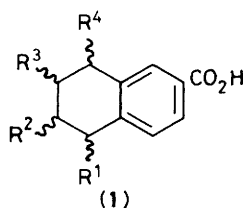


Nickel Catalysed Conversion of Phenol Triflates into Aromatic Nitriles and Acids

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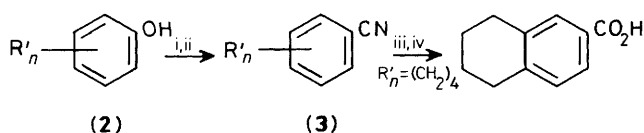
Phenols, as their trifluoromethanesulphonate (triflate) esters, are converted by potassium cyanide in the presence of catalytic tetrakis(triphenyl)phosphinenickel(0) into the corresponding nitriles, thence to the carboxylic acids.

As a part of our studies on the development of biotransformations for organic synthesis,¹ we required access to a series of 5,6,7,8-tetrahydro-2-naphthoic acids (**1**). Surprisingly, these proved to be rarely described in the literature² and no general methods for their synthesis are recorded.



Since the corresponding phenols (**2**) or phenol ethers are widely available, commercially or by synthesis or from natural sources, we sought to devise a process for their conversion into the required acids.

Initially, an adaptation of the well known palladium catalysed cyanation reaction of aryl halides³ was envisaged using Stille's aryl triflate methodology.⁴ In the event, this approach failed completely and we turned to the generally more reactive nickel series of catalysts⁵ in an attempt to promote the cyanation process. Nickel has been used for the cyanation of aryl halides⁶ but the palladium route has been usually preferred.⁷



Scheme. Reagents: i, Ti_2O_3 , pyridine; ii, KCN, $\text{Ni}(\text{PPh}_3)_4$; iii, HCl, EtOH; iv, aq NaOH.

The reaction of aryl triflates, prepared conventionally⁸ (see Scheme), with potassium cyanide at 60 °C in acetonitrile in the presence of tetrakis(triphenyl)phosphinenickel(0) (5 mol %), generated⁹ *in situ* from the nickel(II) complex and metallic zinc in the presence of an excess of phosphine, gave benzonitriles in moderate to good yields where no complicating factors intervene. The results are presented in the Table.

The reaction was best performed at the highest concentration possible, and at least 0.7 M with ≥ 2.0 M being preferred. Solid triflates (runs 2, 6) can give solubility problems in this respect. For the slower reactions it was necessary to add a second (or further) portion of catalyst when t.l.c. or loss of (catalyst) colour indicated that the reaction had stopped (e.g. runs 2, 8). Using this variation, even the highly hindered 2,4,6-trimethylphenol triflate was converted into the nitrile in moderate yield. However the bis-cyanation of 2,3-difluorynaphthalene (run 6) was incomplete, even after prolonged treatment.

The 4-halogen triflates were run in order to assess the relative reactivity of the triflate group against the more commonly used halogen substrates. Although a complete separation of products was not carried out, mass spectral analysis of the product of the 4-bromo compound showed, in addition to the expected benzene-1,4-dicarbonitrile, the products of nickel catalysed homo- and cross coupling.⁵ 4'-trifloxy- and 4'-bromo-biphenyl-4-carbonitriles. The compounds were present in comparable amounts and conversion was low (10% combined yield).

Where the substrate contained no other functionality reactive to the catalyst and where there were no problems of solubility, the conversions occurred in good yield and the method provides a ready access to our target nitriles with the potential for the synthesis of a wide range of functionalised aromatic carboxylic acids.

Finally, the original target, 5,6,7,8-tetrahydro-2-naphthoic acid [**1**; $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}_2$] was obtained by hydrolysis of the nitrile [**3**; $\text{R}'_n = (\text{CH}_2)_4$] with ethanolic

Table. Nickel catalysed conversion of aryl triflates into nitriles

Run no.	Substrate (2 ; OTf replaces OH) R'_n	Conditions		Yield (%)	Product (3)	
		Conc. (M)	Time (h)		M.p. (°C)	Lit. (°C)
1	4-MeO	1.0	2.5	78	57–58	61–62 ¹⁰
2	4-AcNH	1.5 ^a	4	70	205–206	205.5 ¹¹
3	4-EtO ₂ C	0.7	4	76	51–53	54 ¹²
4	4-Ac	1.0	1	74	56–57	57–58 ⁹
5	2,3-(CH ₂) ₄	2.0	2	69	36–37	37 ¹³
6	2-OTf-4,5-(CH ₂) ₄	0.6	4	10 ^b	—	—
7	3,4-(CH ₂) ₄	0.8	0.5	86	liq	—
8	2,4,6-Me ₃	2.0	8 ^c	32	56–57	53 ¹⁴
9	4-Cl	2.0	3	0 ^d	—	—
10	4-Br	2.0	3	0 ^d	—	—

^a Because of its limited solubility, the solid substrate was added *before* the cyanide. ^b The product is a 1:1 mixture of the mono- and di-cyano compounds. ^c Three further portions of catalyst were added at 2 h intervals; 37% of unchanged substrate was recovered. ^d A mixture of products of the replacement of both the triflate and the halogen atom was observed.

hydrogen chloride followed by base cleavage of the intermediate ester in 66% overall yield.

Experimental

General Cyanation Procedure.—Bistriphenylphosphine-nickel bromide (5 mol %), triphenylphosphine (10 mol %), zinc powder (30 mol %), and potassium cyanide (1.1 equiv.) in a dry nitrogen filled flask were treated with a degassed solution of the triflate (1 equiv.) in a minimum of acetonitrile (to give $\geq 2M$ concentration) at 60–65 °C until t.l.c. analysis showed complete consumption of the triflate. The mixture was allowed to cool to room temperature when it was partitioned between water and dichloromethane (10 vols of each). The organic phase was washed with water, dried ($MgSO_4$), filtered, and evaporated and the residue purified by flash chromatography over silica gel H. The nitrile was either crystallised or distilled as appropriate.

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