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Mendeleev Commun., 2014, **24**, 102–104
Mendeleev Communications

Synthesis of 2-(buta-1,3-diynyl)-*N*,*N*-dimethylanilines using reductive methylation step

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DOI: 10.1016/j.mencom.2014.03.013

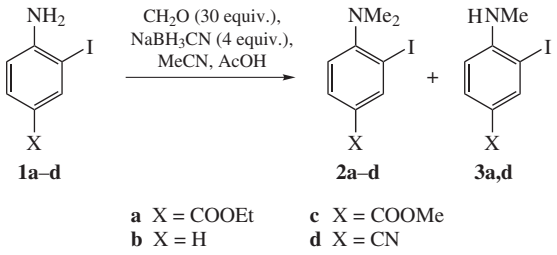
Synthesis of 2-(buta-1,3-diynyl)-*N*,*N*-dimethylanilines based on reductive methylation of *ortho*-iodoanilines using CH_2O–$NaBH_3CN$ and coupling with terminal diacetylens was developed. Altered sequence including dimethylation of 2-(buta-1,3-diynyl)anilines was also successfully achieved and gave higher overall yields in the case of anilines without acceptor substituent in the ring.

Following the studies by Stephens and Castro who stated the formation of indoles in a reaction of 2-iodoaniline with copper acetylenides,[1] intramolecular cyclization involving an amino group and an ethynyl moiety became common to access various indoles.[2] The cyclization is catalysed by bases or transition metal salts, among which Cu, Au or Pd ones proved to be the most efficient and versatile with respect to the nature of the other functional groups in starting substrates.[3] The electrophilic cyclization of *N*,*N*-dimethyl-2-ethynylanilines on treatment with elementary iodine was employed in a synthesis of 3-iodoindoles[4] and other indole derivatives.[5] Upon replacement of the ethynyl substituent by the 1,3-diynyl moiety, the iodocyclization should result in 3-iodo-2-ethynyl-substituted heterocycles. We used this approach as the key step in syntheses of enediyne systems fused to a heterocyclic moiety.[6]

2-(Buta-1,3-diynyl)-*N*,*N*-dimethylanilines are usually used as substrates in electrophilic cyclization. These compounds are obtained by Sonogashira cross-coupling of 2-iodo-*N*,*N*-dimethylaniline with terminal acetylenes.[4(e),7,8] Though direct methylation of anilines is rather simple chemistry, a limited number of syntheses of 2-iodo-*N*,*N*-dimethylanilines have been reported: the classical Hoffmann's procedure using iodomethane in the K_2CO_3–DMF system[4(d)] or in the K_2CO_3–MeCN system[9] and treatment of 2-iodoanilines with dimethyl sulfate[10] or methyl trifluoromethanesulfonate.[11] The efficiency of methylation of anilines depends on the nucleophilicity of the amino group, hence ring substituents affect the product yield. Electron-withdrawing substituents decrease the yield considerably, and methylation of 2-iodoanilines with an alkoxycarbonyl substituent using the Hoffmann reaction gives N,N-dimethylated products in rather low yields (about 40%).[8]

Two examples of reductive methylation of 2-iodoaniline to afford N,N-dimethylated derivatives have been reported: by the Eschweiler–Clarke reaction[12,13] and by treatment with formalin and sodium borohydride as the reducing agent (modification in dilute sulfuric acid).[14] On the other hand, the use of formalin in the presence of sodium cyanoborohydride ($NaBH_3CN$) in MeCN–AcOH in syntheses of aliphatic and aromatic dimethylated amines[15,16] proved to be highly efficient and selective method with respect to the reduction of the imine intermediate in the presence of ester, keto, ether and other functional groups.[17,18] Surprisingly, this technique was not applied previously to the preparation of 2-iodo-*N*,*N*-dimethylanilines and their derivatives from the corresponding 2-iodoanilines.

In order to develop an efficient method for the synthesis of 2-(buta-1,3-diynyl)-*N*,*N*-dimethylanilines, substrates for electrophilic cyclization, we decided to use reductive methylation of 2-iodoanilines with formalin and sodium cyanoborohydride.



1a–d **2a–d** **3a,d**

a X = COOEt **c** X = COOMe
b X = H **d** X = CN

Scheme 1

Table 1 Reductive methylation of *o*-iodoanilines.

Entry	Amine	*T*/°C	Reaction time	Product **2** yield (%)	Product **3** yield (%)
1	**1a**	7–20	7 days	**2a** (38)[b]	**3a** (31)[b]
2	**1a**	19–27	7 days	**2a** (40)[b]	**3a** (38)[b]
3	**1a**	Up to 90[a]	3 days	**2a** (82)	—
4	**1b**	Up to 90[a]	2 h	**2b** (97)	—
5	**1c**	Up to 90[a]	16 h	**2c** (64)	—
6	**1d**	Up to 90[a]	7 days	**2d** (39)[b]	**3d** (27)[b]

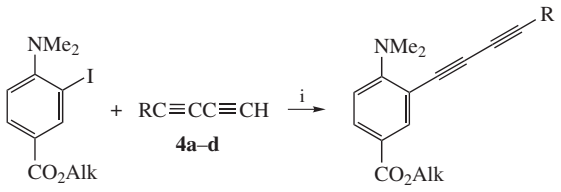
[a]The experiments were carried out without external cooling of the reaction mixture at the time when acetic acid was added. [b]The yields are specified with respect to the starting amine **1a** or **1d** that entered the reaction.

2-Iodoaniline **1b**, 4-amino-3-iodobenzonitrile **1d** and 4-amino-3-iodobenzoic esters **1a**,**c** were chosen as the objects of the study (Scheme 1, Table 1).

Methylation of 4-ethoxycarbonylaniline **1a** with cooling of the reaction mixture to the specified temperatures during the addition of acetic acid (Table 1, entries 1, 2) resulted in the formation of mono- and dimethylated anilines in ~1:1 ratio. Under these conditions, conversion of the starting aniline **1a** did not exceed 86% even after 7 days. Raising the temperature up to 90 °C allowed to obtain 2-iodo-*N*,*N*-dimethylaniline **2a** as a single reaction product in high yield (entry 3). The same conditions proved to be efficient in a synthesis of dimethylated anilines **2b**,**c** (entries 4, 5). However, these conditions did not afford the full conversion of substrate **1d** containing a strong electron-withdrawing nitrile group. In this case *N*-methyl- and *N*,*N*-dimethyl derivatives **3d** and **2d** were isolated in 27% and 39% yields, respectively (entry 6) at 92% conversion of the starting compound. It should be emphasized that scaling up of the reaction also affected

Table 2 Sonogashira coupling of iodoanilines **2a**,**c** with diacetylenes.

Entry	Iodoaniline	Diacetylene	Base	Solvent	Product	Yield (%)
1	**2c**	**4a**	Et_3N	THF	**5a**	—
2		**4b**	Et_3N	THF	**5b**	—
3		**4a**	DIPA	DMF	**5a**	43
4		**4b**	DIPA	DMF	**5b**	48
5		**4c**	DIPA	DMF	**5c**	61–82
6		**4d**	DIPA	DMF	**5d**	61
7	**2a**	**4a**	DIPA	DMF	**6a**	79
8		**4b**	DIPA	DMF	**6b**	45–86
9		**4c**	DIPA	DMF	**6c**	79–82



2a,**c** **5a–d**, **6a–c**

2c, **5** Alk = Me
2a, **6** Alk = Et

4–6 **a** R = C_8H_{17}
b R = Ph
c R = $(CH_2)_4OH$
d R = $(CH_2)_5OH$

Scheme 2 *Reagents and conditions*: i, $Pd(PPh_3)_2Cl_2$ (0.05 equiv.), PPh_3 (0.1 equiv.), NEt_3 (15.0 equiv.) or DIPA (4.0 equiv.), CuI (0.15 equiv.), THF or DMF, 40 °C.

the yield of the products **2a**,**c**. When the syntheses were carried out in less than one gram scale, the reaction gave only the dimethylated derivatives. When the scale was raised to 5–8 g, after three days, the reaction mixture contained all the three components **1**–**3**, which was apparently due to decomposition of sodium cyanoborohydride. Therefore, an additional amount of the reagents (50% of the initial amount) was necessary for complete conversion of the starting compounds **1b**,**c** to dimethylated products.

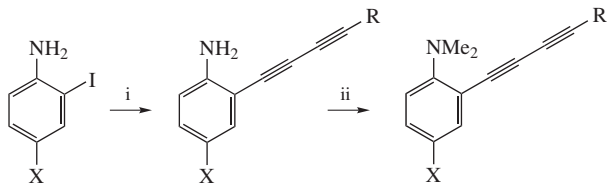
Then, in order to synthesize diacetylenic derivatives **5** and **6**, *i.e.*, substrates for electrophilic cyclization, the N,N-dimethylated products **2a**,**c** were subjected to the Sonogashira cross-coupling[7] with terminal diacetylenes **4a–d** (Scheme 2, Table 2). The latter were obtained by isomerization of internal diacetylenic hydrocarbons and alcohols (in the case of compounds **4a**,**c**,**d**),[19,20] and by *retro*-Favorskii reaction[21] (in the case of phenyldiacetylene **4b**).

The yield of cross-coupling was considerably affected by the nature of the base and the solvent. If the reaction was carried out in THF using triethylamine as the base, no products of the coupling between **2c** and **4a**,**b** were observed (Table 2, entries 1, 2). Replacement of the THF–Et_3N system by a more polar one, namely, DMF with diisopropanolamine (DIPA, 4-azaheptane-2,6-diol) as the base, led to the complete conversion of the aniline **2c** within 8 h to give the target products **5a**,**b** (entries 3, 4). However, the yields were moderate, probably due to the low stability of terminal diacetylenes **4a**,**b** under the reaction conditions. Therefore, the excess of terminal diacetylenes was raised from 1.5 to 3 equiv. in the case of substrate **2a**. This modification allowed to increase the yield of compounds **6a**,**b** (entries 7, 8). A 3.5-fold excess was used for very unstable terminal diacetylenic alcohols **4c**,**d** providing good yields of the cross-coupling products **5c**,**d** and **6c** (entries 5, 6, 9).

It also seemed appropriate to examine the possibility of obtaining substrates for electrophilic cyclization by altering the sequence of reductive methylation and cross-coupling reaction steps. Commercially available 2-iodoanilines **1b**,**c** readily underwent Pd/Cu-catalyzed Sonogashira coupling with terminal diacetylenes using $Pd(PPh_3)_2Cl_2$ and CuI as the catalysts in the Et_3N–THF system at 40 °C (Scheme 3, Table 3). Methylation of the resulting 2-(buta-1,3-diynyl)-substituted anilines **7a**,**b** by treatment with formalin in the presence of sodium cyanoborohydride in the MeCN–AcOH system led to compounds **8a**,**b** in good yields. This sequence proved to be more efficient due to higher overall yields of dimethyl derivatives **8a**,**b**. It should be noted that methylation of anilines **7a**,**b** with iodomethane in the K_2CO_3–DMF system afforded a mixture of N-methylated and N,N-dimethylated 2-(buta-1,3-diynyl)anilines along with quaternized products and allowed to isolate target products **8a**,**b** in yields not higher than 45%.

Table 3 Synthesis of 2-(buta-1,3-dyinyl)-*N*,*N*-dimethylanilines by cross-coupling–N-methylation sequence.

Substituent		Cross-coupling		Methylation	
X	R	Product	Yield (%)	Product	Yield (%)
H (**1b**)	C_8H_{17} (**4a**)	**7a**	90	**8a**	69–76
H (**1b**)	Ph (**4b**)	**7b**	73	**8b**	72–80
CO_2Me (**1c**)	Ph (**4b**)	**7c**	52	**5b**	21



1b,**c** **7a–c** **8a**,**b**, **5b**

Scheme 3 *Reagents and conditions*: i, **4a** or **4b**, $Pd(PPh_3)_2Cl_2$ (0.05 equiv.), PPh_3 (0.1 equiv.), Et_3N (15.0 equiv.), CuI (0.15 equiv.), THF, 40 °C; ii, CH_2O (37% aqueous solution) (30.0 equiv.), $NaBH_3CN$ (4.0 equiv.), AcOH, MeCN.

The presence of two acceptor substituents [4-methoxycarbonyl and 2-(buta-1,3-diynyl)] in compound **7c** considerably decreases the nucleophilicity of the amino group, which affected in prolongation of the reaction time, significantly reduced the conversion and the yield of the product **5b**. Therefore, the reverse sequence of methylation and cross-coupling is preferable in this case.

In conclusion, reductive methylation with formalin and sodium cyanoborohydride is an efficient alternative to the Hoffman reaction for the methylation of 2-iodoanilines, including those containing alkoxycarbonyl substituents at 4-position. Carrying out the reaction without cooling the reaction mixture during the addition of acetic acid allowed to obtain exclusively target N,N-dimethylated aniline derivatives. The application of reductive methylation and the Sonogashira cross-coupling using DMF as the solvent and DIPA as the base is an efficient approach to the synthesis of 2-(buta-1,3-diynyl)-*N*,*N*-dimethylanilines – substrates for the electrophilic cyclization. We also demonstrated that reductive methylation in the presence of sodium cyanoborohydride in the MeCN–AcOH system can be successfully used for the dimethylation of 2-(buta-1,3-diynyl)anilines.

This study was supported by St. Petersburg State University (grant no. 12.38.195.2014) and grant of the President of the RF (MK-3322.2014.3). The researches were carried out using the equipment of the resource centres of St. Petersburg State University: Centre of Magnetic Resonance and Center for Chemical Analysis and Materials Research.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.02.013.

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Received: 20th September 2013; Com. 13/4207