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Communications

Amination of Arenes with Diethyl Azodicarboxylate (DEAD)

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The use of azodicarboxylate as an electrophilic source of nitrogen NH_2^+ or as a heterodiene in reverse electron demanding Diels-Alder reaction is now well documented in the literature.[1-3] A representative example includes the amination of electron-rich arenes[2] or olefinic compounds[3] by electron-deficient azodicarboxylate such as bis(2,2,2-trichloroethyl) azodicarboxylate employing various acids as catalyst. This method first developed by Leblanc, however, has some serious drawbacks in that the numbers of substrate arenes are limited, not mention to the cost of the reaction due to the high price of bis(2,2,2-trichloroethyl) azodicarboxylate.

In our search for *N,N'*-bis(ethoxycarbonyl)arylhydrazines for the preparation of 1,3,4-oxadiazole[4a] and 1,3,4-thiadiazole moieties[4b] found in many biologically active compounds, we have discovered a useful new method through a slight modification of the Leblanc's method. Our new method employs rather a broader range of substrates as well as inexpensive diethyl azodicarboxylate (DEAD).

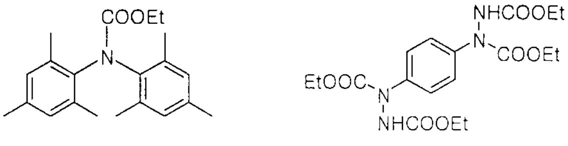
Our recent interest in the use of trifluoromethanesulfonic acid (TfOH) or trifluoroacetic acid (TFA),[5] and the Leblanc's brilliant papers[2] give us some insight on the desired reaction. Table 1 shows the formation of *N,N'*-bis(ethoxycarbonyl)arylhydrazines in high to medium yields under various reaction conditions.

In most cases except for the case of electron-rich arenes (entries a and b), the presence of TfOH is essential for high yield synthesis of corresponding products. As expected from the literature,[2] the position of the incoming hydrazine moiety is *para* to the substituent already present in the arene substrate in all cases. These observations may be explained in terms of the steric bulkiness of the large electrophilic species, *i.e.*, protonated DEAD. For instance, while 1,2-dichlorobenzene gives the corresponding product in a reasonable yield (62%)(entry f), 1,4-dichlorobenzene did not give any products under the standard set of reaction conditions.

The following procedure is typical: To a stirred solution of benzene (3.9 g, 50 mmol) and DEAD (0.87 g, 5 mmol) in trifluoroacetic acid (5 mL) was added TfOH (750 mg, 5 mmol). The reaction mixture was stirred at room temperature for 20 h, after which the mixture was poured into cold 5% aqueous sodium hydrogencarbonate, extracted with diethyl ether, dried with magnesium sulfate, and evaporated to dryness. Column chromatographic purification by silica gel column (hexane/ether, 1 : 1) afforded analytically pure product **2d** (745 mg, 59%) along with *para*-disubstituted derivative **4d** (410 mg, 19%).[6]

Surprisingly, the reaction of mesitylene (entry b), when carried out in the presence of both TfOH and TFA, yielded unexpectedly **3b** as a major product (62%). The ^1H NMR spectrum of **3b** reveals expected signals with some line broadening probably due to the restricted rotation of the mesityl groups along the N-C bonds. Finally, in connection with the reaction of benzene which is the least sterically-demanding arene, a significant amount of 1,4-bisaminated compound **4d** was produced (19%) in addition to **2d**.

In conclusion, we describe here the facile synthesis of



3b **4d**

Figure of **3b** and **4d**

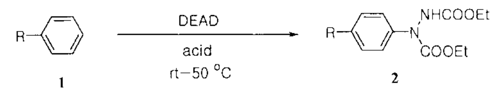
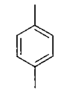
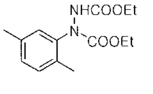
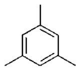
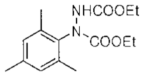
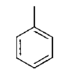
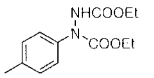
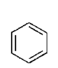
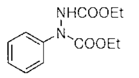
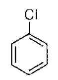
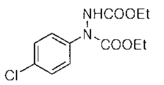
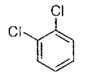
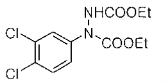
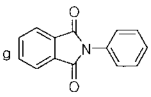
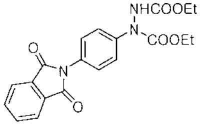
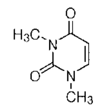
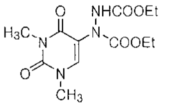


Table 1. Synthesis of N,N'-Bis(ethyoxycarbonyl)arylhydrazine Derivatives **2**

entry	arenes (**1**)[a]	conditions	products (**2**)	yield (%)
a		CF_3COOH 40–50 °C, 6 h		77
b		CF_3COOH 40–50 °C, 8 h		72[b]
c		CF_3COOH + TfOH (1.0 equiv) rt, 6 h		90
d		CF_3COOH + TfOH (1.0 equiv) rt, 20 h		59[c]
e		CF_3COOH + TfOH (1.0 equiv) 40–50 °C, 2 h		83
f		CF_3COOH + TfOH (1.0 equiv) 40–50 °C, 12 h		62
g		CF_3COOH + TfOH (0.2 equiv) 40–50 °C, 2 days		53
h		CF_3COOH + TfOH (0.2 equiv) 40–50 °C, 2 days		43

[a]Mmols (sbustrate): 10 mmol (entries a-f), 1 mmol (entries g, h). [b]Addition of TfOH (1.0 equiv) produced **3b** (62%) and a trace amount of **2b**. [c]1,4-Diaminated compound **4d** was also obtained in 19% yield.

aminated arenes including electron-deficient ones. Application of the methodology to the intramolecular version to form carbazole or phenoxazine derivatives is under progress.

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6. Spectroscopic data of some representative compounds are as follows: *N,N'*-Bis-(ethoxycarbonyl)phenylhydrazine (**2d**); pale yellow oil; 745 mg (59%); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 6H), 4.22 (app quintet, *J* = 7.5 Hz, 4H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.53 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 14.24, 14.27, 62.07, 62.80, 124.15, 126.13, 128.45, 141.57, 154.86, 156.32; ^{13}C NMR (DMSO-d_6) δ 14.32, 14.48, 61.11, 62.18, 123.39, 125.67, 128.55, 142.16, 154.32, 156.10; IR (CH_2Cl_2) 3300, 2984, 1724, 1598, 1493, 1236, 1063 cm^{-1}; MS (70 eV) *m/z* (rel intensity) 77 (18), 107 (100), 119 (18), 135 (14), 152 (18), 180 (75), 252 (M$^+$, 10).
Bis-(2,4,6-trimethylphenyl)carbamic acid ethyl ester (**3b**): oil; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 3H), 1.73 (brs, 6H), 2.23 (s, 3H), 2.25 (s, 3H), 2.29 (brs, 6H), 4.14 (brs, 1H), 4.32 (brs, 1H), 6.72 (brs, 2H), 6.91 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 14.70, 18.85, 19.38, 19.78, 20.60, 20.63, 62.02, 129.44, 129.75, 130.55, 133.73, 135.46, 135.51, 135.91, 136.13, 136.70, 137.11, 155.41; MS (70 eV) *m/z* (rel intensity) 119 (5), 136 (8), 162 (37), 236 (49), 237 (27), 252 (7), 325 (M$^+$, 100).
Bisamination product **4d**: white solid; mp 196-198 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 12H), 4.24 (app quintet, *J* = 7.4 Hz, 8H), 7.17 (brs, 2H), 7.39 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 14.45, 62.40, 63.14, 124.29, 139.49, 154.81, 156.35; MS (70 eV) *m/z* (rel intensity) 29 (68), 135 (40), 148 (32), 194 (31), 209 (61), 281 (73), 353 (54), 426 (M$^+$, 100).