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SYNTHESIS OF AROMATIC AMINES FROM ELECTRON-RICH ARENES AND BIS(2,2,2-TRICHLOROETHYL) AZODICARBOXYLATE

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ABSTRACT: Electron-rich arenes react with bis(2,2,2-trichloroethyl) azodicarboxylate in 3 M lithium perchlorate-diethylether or acetone solution to produce para-substituted aryl hydrazides in high yields. The corresponding aromatic amines are readily obtained by reducing the hydrazides with zinc in acetic acid.

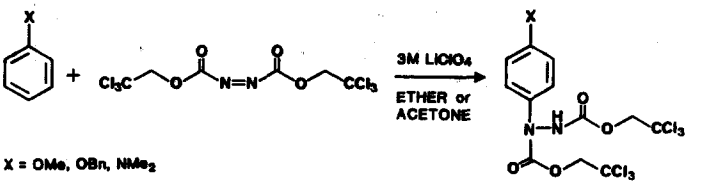
Aromatic amines are important compounds as they are incorporated in different classes of biologically active molecules. Notable examples of active compounds containing derivatized aromatic amines in their structure include antibiotics,[1] analgesics[2] and ß-adrenergic blockers.[3] Furthermore, aromatic amines are key intermediates in the synthesis of a variety of aromatic compounds via diazotization[4] and nucleophilic substitution reactions.[5] Conventional methods for the synthesis of anilines involve an electrophilic aromatic substitution[6] usually via a nitration[7] followed by reduction by catalytic hydrogenation, metals in acidic medium or with hydrides such as $Na_2BH_2S_3$ (Lalancette's reagent).[8] Aromatic amines can be also prepared by a vicarious nucleophilic aromatic substitution of hydrogen (VNS)[9] or nucleophilic substitution of halogen (SNAr)[10] with amines as nucleophiles.

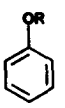
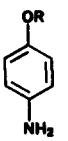
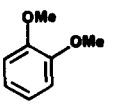
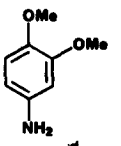
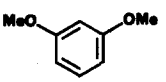
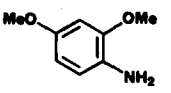
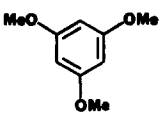
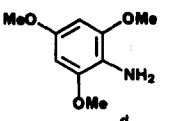
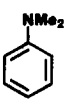
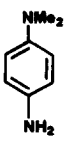
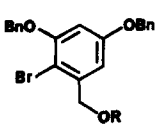
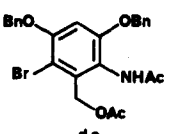
Over the last six years, it has been demonstrated that azodicarboxylates are an effective source of positive nitrogen.[11] For example, azo molecules were used as aminating species in the synthesis of α-amino acids,[12] 2-aminosaccharides,[13] allylic amines[14] and lactams.[15] We rationalized that azo compounds could also served as an aminating agent for arenes provided the substrate and the azo compound itself are sufficiently reactive.

The thermal and acid-catalysed electrophilic reactions of azodicarboxylates with alkylbenzenes and some substituted phenols have already been reported.[16] In these reports however, high temperatures or strongly acidic conditions (H_2SO_4, $BF_3{\cdot}ET_2O$ neat) were required to allow the amination reaction. Also in 1987, Demers and Klaubert have described the preparation of aryl hydrazines from the condensation of aryl lithiums or aryl Grignards with bis(tert-butyl) azodicarboxylate to afford aryl hydrazides.[17] From our previous observations, [13-15] it was anticipated that aromatic amines could be prepared under mild conditions, via the amination of arenes with bis(2,2,2-trichloroethyl) azodicarboxylate (BTCEAD). We detail herein, pratical conditions for the amination of electron-rich arenes.

In an initial attempt we observed that aromatic molecules, even electron-rich substrates, are inert toward conventional and electron-deficient azo reagents such as bis(tert-butyl)- and bis(2,2,2-trichloroethyl) azodicarboxylates. Consequently, activators were required to achieve the present goal. Grieco and co-workers have reported that some organic reactions can be tremendously accelerated when conducted in 3 M lithium perchlorate-diethyl ether or acetone solutions.[18] Under these neutral conditions, it was observed that electron rich arenes do indeed react with bis(2,2,2-trichloroethyl) azodicarboxylate (BTCEAD) to give the desired aminated product (Scheme 1). With anisole (**1**) and 1,2-dimethoxybenzene (**3**) as substrates, the reactions were performed at 65°C in 3 M $LiClO_4$-diethylether solution for the former and at 75°C in acetone for the latter. *As a precaution a sideshield was used for the present reaction.* After aqueous work up and extraction (EtOAc),

SCHEME 1



ARENE	HYDRAZIDE	TIME	(TEMP)	YIELD	AROMATIC AMINE
					
1 R=Me	*9*	24 hr	(65°C)	99%[a]	*17* R=Me 71%[d]
2 R=H	*10*	3 hr	(65°C)	87%[a]	*18* R=H 66%[d]
 *3*	*11*	24 hr	(75°C)	82%[b]	 *19* 89%[d]
 *4*	*12*	2 hr	(rt)	99%[c]	 *20* 76%[d]
 *5*	*13*	5 min	(rt)	77%[c]	 *21* 93%[d]
 *6*	*14*	1 hr	(rt)	76%[c]	 *22* 90%[d]
					
7 R = H	*15*	2.5 hr	(rt)	82%[c]	*23* 73%[d,e] from *15*
8 R = Ac	*16*	18 hr	(rt)	91%[c]	

a) $Cl_3CCH_2O_2CN{=}NCO_2CH_2CCl_3$ 3.0 equiv., ether b) as in a) except 2.5 equiv., acetone c) as in a) except 1.5 equiv. d) Zn dust 1.0 equiv. by weight, HOAc e) Ac_2O, Py, CH_2Cl_2

the hydrazides **9** and **11** were isolated by flash chromatography in 99% and 82% yields, respectively. This aryl amination reaction is selective and is para-directed, the hydrazides **9** and **11** were isolated as a single regioisomer. These conditions are compatible with phenolic compounds, for example, phenol (**2**) was exclusively para-aminated to give **10**. BTCEAD (1.5 equiv.) adds to 1,3-dimethoxybenzene (**4**) at room temperature to give the hydrazide **12** within an hour. In the case of 1,3,5-trimethoxybenzene(**5**), the reaction was completed within a few minutes to provide (**13**) and no bisaminated product was observed. N,N-dimethylaniline (**6**) was found to be also very reactive to readily produce the hydrazide **14** in 76% yield.[19] These mild aminating conditions of arenes can be applied to more sophisticated molecules that will probably not survive strongly acidic nitration conditions. For example, with substrates **7** and **8**, the adducts **15** and **16** were isolated in 82% and 91% yields respectively after 1 hr at room temperature.

The aryl hydrazides (**9-16**) prepared during the present study were easily converted in high yields to their corresponding anilines (**17-23**) by reduction with zinc dust in acetic acid.

In summary, electron-rich arene compounds were regioselectively aminated under neutral conditions.[20] We believe that lithium perchlorate may play two roles in the present reaction which are the activation of the azo compound and the stabilization of the σ-complex that might be involved in the reaction.[21] The conditions used for the present amination of arenes could be eventually applied to other systems and work is progressing in this area in our laboratories.

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