phosphines as used for the palladium catalysis. Good yields and excellent selectivities have been observed.

Table 1
Arylation of malononitriles by aryl halides

Entry	ArX		[Ni]	Time	ArX	$ArCH(CN)_2$	
	R	X	n	(h)	Conv. (%)[a]	Yield (%)[a]	Selectivity[b]
1	H	I	0.1	48	30	30	100
2	H	I	0.2	48	70	70	100
3	CF_3	Br	0	48	10	3	–
4	CF_3	Br	0.1	24	29	27	93
5	CF_3	Br	0.1	48	47	45	96
6	CN	Br	0.1	48	72	65	90
7	CF_3	Cl	0.1	24	25	25	100
8	CF_3	Cl	0.1	48	47	46	98
9	CF_3	Cl	0.2	48	91	85	93

[a] Conversions and yields determined by gas chromatography, titration using naphthalene as internal standard.
[b] Corresponds to the yield in product divided by the conversion of the corresponding aryl halide.

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13. Typical procedure: to a solution of nickel complex $Ni(PPh_3)_3$ (0.5 mmol), generated in situ and under nitrogen from $NiBr_2(PPh_3)_3$ (0.5 mmol), PPh_3 (1 mmol) and Zn (1.5 mmol), in dry tetrahydrofuran, were added the aryl halide (5 mmol) and the malononitrile anion (5.5 mmol), preliminary prepared from malononitrile (5.5 mmol) and *t*-BuOK (11 mmol). The mixture was heated to 60°C with stirring for an appropriate time. After quenching with dilute hydrochloric acid, the product was extracted with diethylether. Purification by silica gel column chromatography (ethyl acetate/hexane, 10/90), followed by recrystallization from hexane afforded the corresponding arylmalonitrile. α-(*p*-Trifluoromethyphenyl)malononitrile: 80% in isolated yield (entry 9); mp = 97°C (hexane); ^{1}H NMR (200.1 MHz, $CDCl_3$) δ 5.17 (s, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.81 (d, J = 8.3 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 27.9, 111 (*C*N), 123.3 (q, J = 271 Hz, *C*F_3), 127.1 (q, J = 3.75 Hz, *C*–C–CF_3), 127.8, 130.0, 133.0 (q, J = 35 Hz, *C*–CF_3); IR (KBr) ν 2880, 2260, 2255, 1925, 1805, 1690, 1629, 1422, 1335, 1240, 1210, 1170, 1140, 1080, 1025, 930, 860, 800, 772, 670 cm^{-1}; MS (EI, 70 eV): m/z (%) = 210 (M^+, 30), 190 (13), 183 (9), 159 (14), 141 (100), 114 (9), 87 (7), 75 (15). Anal. calcd for $C_{10}H_5F_3N_2$: C, 57.14; H, 2.38; N, 13.32. Found: C, 56.90; H, 2.39; N, 13.21. α-(*p*-Cyanophenyl)malononitrile: isolated yield: 60% (entry 6).