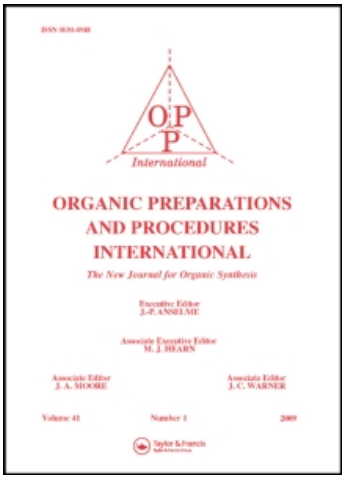

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED IODBMATION OF 2-AMINO-5-NITROBENZONITRILE

Ye Zhang[ab]; Tianrui Ren[ab]; Weiwen Zhu[ab]; Yanhong Xie[ab]
[a] National Key Laboratory of Biochemical Engineering Institute of Process Engineering, Chinese Academy of Sciences, Beijing [b] Graduate University of Chinese Academy of Sciences, Beijing, P. R CHINA

To cite this Article Zhang, Ye , Ren, Tianrui , Zhu, Weiwen and Xie, Yanhong(2007) 'AN IMPROVED IODBMATION OF 2-AMINO-5-NITROBENZONITRILE', Organic Preparations and Procedures International, 39: 1, 90 — 93
To link to this Article: DOI: 10.1080/00304940709458586
URL: http://dx.doi.org/10.1080/00304940709458586

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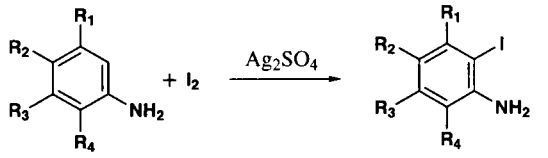
AN IMPROVED IODINATION OF 2-AMINO-5-NITROBENZONITRILE

Submitted by (08/18/06)

Ye Zhang, Tianrui Ren*, Weiwen Zhu and Yanhong Xie

National Key Laboratory of Biochemical Engineering
Institute of Process Engineering, Chinese Academy of Sciences
Beijing 100080
Graduate University of Chinese Academy of Sciences,
Beijing 100049, P. R CHINA
e-mail: trren@home.ipe.ac.cn

Aryl iodides are important intermediates in organic synthesis,[1-3] especially in the Heck reaction as well as the Stille and the Negishi cross-couplings. However, some of aryl iodides are not commercially available. Those that are available are too expensive for practical application. In the course of our current research program, we required several iodoaromatic amines as substrates for the Sonogashira cross-coupling reaction.[4]



1 2

a) $R_1 = R_3 = R_4 = H$, $R_2 = NO_2$
b) $R_1 = R_3 = H$, $R_2 = COOC_2H_5$, $R_4 = NO_2$
c) $R_1 = R_3 = H$, $R_2 = NO_2$, $R_4 = CN$
d) $R_1 = R_3 = R_4 = H$, $R_2 = COOC_2H_5$
e) $R_1 = R_4 = H$, $R_2 = COOCH_3$, $R_3 = Cl$
f) $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$
g) $R_1 = R_2 = R_3 = R_4 = H$
h) $R_1 = R_3 = R_4 = H$, $R_2 = Cl$
i) $R_1 = R_3 = R_4 = H$, $R_2 = F$

Initially, we attempted the synthesis of these compounds by treatment of aromatic amines with iodine in the presence of silver sulfate.[5] Although ordinary iodoaromatic amines (**2a**, **2b** and **2d**) were obtained under the reported conditions,[5, 6] we could not obtain **2c** in greater than 29% yield and **2c** was contaminated with iodine. Attempts to modify this procedure using other catalysts such as silver nitrite[7] or adding more of silver salts and varying the reaction time were also unsuccessful. Finally, we found that yield of **2c** was dramatically improved (70%) by

changing the solvent from ethanol to 1,2-ethanediol, and that the reaction time was shortened considerably. The results of the iodination of **1a**, **1b**, **1c**, **1d**, **1e**, **1f**, **1g**, **1h** and **1i** in 1,2-ethanediol are shown in *Table 1*. In the case of more activated aromatic amines (**1f** and **1g**), the iodination products were obtained in moderate yields (41% and 46% respectively). However, we failed to obtain the iodination product of **1i** whether in 1,2-ethanediol or in ethanol.

Table 1. Iodination of Aniline Derivatives in 1,2-Ethanediol

Cmpd	Yield (%)	mp. (°C)	*lit.* mp. (°C)	Elemental Analyses (Found) C	H	N
2a	75[a]	157-158	157-159[8]			
2b	91	134-136	136[9]			
2c	70	202-204	----	29.09(29.21)	1.39(1.45)	14.54(14.68)
2d	86	85	83[10]			
2e	58	155-157	----	30.85(30.76)	2.27(2.25)	4.50(4.65)
2f	41	38-39	39-40[11]			
2g	46	53-55	52-55[12]			
2h	73	42-43	44[13]			
2i	0	----	----		----	

a) Yield is 86% in ethanol.

EXPERIMENTAL SECTION

Commercially available reagents were purchased from Aldrich and used without further purification. All melting points were recorded using capillary melting point apparatus and are uncorrected. The IR spectra were determined neat or as KBr pellets on a Shimadzu FTIR-8300 spectrometer. ^{1}H NMR was acquired using Bruker DPX300 spectrometer in $CDCl_3$ solution with TMS as the internal standard. The elemental analyses were performed at the Institute of Chemistry, Chinese Academy of Sciences. Analytical thin layer chromatography (TLC) was carried out using MN Kieselgel G/ UV 254 (Art. 816320) glass-backed plates. Yields were not optimized.

2-Amino-3-iodo-5-nitrobenzonitrile (2c). Typical Procedure.- 2-Amino-5-nitrobenzonitrile (163 mg, 1mM) was added to a mixture of iodine (254 mg, 1mM) and silver sulfate (312 mg, 1mM) in 1,2-ethanediol (20 mL) at room temperature. The mixture was stirred at RT for 4 h. After completion of the reaction (monitored by TLC), water (20 mL) was added to the reaction mixture and the mixture was extracted with ethyl acetate. Then, the organic layer was washed with aqueous $Na_2S_2O_3$, dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed on silica gel (hexane/ethyl acetate 7: 3) to give pure 2-Amino-3-iodo-5-nitrobenzonitrile (202 mg, 70%) as a yellow solid.

Table 2. IR and ^{1}H NMR Spectra of the Iodination of Aniline Derivatives

Product	IR (KBr) (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) (δ), J (Hz)
2a	3485, 3360, 2840, 1610	8.56 (d, J = 2.5 Hz, 1H), 8.03-8.07 (m, 1H), 6.70 (d, J = 9.0 Hz, 1H), 4.87 (br, s, 2H)
2b	3460, 3345, 1600, 1450	8.81 (d, J = 2.0 Hz, 1H), 8.51 (d, J = 2.0 Hz, 1H), 7.01 (br, s, 2H), 4.33-4.37 (m, 2H), 1.39 (t, 3H)
2c	3500, 3350, 2850, 1500	8.71 (d, J = 3.0 Hz, 1H), 8.36 (d, J = 3.0 Hz, 1H), 5.59 (br, s, 2H).
2d	3660, 1685, 1590, 1285	8.25 (d, J = 2.0 Hz, 1H), 7.71-7.75 (m, 1H), 6.65 (d, J = 8.6 Hz, 1H), 4.41 (br, s, 2H), 4.22-4.26 (m, 2H), 1.29 (t, 3H)
2e	3500, 3330, 2950, 1450	8.25 (s, 1H), 6.74 (s, 1H), 4.52 (br, s, 2H), 3.86 (s, 3H)
2f	3415, 3340, 1450, 1155	7.46 (d, J = 1.3 Hz, 1H), 6.93-6.97 (m, 1H), 6.65 (d, J = 8.0 Hz, 1H), 3.90 (br, s, 2H), 2.21 (s, 3H)
2g	3390, 3358, 3345, 3295	7.64 (t, 1H), 7.15 (t, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.48 (t, 1H), 4.09 (br, s, 2H)
2h	3385, 3290, 3185, 1625	7.60 (d, J = 2.4 Hz, 1H), 7.08-7.12 (m, 1H), 6.65 (d, J = 8.6 Hz, 1H), 3.96 (br, s, 2H)
2i	----	----

Acknowledgment.- We thank the National Natural Science Foundation of China (No. 20672113) for financial support.

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AN IMPROVED METHOD FOR THE PREPARATION OF 2-(2'-AMINO-ARYL)OXAZOLINES FROM SUBSTITUTED ISATOIC ANHYDRIDES AND 2-CHLOROETHYLAMINE HYDROCHLORIDE

Submitted by David A. Hunt
(09/08/06)

Department of Chemistry, The College of New Jersey
P. O. Box 7718, Ewing, NJ 08628-0718
e-mail:hunt@tcnj.edu

2-(2'-Aminoaryl)oxazolines (**4**) and their derivatives have been studied as ligands for a variety of metal chelates[1] and are known to possess biological activity in both free ligand[2,3c] and chelated[1b] forms. The standard methods for preparation of 2-(2'-aminoaryl)oxazolines employ a nucleophilic ring opening of 2H-3,1-aryloxazine-2,4(1H)-diones [*i. e.*, substituted isatoic anhydrides (**1**)] with an ethanolamine followed by cyclization of the intermediate β-hydroxyethylamide **3** with catalysts such as $ZnCl_2$,[1b] H_2SO_4,[3] AcOH/ NaOAc,[4] kaolinitic clay,[5] and $P(OEt)_3$[6] under reflux in a high boiling solvent. While the intermediate β-hydroxyethyl amide **3** is typically not isolated, it is clear that this preparative method may not be applicable to substrates which may be sensitive to these reaction conditions.

Herein is described a straightforward alternative one-pot procedure employing mild basic conditions which affords a variety of 2-(2'-aminoaryl)oxazolines in moderate to good yields. Conducting the reaction of a substituted isatoic anhydride as the starting material with 2-chloroethylamine hydrochloride and 2.5 equivalents of triethylamine as the HCl scavenger in anhydrous *N,N*-dimethylformamide at temperatures ranging from 70-85°C provides the desired