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Indium(I) bromide-mediated bromocyanomethylation of carbonyl compounds

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Abstract

Bromocyanomethylation of a variety of carbonyl compounds to produce the corresponding 2-bromo-3-hydroxynitriles has been achieved in moderate to good yields by the action of dibromoacetonitrile and indium(I) bromide. Moderate diastereoselectivity was observed. Exclusive mono-coupling at the carbonyl group was found with 1,2-diketones and α-haloketones.

Several organic transformations promoted by organoindium reagents have been described recently.[1] Some well-established processes include the indium-promoted reaction of allyl halides and α-halo-esters with carbonyl compounds, to give homoallylic alcohols and β-hydroxy esters,[2] respectively. Similarly, it was demonstrated that organoindium sesquihalides,[3] identified as the intermediate in these reactions, also react with enamines to afford homoallylamines. The α-halo-organoindium reagents obtained from indium metal and Br_2CR_2 (R = -CN, $-CO_2Et$),[4] form a second class of reagents which have been successfully employed in the cyclopropanation of electron-deficient alkenes, and in the epoxidation of carbonyl compounds (R = $-CO_2Et$).

Although the use of indium has been the subject of increasing interest for C–C bond-formation, the use of indium(I) compounds,[5] such as indium(I) halides, remains virtually unexplored. The present work describes bromocyanomethylation reactions of carbonyl compounds promoted by InBr (Eq. (1)),[6] leading to the corresponding 2-bromo-3-hydroxynitriles **3**. A typical procedure involved the addition of $CHBr_2CN$ (470 mg, 2.3 mmol) to a stirred and cooled (–5°C) suspension of InBr (300 mg, 1.54 mmol) and benzaldehyde (1.54 mmol) in tetrahydrofuran (5 mL) under nitrogen. Stirring was continued until the complete consumption of the insoluble InBr (see Table 1 for the time required). The solution obtained was then acidified with HCl (0.1 M, 5 mL) and the aqueous solution extracted twice with ethyl acetate (60 mL); the extract was sequentially washed with a saturated solution of $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and evaporated to

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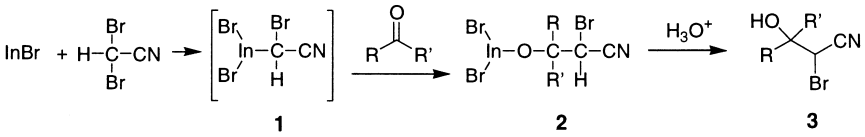
dryness. The reaction product **3a** was separated by column chromatography on silica gel (hexane:ethyl acetate = 5:1), analysed (C, H and N) and characterised by NMR (^{1}H and ^{13}C), infrared spectroscopy and mass spectrometry. Yields and other reaction conditions are given in Table 1.



(1)

Table 1
Synthesis of 2-bromo-3-hydroxynitriles promoted by InBr

Entry	R	R'	Product	Time (h)	Yield (%)	Ratio (syn/anti)
1	C_6H_5	H	**3a**	3	63	1/1,5
2	4-NO_2-C_6H_4	H	**3b**	2	66	1/1
3	4-Cl-C_6H_4	H	**3c**	2	78	1/1,18
4	2-CH_3O-C_6H_4	H	**3d**	4	65	1,32/1
5	C_6H_5CH=CH	H	**3e**	3	70	1/1,85
6	$(CH_3)_3C$	H	**3f**	2	59	1/9
7	$(CH_3)_2CH$	H	**3g**	5	52	1/4,55
8	CH_3CH_2	H	**3h**	6	56	1/2
9	$(CH_2)_5$		**3i**	8	54	-
10	2-cyclohexen		**3j**	8	51	a
11	C_6H_5	CH_3	**3k**	10	52	3/1
12	2-C_5H_4N	CH_3	**3l**	6	60	a
13	C_6H_5	CH_2Br	**3m**	6	51	a
14	CH_3	$ClCHCH_3$	**3n**	4	43	a
15	C_6H_5	$CHCl_2$	**3o**	6	52	1/5
16	CH_3	CH_3CO	**3p**	4	52	a
17	C_6H_5	C_6H_5CO	**3q**	12	41	a

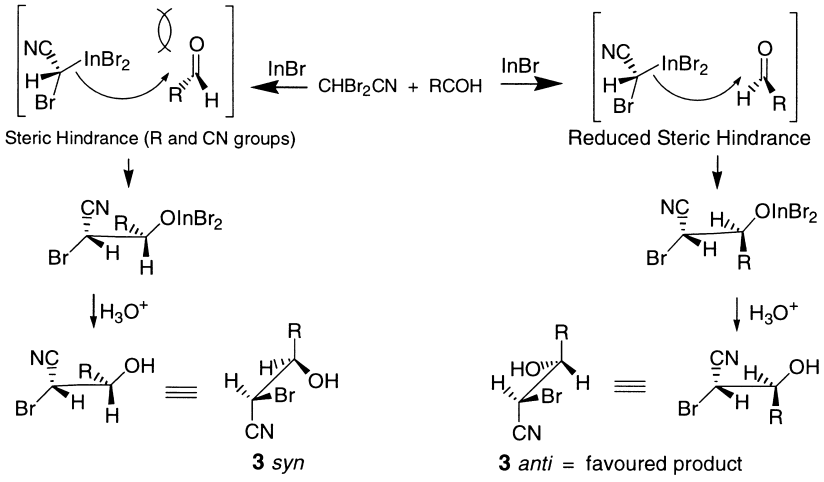
[a] Diastereoselectivity syn:anti ratio not measured.

The proposed mechanism leading to **3** involves the oxidative insertion of InBr into the carbon–bromine bond of dibromoacetonitrile to give the organoindium(III) species **1**. Coupling between the bromocyanomethyl group and the carbonyl compound leads to the indium alkoxide **2**, which upon acid hydrolysis gives the final product **3**. The proposed intermediate **1** is analogous to the X_2InCH_2X and X_2InCHX_2 derivatives obtained from InX and CH_2X_2 and CHX_3, respectively,[7,8] which have been unambiguously characterised by X-ray methods.

Table 1 shows that a variety of carbonyl compounds were successfully transformed into **3**. Aldehydes, particularly aromatic (entry 1) react faster and produce better yields than the structurally related ketones (entry 11). Aromatic carbonyl compounds containing electron

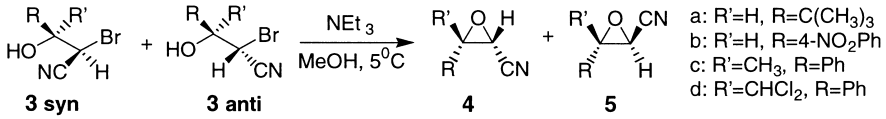
withdrawing groups (entries 2 and 3) or electron donating groups (entries 4 and 12) were transformed to the corresponding derivatives **3**. α,β-Unsaturated carbonyl substrates, such as cinnamaldehyde (entry 5) and 2-cyclohexen-1-one (entry 10) gave 1,2-addition products exclusively. Carbonyl compounds containing an hydroxyl group, such as ethylacetoacetate and salicylaldehyde, did not react and were completely recovered at the end of the reaction, suggesting that acidic substituents on the carbonyl compound inhibit reaction.

Product formation proceeded with poor diastereoselectivity for aromatic (entries 1–4) and α,β-unsaturated (entry 5) aldehydes, but *anti*-addition was found to be preferred when aliphatic aldehydes were used. The *anti*:*syn* diastereomeric ratio decreases in the following order: pivalaldehyde > isobutyraldehyde > propionaldehyde (entries 6–8), suggesting a mechanism governed by steric hindrance effects (Scheme 1), in which the two heteroatoms (Br and O) will align *anti* to each other to eliminate electron–electron repulsion.[9] The spatial orientation of the R group of the aldehyde and the cyano group of the organometallic reagent on the transition state will determine diastereoselection; *gauche* orientation (left-hand pathway) imposes maximum steric hindrance raising the energy of the transition state; consequently, the right-hand pathway leading to the *anti* product will be favoured.



Scheme 1.

The organoindium species **1** reacts with α-halo ketones (entries 13–15) chemospecifically to give the corresponding derivatives **3**, with no signs of dehalogenation and/or substitution. With 1,2-diketones, only mono addition products were isolated (entries 16 and 17). The present reaction is directly related to the Darzens condensation between α-halo-nitriles and carbonyl compounds, giving rise to the formation of glycidic nitriles.[10] An obvious synthetic application of **3** is the preparation of glycidic nitriles, via epoxidation (Eq. (2)), and indeed this can be achieved by addition of an equimolar amount of triethylamine to a cold (5°C) solution of **3** in methanol. After 3 hours, all the volatiles were removed and the residue was partioned in H_2O/CH_2Cl_2; the organic solvent was dried (Na_2SO_4), filtered, and evaporated to dryness to give the corresponding glycidic nitriles; ^1H NMR spectroscopy showed quantitative conversion to the oxiranes, integration revealed a 1:9 ratio for oxiranes **4a**:**5a** and a 1:1 ratio for **4b**:**5b**. These results clearly confirm the *syn*:*anti* ratio reported in Table 1 (entries 6 and 2, respectively).



(2)

The ^{1}H NMR of the mixtures of glycidic nitriles **4c**, **5c** and **4d**, **5d** were assigned on the basis on NOE difference spectroscopy. The molar ratio **4c**:**5c** of 3:1 again confirms the data in Table 1 (entry 11). Finally, epoxidation of the alcohol derived from α,α-dichloroacetophenone (entry 15) occurred chemoselectively to give the epi-α,α-diclorohydrin derivatives **4d** and **5d** in a molar ratio of 1:5.

The reaction between carbonyl compounds and dibromoacetonitrile mediated by InBr is an attractive method for the preparation of 2-bromo-3-hydroxy nitriles. Good stereocontrol, leading to the *anti*-diastereomer, was observed from bulky aliphatic aldehydes. These compounds allow easy entry into the formation of glycidic nitriles, including their *epi*-α-chloro and *epi*-α,α-dichloro derivatives, which are synthetically useful building blocks in organic synthesis.

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