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An improved method for direct conversion of heteroaryl-aldehydes to heteroaryl-acetonitriles

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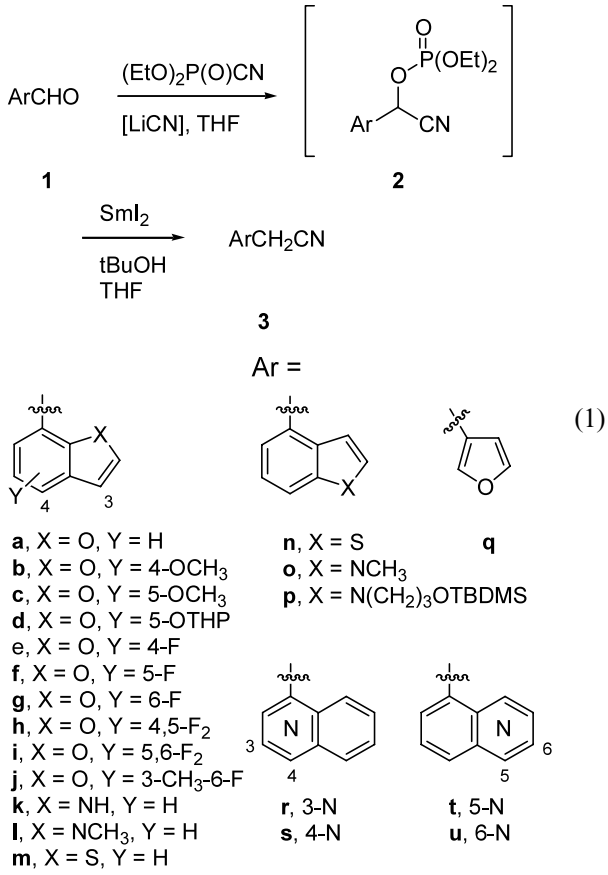
Abstract—Treatment of heteroaryl-aldehydes with diethyl cyanophosphonate in the presence of a catalytic amount of LiCN affords phosphorylated cyanohydrins which are reduced in situ with SmI_2 to give heteroaryl-acetonitriles in generally good overall yields (50–100%). The generality of the process is demonstrated. © 2003 Published by Elsevier Science Ltd.

For an SAR study we required a variety of heteroaryl-acetonitriles **3**. A number of heteroaryl-aldehydes **1** were available to us, however, few reagents are known to directly homologate the aryl-aldehydes to aryl-acetonitriles in good yields.[1] To effect this transformation, we were drawn initially to the method of Kurihara involving formation of phosphorylated cyanohydrins and subsequent reduction with SmI_2.[2] Although the original report included 2-acetylpyridine as the sole heteroaryl system and several reports in addition to those of Kurihara have appeared involving alkyl and aryl ketones,[3] it was not clear that the process was amenable to a wide range of heteroaryl-aldehydes. Of additional concern was the routine use of excess LiCN (3 equiv.) and diethyl cyanophosphonate (3 equiv.), which we speculated necessitated the reported isolations and/or chromatographic purifications of the cyanohydrins prior to the reduction step. We reasoned that with simple systems the process could perhaps be initiated with catalytic amounts of LiCN.[4] If so, it might be possible to generate **2** and convert it in situ to the desired product **3**. Herein we describe a simple and effective modification of this procedure utilizing a catalytic amount of LiCN (0.1 equiv.) and smaller quantities (1.2–1.3 equiv.) of diethyl cyanophosphonate which allows the direct conversion of **1** to **3** in situ and converts the process to essentially a one-pot procedure (Eq. (1)). We demonstrate the utility of the process with a variety of heteroaryl-aldehydes (Table 1).



(1)

Treatment of heteroaryl-aldehydes **1** with diethyl cyanophosphonate in THF containing 10 mol% LiCN·THF resulted in complete consumption of starting aldehydes (TLC) in 4–16 h and it was assumed[2] that

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Table 1. Conversion of heteroarylaldehydes **1** into heteroarylacetonitriles **3**[a,b,c]

Aldehyde	SmI_2 (equiv.)	Product	Yield (%)
1a	2.5	**3a**	98
1b	4.3	**3b**	78
1c	3.0	**3c**	92
1d	3.3	**3d**	99
1e	4.5	**3e**	85
1f	3.0	**3f**	69
1g	2.3	**3g**	100
1h	2.3	**3h**	96
1i	4.3	**3i**	90
1j	2.7	**3j**	81
1k	2.4	**3k**	50
1l	2.6	**3l**	79
1m	2.5	**3m**	84
1n	2.5	**3n**	76
1o	2.5	**3o**	96
1p	2.3	**3p**	89
1q	2.5	**3q**	63
1r	2.5	**3r**	59
1s	2.5	**3s**	77
1t	2.5	**3t**	57
1u	2.5	**3u**	69

[a] 0.1 equiv. of LiCN·1.5 THF was used in all cases except **1j**, where 0.14 equiv. was used; equiv. based on LiCN.
[b] 1.2–1.3 equiv. of $(EtO)_2P(O)CN$ used in each case.
[c] 1.0–1.2 equiv. of *t*BuOH used in each case.

the material formed was the phosphoryl cyanohydrin **2**. *t*BuOH was added and the mixture was then transferred via cannula into a 0.1 M solution of SmI_2 in THF (Aldrich). During the transfer, if the blue color of the SmI_2 dissipated to green or yellow, the transfer was stopped, additional SmI_2 solution was added and the transfer resumed. At the end of the transfer, additional SmI_2 was added if necessary until the blue color persisted. Alternatively, *t*BuOH was added to the solution of **2** followed by addition of the SmI_2/THF solution until the reaction mixture was a dark blue color. Fresh bottles of SmI_2 were usually employed; when aged bottles where used, excess was occasionally required.[5] Standard workup and plug filtration or flash chromatography through silica gel afforded the product **3** in generally good yields (50–100%, unoptimized) for a variety of heteroaryl-aldehydes (Table 1).[6]

Advantages to this procedure include the use of mild conditions and readily available materials. In addition, previous work[2,3] has demonstrated the compatibility of various functional groups to the conditions employed, including carbamates, esters, amines, alcohols, amides, and sulfonamides, adding to the generality of this one-pot procedure for the conversion of heteroaryl-aldehydes to heteroaryl-acetonitriles.

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4. Others have attempted to use catalytic amounts of LiCN without success.[3a]
5. We avoided routinely checking the titre of the SmI_2 solutions or generating it in situ in order to limit the number of required operations to a minimum, thus adding to the overall simplicity of the process. A crude determination of the amount of reductant required is accomplished simply by visually following the color of the reactions.
6. The synthesis of **3l** from commercially available indole-7-carboxaldehyde is given as a representative procedure. To a solution of indole-7-carboxaldehyde (20.0 g, 137 mmol) and dimethylsulfate (19.1 g, 151 mmol) in DMF (400 mL) at 0°C was added a 60% dispersion of NaH in mineral oil (6.60 g, 165 mmol). The reaction was stirred and allowed to warm to rt over 30 min. The reaction was quenched with H_2O, and diluted with EtOAc (1 L) and H_2O. The two layers were separated and the aqueous layer was extracted with EtOAc (250 mL). The combined organic

layers were washed with H_2O (3×500 mL), brine, saturated aq LiCl, and brine. The solution was dried ($MgSO_4$), filtered and concentrated to afford 1-methyl-1*H*-indole-7-carboxaldehyde as an off white solid that was used directly. A solution of this aldehyde, LiCN·1.5 THF complex (1.94 g, 13.7 mmol), and diethyl cyanophosphonate (27.1 mL, 179 mmol) in THF (400 mL) was stirred at rt overnight. *t*-Butanol (13.1 mL, 137.7 mmol) was introduced and the mixture was transferred via cannula into a 0.1 M solution of SmI_2 in THF (3.6 L, 360 mmol) and the mixture stirred for 30 min. The mixture was concentrated to dryness, the residue was taken up in EtOAc (2 L), and the solution was washed with 1N HCl (3×500 mL), saturated aq $NaHCO_3$, and brine. The solution was dried ($MgSO_4$), passed through a pad of silica gel, and concentrated to give **3l** (18.4 g, 79%) of sufficient purity (~95%) for most applications. Flash chromatography (90% hexane/EtOAc) afforded pure **3l** as an off-white crystalline solid. ^1H (400 MHz, DMSO-d_6) 7.51 (d, $J=7.5$ Hz, 1H), 7.28 (d, $J=3$ Hz, 1H), 7.09 (d, $J=7.5$ Hz, 1H), 6.99 (dd, $J=7.5$, 7.5 Hz, 1H), 6.43 (d, $J=3$ Hz, 1H), 4.58 (s, 2H), 4.07 (s, 3H). ^{13}C NMR (75.5 MHz, DMSO-d_6) 133.56, 131.89, 130.06, 122.38, 120.74, 119.53, 119.16, 114.47, 100.59, 35.86, 20.43. IR ($CHCl_3$, cm^{-1}) 2252. MS (electrospray, m/z) 171 (M^++1). Anal. calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 78.01; H, 5.97; N, 16.49.