



Indium(I) bromide-mediated dichlorocyanomethylation of carbonyl compounds. The preparation of 2,2-dichloro-3-hydroxynitriles

J. A. Nóbrega,^a Simone M. C. Gonçalves^a and C. Peppe^{b,*}

^aDepartamento de Química Fundamental, Universidade Federal de Pernambuco, Recife-PE 50.670-901, Brazil

^bLaboratório de Materiais Inorgânicos, Departamento de Química, Universidade Federal de Santa Maria-RS 97105-900, Brazil

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Abstract—Carbonyl compounds were efficiently transformed into their corresponding 2,2-dichloro-3-hydroxynitrile derivatives by the action of trichloroacetonitrile and indium(I) bromide. © 2001 Elsevier Science Ltd. All rights reserved.

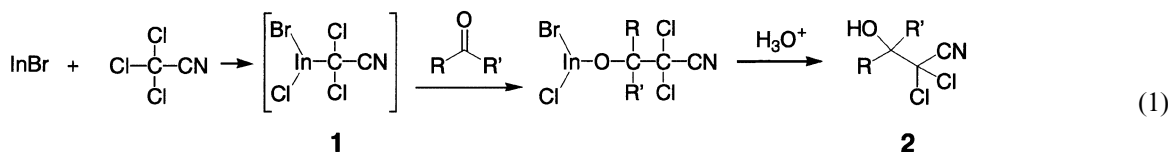
Although indium metal has been employed for C–C bond formation,¹ the use of indium(I) compounds, such as indium(I) halides, remains virtually unexplored. We have observed the InBr-mediated chemoselective production of 2-bromo-3-hydroxynitriles from dibromoacetonitrile and carbonyl compounds,² while the In-mediated reaction gave low yields of a complex mixture of products.³ This encouraged us to investigate indium(I) halides-mediated reactions as an alternative when the metal-mediated process is not efficient.

We report here the dichlorocyanomethylation of carbonyl compounds to the corresponding 2,2-dichloro-3-hydroxynitriles, **2** promoted by InBr (Eq. (1)).⁴ The proposed active organoindium species is the intermediate **1**, formed by the oxidative insertion of the monobromide into one of the carbon–chlorine bonds of Cl₃CCN. Coupling between **1** and the carbonyl compound, followed by hydrolysis of the indium alcoxide, leads to **2** (Eq. (1)).

Table 1 shows that a variety of carbonyl compounds were successfully transformed into **2** in good to excellent yields, revealing the generality of the reaction. The literature registers one attempt to couple carbonyl compounds with the [−]CCl₂CN nucleophile generated under the Darzens conditions (sodium methoxide/methanol); the result is the production of a complex mixture; the desired products **2** were isolated in low yields for very few cases.⁵ We conclude that generation of the [−]CCl₂CN nucleophile from **1** allows a novel and highly efficient protocol for the preparation of 2,2-dichloro-3-hydroxy-acetonitriles, with significant improvements over previous methodologies.

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* Corresponding author. E-mail: peppe@quimica.ufsm.br

Table 1. InBr-mediated preparation of 2,2-dichloro-3-hydroxynitriles

Entry	R	R'	Product	Time (h)	Yield (%)
a	(CH ₃) ₂ CH	H	2a	2	70
b	(CH ₃) ₃ C	H	2b	2	68
c	(C ₆ H ₅) ₂ CH	H	2c	1.5	76
d	(CH ₂) ₅	H	2d	2.5	65
e	4-Cl-C ₆ H ₄	H	2e	1	90
f	4-O ₂ N-C ₆ H ₄	H	2f	1	93
g	4-CH ₃ O-C ₆ H ₄	H	2g	1	86
h	C ₄ H ₃ O ^a	H	2h	1	85
i	C ₆ H ₅ CH=CH	H	2i	1	88
j	2-Cyclohexen	H	2j	3	75
k	C ₆ H ₅	CH ₃	2k	2	73
l	CH ₃	COOC ₂ H ₅	2l	2	64
m	C ₆ H ₅	COC ₆ H ₅	2m	3	60

^a 2-Furaldehyde.

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4. A typical procedure involves the addition of CCl₃CN (111 mg, 0.76 mmol) to a stirred and cooled (–5°C) suspension of InBr (150 mg, 0.76 mmol) and *p*-methoxybenzaldehyde (0.76 mmol) in tetrahydrofuran (5 mL) under nitrogen. After the complete consumption of the insoluble InBr, the reaction was monitored by TLC until complete consumption of the carbonyl compound (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 sequen-

tially washed with a saturated solution of NaHCO₃ and brine, dried (Na₂SO₄), filtered, and evaporated to dryness. The reaction product **2g** was separated by column chromatography on silica gel (hexane/ethyl acetate=5/1), analysed: calcd (%) for C₁₀H₉Cl₂NO₂: C, 48.82; H, 3.66; N, 5.69. Found: C, 48.80; H, 3.66; N, 5.71 and characterised by ¹H NMR (in CDCl₃, ppm from TMS): 3.65 (s, 1H, OH), 3.80 (s, 3H, OCH₃), 5.03 (s, 1H, CHO), 6.90 (d, 2H, *J*=8.8 Hz, CH_{ar. meta}), 7.46 (d, *J*=8.8 Hz, CH_{ar. ortho}). ¹³C NMR (in CDCl₃, ppm from TMS): 55.29 (OCH₃), 73.10 (CCl₂CN), 80.68 (CHO), 113.72 (CH_{ar. meta}), 114.16 (CN), 125.93 (HO(CCl₂CN)H-C_{ar ipso}), 129.63 (CH_{ar. ortho}), 160.77 (CH₃O-C_{ar ipso}); infrared spectroscopy (cm⁻¹): 3480 (ν OH), 2255 (ν CN); and mass spectrometry (M⁺=245/247/249 m/e). Yields and other reaction conditions are given in Table 1. Analytical and spectroscopic data for **2a–i** is available upon request.

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