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Preparation of Polyfunctional Nitriles by the Cyanation of Functionalized Organozinc Halides with p-Toluenesulfonyl Cyanide.

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Summary

Various alkyl, alkenyl, alkynyl, benzylic, aromatic or heterocyclic organozinc halides bearing functional groups such as an ester, a boronic ester, a cyanide, a halide or a trialkoxysilyl group react under mild conditions with p-toluenesulfonyl cyanide affording polyfunctional nitriles in 69-93 % yields.

Organozinc halides are readily prepared by the insertion of zinc dust into organic halides[1] or by a low temperature transmetalation of organolithiums with zinc salts[2]. They display an excellent functional group tolerance allowing the convenient preparation of polyfunctional organozinc compounds.

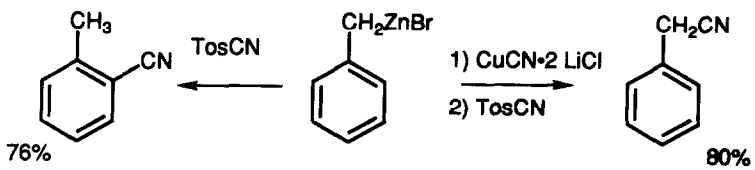
Scheme I

$$\underset{\mathbf{1}}{\text{FG-RZnX}} + \underset{\mathbf{2}}{\text{TosCN}} \xrightarrow[0\ ^\circ\text{C to } 25\ ^\circ\text{C, } 2\ \text{h}]{\text{THF}} \underset{\mathbf{3}}{\text{FG-RCN}} \qquad (1)$$

However their moderate reactivity toward most carbon electrophiles requires a transmetalation to the more reactive organocoppers or to use transition metal catalysts (Pd, Ti)[3] to achieve high yield reactions. We have now found that commercially available *p*-toluenesulfonyl cyanide (TosCN) **2**[4] reacts readily with various classes of organozinc compounds affording polyfunctional nitriles in good yields. The presence of sensitive functionalities represents a clear advantage over older procedures using organomagnesium or - lithium compounds[5]. Thus 5-acetoxypentylzinc iodide **1a** (1.5 equiv) reacts with TosCN providing the nitrile **3a** (THF, 0 °C to 25 °C, 1 h, 83 % yield). (E)-Pinacol 5-iodo-1-pentenylboronate cannot be converted directly to the corresponding nitrile **3b** by reaction with NaCN in DMSO. However the conversion of this iodide to the zinc derivative **1b** (Zn dust, THF, 0 °C, 16 h) followed by the reaction with TosCN affords cleanly the nitrile **3b** (entry 2, 70 % yield). Interestingly, a sensitive triethoxysilyl group is well tolerated and furnishes after a water free workup (dilution with hexane and filtration of the metallic salts over celite) 3-triethoxysilylpropionitrile **3c** in 67 % yield, a potential building-block for the preparation of polyfunctional silicones (entry 3). Secondary alkylzinc halides such as cyclohexylzinc iodide react similarly (entry 4).

(E)-5-chloro-1-iodopentene is converted by a low temperature iodine-lithium exchange [2,6], followed by a transmetalation with ZnI_2 to the zinc derivative **1e** which reacts readily with TosCN (0 °C to 25 °C, 4 h) and gives pure (E)-6-chloro-2-hexenenitrile **3e** (100 % E, 72 % (entry 5)). The method can be extended to the preparation of aromatic and heteroaromatic nitriles such as **3f-i** in satisfactory yields (69-81 %; entries 6-9) and to conjugated acetylenic nitriles **3j-k** (81-90 % yield) which are obtained from the corresponding alkynylzinc iodides (**1j-k**, entries 10-11). An interesting behavior is observed with benzylic organometallics. Whereas the reaction of TosCN with benzylzinc bromide selectively provides 2-methylbenzonitrile (76 %)[7], the reaction of the corresponding copper derivative (prepared by the addition of CuCN•2 LiCl to **4** at -20 °C)[8] leads to benzylcyanide (eq. 2). The reaction proceeds well with functionalized benzylic organometallics bearing a cyanide (**1l**) or an ester in *para* position leading

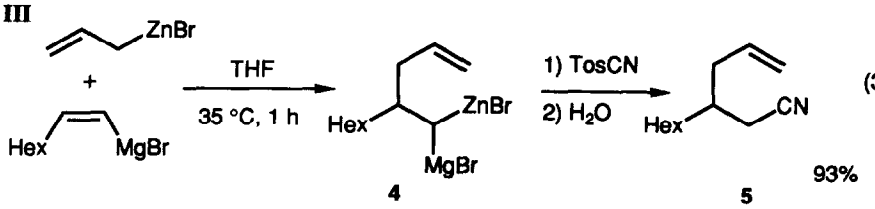
Scheme II



(2)

to the polyfunctional aromatic derivatives **3l** (69 %) and **3m** (75 %; entries 12 and 13). Interestingly, the reaction with unsymmetrically substituted benzylic zinc halides such as **1n-o** proceeds with complete regioselectivity producing only one regioisomeric cyanide (entries 14 and 15). α-Substituted benzylic zinc bromides like 1-ethylbenzylzinc bromide **1p** react in the same way with TosCN furnishing in 72 % yield o-propylbenzonitrile **3p** (entry 16). Finally, the reaction of a bimetallic reagent of magnesium and zinc **4** prepared by an allylzincation[9] produces selectively after hydrolysis the nitrile **5** in 93 % yield (eq. 3).

Scheme III



(3)

In summary, we have shown that the cyanation of a wide range of zinc organometallics with TosCN proceeds in satisfactory yields[10]. In contrast to the cyanation of organolithium or magnesium reagents, it allows the preparation of polyfunctional nitriles.

Table 1. Nitriles **3** Prepared by the Reaction of Organozinc Halides **1** with TosCN **2**.

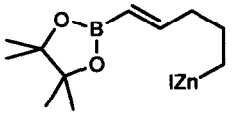
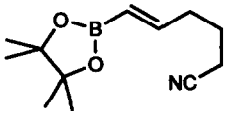
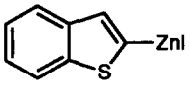
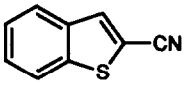
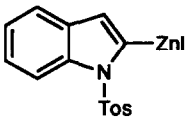
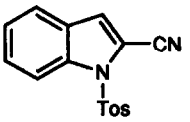
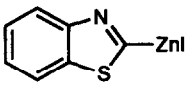
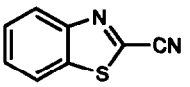
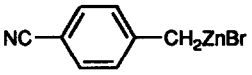
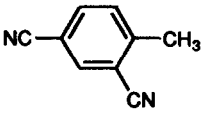
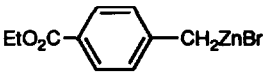
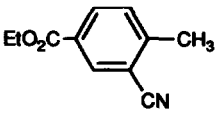
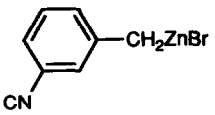
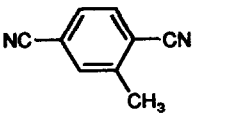
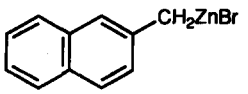
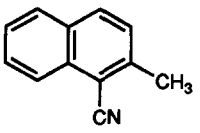
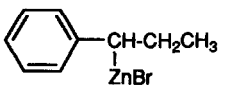
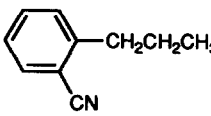
Entry	Organozinc halide **1**		Product of Type **3**		Yield (%)
1	$AcO(CH_2)_5ZnI$	**1a**	$AcO(CH_2)_5CN$	**3a**	83
2		**1b**		**3b**	70
3	$(EtO)_3SiCH_2CH_2ZnI$	**1c**	$(EtO)_3SiCH_2CH_2CN$	**3c**	67
4	c-Hex-ZnI	**1d**	c-Hex-CN	**3d**	84
5		**1e**		**3e**	72
6	*p*-Cl-PhZnI	**1f**	*p*-Cl-PhCN	**3f**	81
7		**1g**		**3g**	69
8		**1h**		**3h**	76
9		**1i**		**3i**	78
10	$Hex-C\equiv C-ZnI$	**1j**	$Hex-C\equiv C-CN$	**3j**	90
11	$Cl(CH_2)_3-C\equiv C-ZnI$	**1k**	$Cl(CH_2)_3-C\equiv C-CN$	**3k**	81
12		**1l**		**3l**	69
13		**1m**		**3m**	75
14		**1n**		**3n**	67

Table 1. (continued).

15		**1o**		**3o**	72
16		**1p**		**3p**	72

a) Isolated yields of analytically pure products (^{1}H-, ^{13}C-NMR, IR, HR-MS or microanalysis).

Acknowledgments

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10. Typical procedure for **(E)-6-chloro-2-hexenenitrile (3e)**: A three-necked flask equipped with a thermometer, a gas inlet, and an addition funnel was charged under argon with (E)-5-chloro-1-iodo-1-pentene (1.38 g, 6.0 mmol) in THF (5 mL) and cooled to -100 °C (liquid N_2 / ether bath), and *n* BuLi (6.3 mmol, 1.6 M in hexane) was added over 4 min. The resulting colorless solution was stirred for 3 min at -100 °C, and a THF (5 mL) solution of ZnI_2 (1.91 g, 6.0 mmol) was added. After warming up to 0 °C for 2 min and cooling back to -78 °C *p*-toluenesulfonyl cyanide (0.90 g, 5.0 mmol) in THF (5 mL) was added, and the reaction mixture was warmed to room temperature and stirred for 3 h. After the usual workup and evaporation of the solvents, the crude residue obtained was purified by flash chromatography (hexane/ether 10:1), yielding **(3e)** (466 mg, 72 %) as a clear oil (100 % E by GLC analysis and ^{13}C -NMR analysis).

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