

Addition Of Trimethylsilyl Cyanide To Aromatic Ketones Promoted By Organic Solutions Of Lithium Salts

Gérard Jenner

Laboratoire de Piézochimie Organique (UMR 7509), Institut de Chimie, Université Louis Pasteur,
67008 Strasbourg (France)

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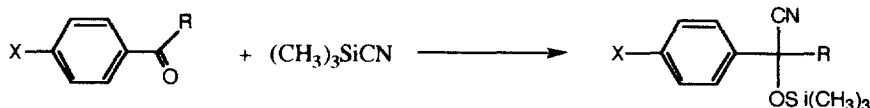
Abstract : Cyanosilylation of aromatic ketones is strongly promoted in organic solutions of specific lithium salts (perchlorate and tetrafluoroborate). Acetonitrile solutions of LiBF_4 are safe and efficient media for this reaction.

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Trimethylsilyl cyanide is simultaneously a convenient silylation and cyanation reagent ¹. Its addition to keto compounds affords cyanohydrin trimethylsilyl ethers which are useful intermediates for the synthesis of cyanohydrins and related compounds. The reaction is well known ², yet its course is very dependent on the catalyst used. Among them, the most efficient appear to be lanthanide compounds such as $\text{Yb}(\text{CN})_3$ ³ and $\text{Yb}(\text{OTf})_3$ ² [OTf = triflate], ZnI_2 ⁴, $\text{Cu}(\text{OTf})_2$ ⁵ and the base complex $\text{KCN} / 18\text{-crown-6}$ ⁶. No reaction is observed in the absence of catalyst. On the other hand, nucleophilic additions involving silylated enol ethers ⁷ or (trimethylsilyl)dialkylamines ⁸ have been shown to be promoted by diethyl ether solutions of lithium perchlorate (LPDE). The catalytic properties of LPDE as a mild Lewis acid are now well assessed ⁹ through specific solute- Li^+ interactions with complexation to diethyl ether and to less nucleophilic bulky counterions such as ClO_4^- . However, the inherent explosive capacity of perchlorates limits their use for only very specific cases on a small scale. An alternative catalytic medium was recently proposed. Organic solutions of lithium trifluoromethane sulfonimide were found to catalyze Diels-Alder reactions ¹⁰. The confidential access to this lithium salt prompted us to test other lithium salts, for example LiBF_4 (LTFB) and LiPF_6 (LHFP). An earlier paper reported the catalytic role of LiBF_4 in the intramolecular Diels-Alder reaction of a trienone ¹¹.

We report herein the cyanosilylation of aromatic ketones by trimethylsilyl cyanide (TMSCN) catalyzed by organic solutions of lithium perchlorate and lithium tetrafluoroborate ¹².

Tel.: (33) 03.88.41.68.15; Fax: (33) 03.88.60.42.48; E-mail: jenner@chimie.u-strasbg.fr



The yields obtained under various conditions in the cyanosilylation of acetophenone are shown in Table 1.

Table 1. Cyanosilylation of acetophenone (20°C)^a

Catalyst	Pressure MPa	Medium	Time h	Yield %
none	300	dichloromethane	21	0
none	0.1	water	21	0
Yb(OTf) ₃ (5 % molar)	0.1	dichloromethane	21	41
ZrCl ₄ (5 % molar)	0.1	dichloromethane	8	0
KCN / 18-crown-6 (18 % molar)	0.1	dichloromethane	8	26
BiCl ₃ (5 % molar)	0.1	dichloromethane	8	6
ZnI ₂ (15 % molar)	0.1	dichloromethane	8	77
LPDE	0.1	3M LPDE	8	98
LTFBA ^b	0.1	3M LTFBA	8	95
LHFP ^c	0.1	acetonitrile	8	0

^a Ketone (0.45 mmol), TMSiCN (0.5 mmol), 3M LPDE or 3M LTFBA (0.4 mL), T (20°C)

^b Solution of LiBF₄ in acetonitrile

^c Heterogeneous solution of lithium hexafluorophosphate (1.5 mmol) in acetonitrile (0.5 mL). See text.

Table 1 clearly shows that the reaction went to completion in LPDE and LTFBA. ZnI₂ was confirmed as a potent catalyst whereas the lanthanide compound ¹³, the catalytic couple KCN / crown ether, ZrCl₄ and BiCl₃ were less suitable. Amid the lithium salts, LHFP was completely inactive (LHFP is sparingly soluble in acetonitrile). As a recent paper reported high pressure silylcyanation with a titanium catalyst ¹⁴, we carried out the title reaction at 300 MPa. There was no reaction in the absence of a catalyst. Also, hydrophobic effects were unable to drive the reaction (run in water) ¹⁵.

Adopting LPDE or LTFBA as medium and catalyst simultaneously various aromatic ketones were reacted with TMSiCN at ambient pressure and temperature (Table 2). In most cases the yields were excellent, sometimes quantitative making the method a useful synthetic way for a straightforward preparation of silylated cyanohydrins and cyanoalcohols in a subsequent step. Comparison of the efficiency of both catalytic media shows that LPDE can be adequately replaced by LTFBA which is easier and much safer to handle and even gives slightly better yields in most reactions. The presence of substituting groups X on the aromatic ring affects the reactivity. As expected, electron-withdrawing groups (NO₂, halogens) promote cyanosilylation of the carbonyl bond whereas electron-releasing groups (CH₃, NH₂) retard it. In particular, para-amino substituted aromatic ketones were less much reactive.

The effect of the catalyst concentration and the medium was studied in the subsequent step (Table 3). The limited solubility of LiBF₄ in common solvents (chloroform, dichloromethane, diethyl ether) prevented an extensive solvent study. No reaction occurred in these media. However, LiBF₄ was soluble in tetrahydrofuran. At variance with lithium perchlorate, the catalytic efficiency of lithium tetrafluoroborate was manifested at

relatively low molar ratios, adding to the advantage of using LTFBA instead of LPDE. The catalytic activity persisted though at a lower degree, when tetrahydrofuran was substituted for acetonitrile. Contrastingly with LPDE (Li cation functioning as Lewis acid), the role of LTFB as catalyst in Diels-Alder reactions was ascribed to its low stability making it similar to BF_3 . Acetonitrile can form a complex $\text{CH}_3\text{CN}^+\text{-BF}_3$ which would be the catalytic species¹¹. If this is true, the O atom of tetrahydrofuran would play the same role as the N atom.

Table 2. Effect of LPDE and LTFBA on the cyanosilylation of aromatic keto compounds^a

X	R	Time h	Yield ^b (%)	
			LPDE	LTFBA
H	H	2	95	100
H	CH ₃	8	98 (77)	92
F	CH ₃	7	94	100
Cl	CH ₃	8	93 (87)	100
Br	CH ₃	8	86	99
NO ₂	CH ₃	7	100 (85)	100
NO ₂	CH ₂ Br	7	100	100
NH ₂	CH ₃	7	14 (c)	15
CH ₃ (4')	CH ₃	8	64	47
CH ₃ (3')	CH ₃	8	no run	49
OH	CH ₃	7	(d)	no run
H	Ph	8	14	61
CH ₃	Ph	8	61	55
NH ₂	Ph	24	4 (c)	10

^a Ketone (0.2-0.5 mmol), TMSCN (0.3-0.6 mmol), 3M LPDE or 3M LTFBA (0.4 mL), T (20°C)

^b Determined by ¹H NMR. In parentheses, the yield obtained under identical conditions with ZnI₂ (15 % molar) in CH₂Cl₂.

^c Complex mixture in the presence of zinc iodide

^d Three products were formed in 31 % overall yield. They were shown to result from silylation of the hydroxyl group and cyanosilylation of the starting and intermediate ketones

Table 3. Effect of catalyst concentration and medium^a

Catalyst	Catalyst : ketone (molar ratio)	Medium	Yield (%)
LiClO ₄	0.1	diethyl ether	low
LiBF ₄	0.1	acetonitrile	22
LiClO ₄	0.3	diethyl ether	21
LiBF ₄	0.3	acetonitrile	77
LiBF ₄	1.4	acetonitrile	98
LiBF ₄	3.0	acetonitrile	95
LiBF ₄	3.0	tetrahydrofuran	59

^a Acetophenone (0.45 mmol), TMSCN (0.5 mmol), total volume (0.5 mL), 20°C, 8h

Conclusion

In summary, solutions of lithium perchlorate in diethyl ether or lithium tetrafluoroborate in acetonitrile are highly efficient catalytic media for cyanosilylation of ketones, particularly aromatic ketones which are often unreactive under different catalytic conditions¹³. The procedure is particularly well adapted to the Strecker-like synthesis of α -aminonitriles by adding an amine to the LPDE¹⁶ solution of a TMSCN-aldehyde mixture. The present results show that the hazards of LPDE can be avoided by preferential use of the safer LTFBA.

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12. LiClO₄ · 3H₂O was dried at 180°C until constant weight (about 20-24 h). Dried diethyl ether was added under mixing so as to form a 3M solution. The solution was kept at 0°C until use. Acetonitrile and THF solutions of LiBF₄ were prepared in the same way.
13. Yb(OTf)₃ (20 % molar) was reported as ineffective in this reaction (see ref. 2). A recent paper confirmed the absence of reactivity in the aqueous cyanosilylation of either aromatic aldehydes or ketones when InF₃ (30 % molar) was used as a catalyst : Loh, T.P.; Xu, K.C.; Ho, D.S.; Sim, K.Y. *Synlett*, **1998**, 369-370.
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