ORGANIC LETTERS

2013
Vol. 15, No. 16
4194–4197

Direct Oxidative Conversion of Methylarenes into Aromatic Nitriles

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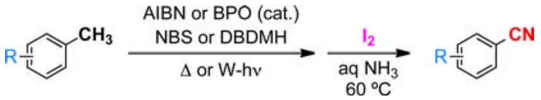
Received July 8, 2013

ABSTRACT



A variety of methylarenes were successfully converted into the corresponding aromatic nitriles in good to moderate yields by the treatment with NBS or DBDMH in the presence of a catalytic amount of AIBN or BPO, followed by the reaction with molecular iodine in aq NH_3 in a one-pot procedure. The present reaction is a useful and practical transition-metal-free method for the preparation of aromatic nitriles from methylarenes.

Study of the practical transition-metal free methods for the preparation of aromatic nitriles is very important since they are precursors for the preparation of amides, esters, primary amines, carboxylic acids, aldehydes, ketones, and nitrogen-containing heterocycles, such as tetrazoles and oxazoles.[1] They have also great importance in the synthesis of agrochemicals, therapeutic drugs, functional materials, natural products, dyes, and pigments.[1,2] Today, the most conventional methods for the preparation of aromatic nitriles are the dehydration of primary aromatic amides[3,4] with $SOCl_2$, TsCl/Py, P_2O_5, $POCl_3$, $COCl_2$, $(EtO)_3P/I_2$, Ph_3P/CCl_4, or $(COCl)_2$/DMSO and the Sandmeyer reaction of aromatic diazonium ion with toxic CuCN.[4,5] Recently, the direct transformation of aromatic bromides into the corresponding aromatic nitriles was actively studied with CuCN in *N*,*N*-dimethylformamide (DMF) at 153 °C (the Rosenmund−von Braun reaction),[6a] and related reactions with palladium and metal cyanide were

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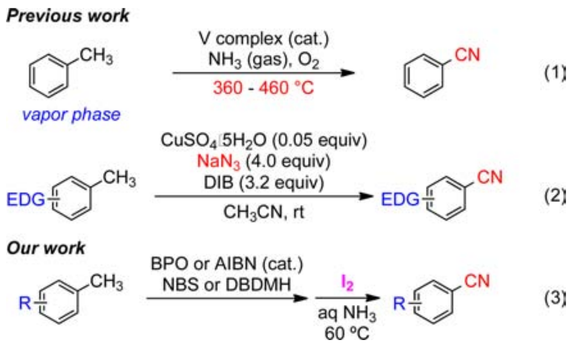
10.1021/ol401906q

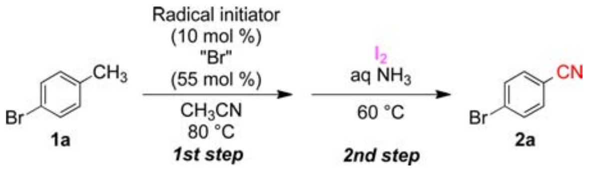
reported.[6b−q] However, all of these reactions require toxic metal cyanides. Typical examples of cyanide-free and transition-metal-free methods for the preparation of aromatic nitriles are the reaction of electron-rich aromatics with chlorosulfonylisocyanate to form *N*-chlorosulfonyl amides and the subsequent treatment with DMF to give aromatic nitriles, together with generation of SO_3 and HCl,[7a,b] and the reaction of indoles or pyrroles with triphenylphosphine−thiocyanogen (TPPT).[7c] Three methods reported by us recently are the reaction of bromoarenes, methoxybenzene, dimethoxybenzenes, and 1,3-difluorobenzene with *n*-BuLi and subsequently DMF, followed by the reaction with molecular iodine and aq NH_3;[8a,b] the reaction of electron-rich aromatics, such as dimethoxybenzenes, with $POCl_3$−DMF, followed by the reaction with molecular iodine and aq NH_3;[8c,d] and the reaction of bromoarenes with Mg and then DMF, followed by the reaction with molecular iodine and aq NH_3.[8e,f] On the other hand, studies of the direct oxidative conversion of methylarenes into aromatic nitriles are extremely limited, as shown in Scheme 1. One conversion method requires high temperatures (360−460 °C) using ammonia and oxygen in the presence of $(VO)_2P_2O_7$ catalyst[9a] (Scheme 1, eq 1).

Scheme 1. Established Methods for Transformation of Methylarene to Aromatic Nitrile



Another conversion method involes the reaction of methylarenes with excess amounts of NaN_3 and (diacetoxyiodo)benzene (DIB) in the presence of $CuSO_4$ catalyst at room temperature,[9b] which requires toxic NaN_3 and is effective for only electron-rich methylarenes (Scheme 1, eq 2). Here, we would like to report a cyanide-free and transition-metal-free one-pot conversion of methylarenes into aromatic nitriles by treatment with *N*-bromosuccinimide (NBS) or 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in the presence of a catalytic amount of benzoyl peroxide (BPO) or 2,2′-azobis(isobutyronitrile) (AIBN), followed by the reaction with molecular iodine in aq NH_3 (Scheme 1, eq 3) because we know for a fact that benzylic halides can be effectively converted into the corresponding aromatic nitriles with molecular iodine and aq NH_3 (60 °C for a few hours).[10] Thus, 4-bromotoluene **1a** was treated with NBS or DBDMH in the presence of a catalytic amount of BPO or AIBN in carbon tetrachloride at 80 °C, followed by the treatment with molecular iodine and aq NH_3 for 4 h at 60 °C, as the Wohl-Ziegler reaction is generally carried out in carbon tetrachloride.[11] After optimization studies, we found that BPO and AIBN showed the same reactivity as a radical initiator (entries 1 vs 2), DBDMH had higher reactivity than NBS (entries 1 vs 3), and acetonitrile exhibited higher reactivity than carbon tetrachloride in the Wohl-Ziegler reaction (entries 1 vs 4), to give 4-bromobenzonitrile **2a** in good yields, as shown in Table 1. Then, using the optimum conditions (Table 1, entry 7), the conversion of 1-methylnaphthalene **1l** into 1-cyanonaphthalene **2l** with DBDMH in the presence of BPO, followed by treatment with molecular iodine and aq NH_3, was performed. However, 4-bromo-1-methylnaphthalene was obtained in 84% yield, together with 1-cyanonaphthalene in 9% yield, as shown in entry 1 of Table 2. Thus, under warming conditions, the polar bromination of 1-methylnaphthalene occurred to give mainly 4-bromo-1-methylnaphthalene. After optimization studies to suppress the polar bromination of aromatics, it was found that

Table 1. One-Pot Transfomation of 4-Bromotoluene to 4-Bromobenzonitrile



	first step			second step		
entry	radical initiator	“Br”	time (h)	I_2 (equiv)	time (h)	yield (%)
1	BPO	DBDMH	2	2.5	4	86
2	AIBN	DBDMH	2	2.5	4	86
3[a]	BPO	NBS	2	2.5	4	52
4[b]	BPO	DBDMH	2	2.5	4	55
5[c]	BPO	DBDMH	2	2.5	4	76
6	BPO	DBDMH	2	4.0	4	83
7	BPO	DBDMH	3	2.5	12	87
8		DBDMH	2	2.5	4	11

[a] NBS (1.1 equiv) was used. [b] Reaction was carried out in CCl_4. [c] Reaction was carried out at 90 °C.

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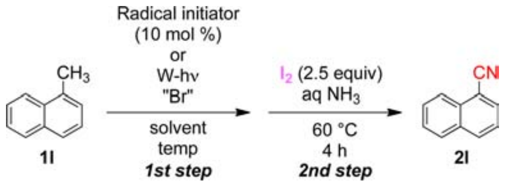
irradiation of the mixture of 1-methylnaphthalene **1l** and NBS in carbon tetrachloride with a tungsten lamp (200 W, *W-hv*) gave 1-cyanonaphthalene **2l** in 88% yield (Table 2, entry 6). Thus, those two reaction systems, namely, DBDMS with BPO in refluxing acetonitrile (method A) for electron-deficient methylarenes and NBS under irradiation with a tungsten lamp in carbon tetrachloride at room temperature (method B) for electron-rich methylarenes, are recommended for the conversion of methylarenes **1** into aromatic nitriles **2**.

Table 2. One-Pot Transfomation of 1-Methylnaphthalene to 1-Cyanonaphthalene

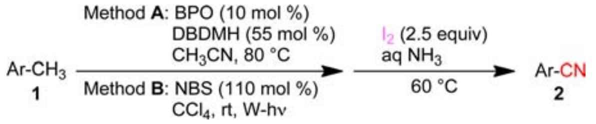


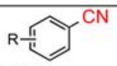
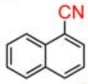
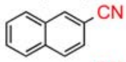
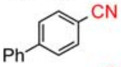
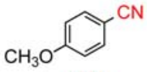
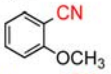
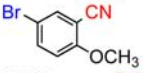
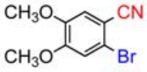
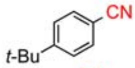
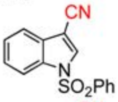
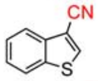
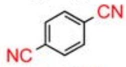
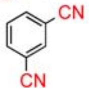
	first step					
entry		"Br" (mol %)	solvent	temp (°C)	time (h)	yield (%)
1	BPO	DBDMH (55)	MeCN	80	2	9 (84)[b]
2	AIBN	DBDMH (55)	CCl_4	60	2	54
3	*hν*[a]	NBS (110)	CCl_4	rt	1	80
4	*hν*[a]	NBS (110)	CCl_4	rt	1	52
5	*hν*[a]	DBDMH (55)	CCl_4	rt	1	4
6	*hν*[a]	NBS (110)	CCl_4	rt	2	88

[a] The first step reaction was carried out under tungsten lamp irradiation. [b] The number in parenthess indicates the yield of 4-bromo-1-methylnaphthalene.

Then, these two methods (methods A and B) were used for the conversion of various methylarenes **1** into aromatic nitriles **2**, as shown in Table 3. For electron-deficient methylarenes **1**, such as 2-bromotoluene **1b**, 3-bromotoluene **1c**, 4-chlorotoluene **1d**, 4-iodotoluene **1e**, 4-benzoyltoluene **1f**, 4-methanesulfonyltoluene **1g**, 4-cyanotoluene **1h**, and 4-nitrotoluene **1i**, both methods A and B furnished the corresponding aromatic nitriles **2** in good to moderate yields (entries 1−9), while the same treatment of methyl 4-methylbenzoate **1j** using methods A and B gave 4-cyanobenzamide **2j** in good yields instead of methyl 4-cyanobenzoate (entry 10). This is due to the occurrence of amidation of formed methyl 4-cyanobenzoate by aq NH_3 at 60 °C. For toluene **1k**, 2-methylnaphthalene **1m**, 4-methylbiphenyl **1n**, and 4-methyl-*tert*-butylbenzene **1s**, both methods A and B gave the corresponding aromatic nitriles **2k**, **2m**, **2n**, and **2s** in good to moderate yields (entries 11−14 and 19). It should be noted that method A could not be used for 4-methoxytoluene **1o** and 2-methoxytoluene **1p** because of polar bromination of the aromatic rings. However, using method B, 4-methoxytoluene **1o** and 2-methoxytoluene **1p** were smoothly transformed into 4-methoxybenzonitrile **2o** and 2-methoxybenzonitrile **2p** in good yields, respectively (entries 15 and 16). Moreover, when method B was used for 2-methoxytoluene **1p** and 4-methyl-1,2-dimethoxybenzene **1r** with 2.2 equiv of NBS, brominated aromatic nitriles, such as 5-bromo-2-methoxybenzonitrile **2q** and 2-bromo-4,5-dimethoxybenzonitrile

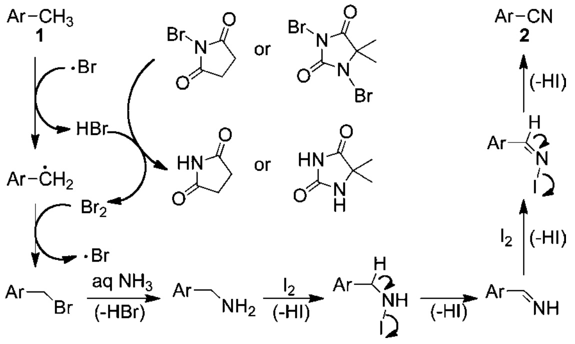
Table 3. One-Pot Transfomation of Methylarenes to Aromatic Nitriles



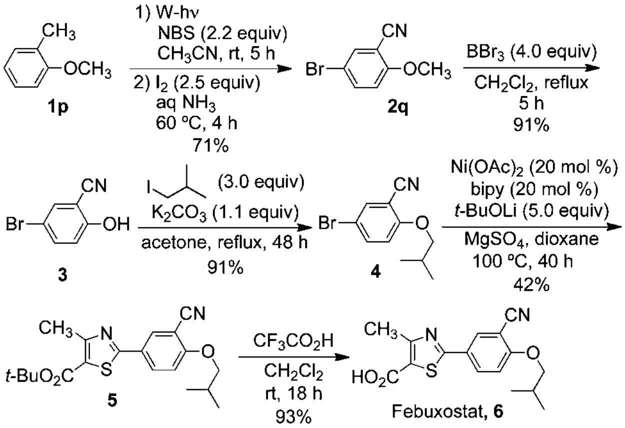
entry	product		yield (%) (time^{1st} (h), time^{2nd} (h)) Method **A**	Method **B**
				
1	R = 4-Br	**2a**	87 (3, 12)	88^{a,b} (2, 4)
2	R = 2-Br	**2b**	84^{c} (4, 48)	56 (2, 4)
3	R = 3-Br	**2c**	71^{c} (4, 48)	69^{b} (2, 4)
4	R = 4-Cl	**2d**	80^{d} (21, 12)	63 (2, 4)
5	R = 4-I	**2e**	82^{c} (2, 18)	68^{b} (2, 4)
6	R = 4-COPh	**2f**	74^{d} (12, 8)	60 (2, 5)
7	R = 4-SO_2CH_3	**2g**	60 (12, 4)	75^{b} (2, 18)
8	R = 4-CN	**2h**	87 (2, 15)	85 (2, 15)
9	R = NO_2	**2i**	71^{d} (13, 12)	61 (4, 12)
10	R = 4-$CONH_2$	**2j**	75^{e} (2, 4)	78^{e} (4, 18)
11	R = H	**2k**	80^{c,f} (4, 4)	61 (2, 4)
12		**2l**	71^{c,g,h,i} (2, 4)	88 (2, 4)
13		**2m**	60^{c,g} (2, 4)	77 (2, 4)
14		**2n**	82^{c,j} (2, 16)	53 (2, 4)
15		**2o**	0 (2, 4)	90 (2, 4)
16		**2p**	-	92 (2, 4)
17		**2q**	-	71^{a,k} (5, 4)
18		**2r**	-	72^{k} (6, 4)
19		**2s**	76^{c} (2, 4)	82 (2, 4)
20		**2t**	0 (2, 4)	40^{l} (2, 4)
21		**2u**	0 (2, 4)	48^{b,m} (4, 18)
22		**2h**	64^{c,n} (2, 4)	74^{g,n} (2, 4)
23		**2w**	63^{c,n} (2, 12)	59^{n} (2, 12)

[a] CH_3CN was used instead of CCl_4. [b] DBDMH (1.0 equiv) was added instead of NBS. [c] CCl_4 was used instead of CH_3CN. [d] DBDMH (0.75 equiv) was added. [e] Methyl 4-methylbenzoate was used. [f] The reaction was carried out on a 3 mmol scale. [g] The reaction was carried out at 60 °C. [h] NBS (1.1 equiv) was added instead of DBDMH. [i] AIBN (0.1 equiv) was added instead of BPO. [j] DBDMH (1.0 equiv) was added. [k] NBS (2.2 equiv) was added. [l] The reaction was carried out in diluted conditions (0.1 M). [m] I_2 (3.5 equiv) was added at the second step. [n] NBS (2.2 equiv) was added at the first step, and I_2 (5.0 equiv) and aq NH_3 (6 mL) were added at the second step.

Scheme 2. Plausible Reaction Mechanism for Transformation of Methylarenes into Nitriles



Scheme 3. Synthesis of Febuxostat



2r were selectively obtained (entries 17 amd 18). *N*-Benzenesulfonyl-3-methylindole **1t** and 3-methylbenzothiophene **1u** were also converted into *N*-benzenesulfonyl-3-cyanoindole **2t** and 3-cyanobenzothiophene **2u** in moderate yields, respectively, by method **B** (entries 20 and 21). Furthermore, *p*-xylene **1v** and *m*-xylene **1w** were also converted into terephthalonitrile **2h** and isophthalonitrile **2w** in moderate yields, respectively, by methods **A** and **B** using twice the amounts of DBDMS or NBS reagent (entries 22 and 23). The present reaction pathway is shown in Scheme 2. At the initial step, the Wohl–Ziegler reaction of methylarenes with DBDMH or NBS in the presence of BPO or AIBN under warming conditions or irradiation conditions with a tungsten lamp occurs to form the corresponding arylmethyl bromides. By adding molecular iodine and aq NH$_3$ to the reaction mixture, the S$_N$2 reaction of arylmethyl bromides by NH$_3$ occurs to form arylmethylamines. Once arylmethylamines are formed, they are smoothly converted into the corresponding aromatic nitriles via the formation of imines and *N*-iodoimines.[12] Finally, the present method was applied to the preparation of Febuxostat precursor **5**, a nonpurine selective inhibitor of xanthine oxidase.[13] 2-Methoxytoluene was treated with NBS (method **B**) under irradiation conditions to form 5-bromo-2-methoxybenzonitrile **2q**, as shown in Scheme 3. Then, compound **2q** was demethylated with BBr$_3$ and treated with 1-bromo-2-methylpropane to form 5-bromo-2-isobutoxybenzonitrile **4**. Compound **4** was coupled with 4-methyl-5-*t*-butoxycarbonylthiazole in the presence of Ni(OAc)$_2$ and *t*-BuOLi to generate Febuxostat precursor **5**.[14] Once precursor **5** is formed, Febuxostat was easily obtained in 93% yield by treatment with CF$_3$CO$_2$H.

In conclusion, a variety of methylarenes were smoothly converted into the corresponding aromatic nitriles in good to moderate yields by the treatment with NBS or DBDMH in the presence of a catalytic amount of AIBN or BPO, followed by the reaction with molecular iodine in aq NH$_3$ in a one-pot procedure. The present reaction is a useful, practical, and transition-metal-free method for the preparation of aromatic nitriles from methylarenes.

Acknowledgment. Financial support in the form of a Grant-in-Aid for Scientific Research (No. 25105710) from the Ministry of Education, Culture, Sports, Science, and Technology in Japan, Iodine Research Project in Chiba University, is gratefully acknowledged.

Supporting Information Available. Experimental procedures, spectral data, and copies of NMR spectra. This material is available free of change via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.