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Synthesis of Monoaryl Hydrazides via the BF_3 Catalyzed Reaction of Diethyl Azodicarboxylate with Substituted Benzenes

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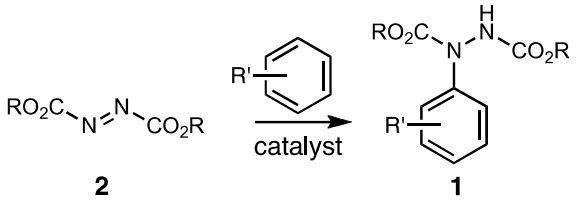
Abstract DiethylAzodicarboxylate (DEAD) reacted readily with sufficiently activated aromatic compounds in the presence of 25 mol% BF_3•$O(Et)_2$ as Lewis acid catalyst to afford monoarylhydrazides in reasonable-to-high yields (41-94%).

Keywords Arenes, Azodicarboxylates, Electrophilic Aromatic Substitution

1. Introduction

Monoarylhydrazides (**1**, Scheme 1) are important intermediates for the synthesis of a variety of biologically active heterocycles including indoles[1], oxadiazolones[2], and pyrazolones[3]. Thus, it is not surprising that the pursuit of new and improved methods for the synthesis of aryl hydrazides remains an active area of research[4].



Scheme 1. Synthesis of MonoarylHydrazides via Electrophilic Aromatic Substitution of Azodicarboxylates

Many routes for the synthesis of monoarylhydrazides have been devised including metal-mediated coupling of unsubstitutedhydrazides to haloaromatics[5], Pd orCu-catalyzed coupling of dialkylazodicarboxylates to arylboronic acids[4e,6],the addition of organometallic reagents to azodicarboxylates[7], and electrophilic aromatic substitution (EAS) of dialkylazodicarboxylates 2 onto aromatic rings (see Scheme 1)[8]. EAS reactions are a particularly economical synthetic method since most of the other methods rely upon access to haloaromatic starting materials that are typically formed from EAS reactionsthemselves. Several methods have been reported for effecting EAS reactions of azodicarboxylates with aromatic rings[8]. However, they generally require strongly acidic conditions (e.g., mixtures of TfOH and CF_3CO_2H)[9],expensive metal catalysts (e.g., $Sc(OTf)_3$, $InCl_3$, $AuCl_3$)[4b,10], or the use of the highly electron-deficient (and expensive)bis(2,2,2-trichloroethyl) azodicarboxylate[4b,9a,11]. The Lewis acid catalyst BF_3•$O(Et)_2$ is easy to work with and inexpensive. While there have been a few isolated reports of BF_3-catalyzed EAS reactions of readily available diethyl azodicarboxylate (DEAD, **2**, where R = Et) with aromatic substrates[12], we could find no studies that investigated the scope or limitations of the reaction. The results of our preliminary investigations on these reactions are presented here.

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2. Results and Discussion

In the few studies that reported the use of the Lewis acid BF_3 to catalyze the EAS reactions of DEAD with aromatic compounds, one or more equivalents of the acid catalyst were utilized[12]. Indeed, the addition of one equivalent of BF_3•$O(Et)_2$ to an equimolar mixture of DEAD (2.5 mmol) and anisole in CH_2Cl_2 as solvent resulted in formation of the desired adduct **3a** (Figure 1) in reasonable yield (64%). We were able to decrease the catalyst load to 25 mol% without affecting the product yield (64%) although the reaction required somewhat longer reaction time (1 h vs 0.5 h). In both cases, a disubstituted product was formed in addition to the desired monoadduct. This is not surprising given that the monoadductis expected to be electronically activated relative to starting anisole. Using 2 equivalents of anisole was enough to virtually eliminate the formation of the disubstituted product and the yield of **3a** increased to 90%. We subsequently found that with other substrates, such as 1,3-dimethoxybenzene to form **3c** (*vide infra*), upwards of 10 equivalents of the aromatic substrate were required to

squelch formation of di- and polysubstituted products. Fortunately, however, in these cases unreacted aromatic starting material could be readily recovered (after quenching of the BF_3 catalyst) via either direct distillation from the crude reaction mixture or column chromatography.

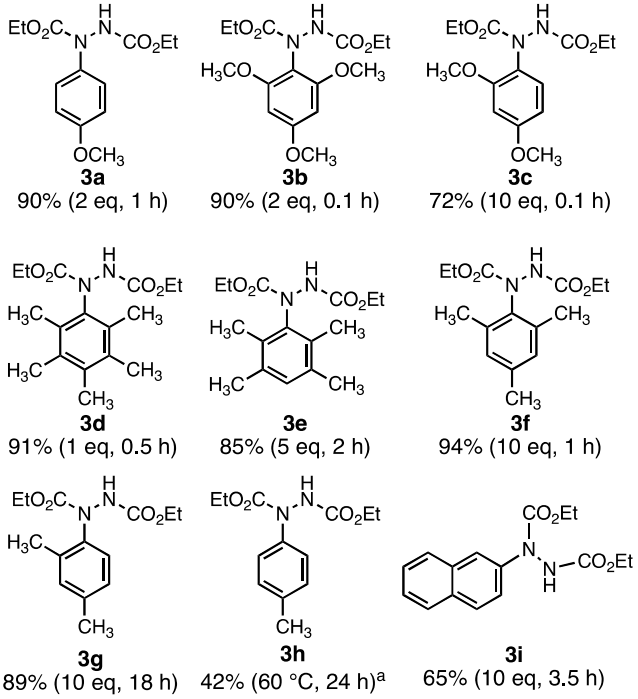

Figure 1. Products of the EAS reactions of DEAD with various aromatic substrates. All reactions were conducted according to the General Procedure described in the experimental unless otherwise noted. Percent yields are for purified products. In parentheses are indicated equivalents of substrate, reaction time, and temperature if relevant. [a]Toluene was used as the solvent in the reaction. The ratio of para:ortho adduct was ~70:30 as determined by ^{1}H NMR integration

A variety of aromatic substrates were subjected to the same reaction conditions previously optimized for anisole (i.e., 0.25 equivalents of BF_3, 1-10 equivalents of aromatic substrate) to afford the expected monoadducts in good to excellent yields (Figure 1). 1,3,5-Trimethoxybenzene reacted similarly to anisole to form **3b** in high yield. Curiously, however, the reaction of DEAD with two equivalents of 1,3-dimethoxybenzene afforded **3c** in only 33% yield, the remainder of the product being disubstituted. Employing 5 equivalents of 1,3-dimethoxybenzene increased the yield to 59%, but formation of the disubstituted product persisted. We wondered whether in this case the BF_3 catalyst was prone to complexation with monoadduct **3c** and acted to direct further substitution onto the complexed ring, thus accounting for the unusual preference for disubstitution. We tested this theory by adding DEAD to a premixed solution of 1,3-dimethoxybenzene (5 eq) and a full equivalent of BF_3 thereby maximizing the interaction of DEAD with non-complexed BF_3 and aromatic substrate. However, a yield nearly identical to the reaction conducted under standard conditions was observed (60%). Under the standard conditions, but with 10 equivalents of substrate, **3c** was formed in 72% yield.

A series of methylated arenes including pentamethylbenzene, durene, mesitylene and *m*-xylene all afforded excellent yields of the expected hydrazide products **3d-g**, respectively (Figure 1).

The reaction appears to be successful with aromatic compounds at least as electronically activated as toluene. For example, whereas *m*-xylene readily engaged in reaction at room temperature to afford **3g**, reaction with toluene required heating to 60°C and employing toluene as solvent for the reaction. Even then, only a modest yield (42%) of adduct **3h** was observed (although this compares favorably with the yield recently reported[38%] for the corresponding $AuCl_3$-catalyzed reaction of the highly electrophilic bis(2,2,2-trichloroethyl) azodicarboxylate with toluene)[4b]. Unfortunately, no reaction with benzene (as solvent) was observed even after heating the reaction mixture to 80°C. However, unsubstituted naphthalene afforded a reasonable yield (65%) of hydrazide **3i** (Figure 1).

Finally, we have also begun testing the reactivity of other commercially available azodicarboxylates. In particular, diisopropylazodicarboxylate (**2**, where R = iPr) and di-*tert*-butyl azodicarboxylate (**2**, where R = *tert*-Bu) were subjected to the reaction conditions optimized for DEAD. Diisopropylazodicarboxylate reacted with anisole to afford hydrazide **4** in 90% yield (Figure 2)[12e]. Di-*tert*-butyl azodicarboxylate was found to be unstable to the reaction conditions and only black tarry product mixtures were obtained.

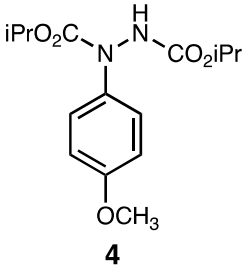

Figure 2. Product of Reaction of Diisopropylazodicarboxylate with Anisole

These initial studies have proven that BF_3•$O(Et)_2$ is an effective Lewis acid catalyst for promotion of the addition of DEAD to substituted benzenes. We are currently continuing to optimize the reaction conditions in terms of solvent effects and catalyst load. We are also extending the studies to more complex aromatic substrates. We will report on our complete findings in due course.

3.Experimental

3.1. General Procedure for the Reaction of Diethyl Azodicarboxylate (DEAD) with Substituted Benzenes

To a stirring solution of aromatic substrate (1-10 equivalents as per Figure 1) in 8 mL CH_2Cl_2 was added 0.44 g (2.5 mmol) of DEAD as a solution in 2 mL CH_2Cl_2

followed by 80 μL (0.63 mmol, 25 mol%) of BF_3•$(Et)_2O$ via syringe. The resulting solution stirred until the DEAD was completely consumed (as determined by TLC). The reaction mixture was washed with H_2O (10 mL), and the resulting organic layer dried over Na_2SO_4, filtered, and concentrated.The product was purified via column chromatography (SiO_2, using mixtures of EtOAc and hexanes as eluent).

3.1.1. Diethyl 1-(4-methoxyphenyl)hydrazine-1, 2-dicarboxylate (**3a**)

According to the general procedure using 0.54 g (5 mmol, 2 eq) of anisole, 0.70 g (2.26 mmol, 90% yield) of **3a** was isolated as a colorless viscous oil.

^{1}H NMR (60 MHz, $CDCl_3$): 7.92 (br s, 1H, NH), 7.35 (d, 2H, J = 9.2 Hz), 6.81 (d, 2H, J = 9.2 Hz), 4.19 (q, 2H, J = 7.1 Hz), 4.18 (q, 2H, J = 7.1 Hz), 3.74 (s, 3H), 1.22 (br t, 6H, J = 7.1 Hz).

^{13}C NMR (14 MHz, $CDCl_3$): 158.2, 156.6, 155.5, 135.0, 126.6, 113.9, 62.8, 62.0, 55.4, 14.4(2C).

HRMS (EI) m/z$[M+Na]^+$ calculated for $C_{13}H_{18}N_2NaO_5$: 305.1108. Found 305.1110.

3.1.2. Diethyl 1-(2,4,6-trimethoxyphenyl)hydrazine-1, 2-dicarboxylate (**3b**)

According to the general procedure using 0.84 g (5 mmol, 2 eq) of 1,3,5-trimethoxybenzene, 0.77 g (2.25 mmol, 90% yield) of **3b** was isolated as a white solid; mp 145-146℃.

^{1}H NMR (60 MHz, $CDCl_3$): 7.09 (br s, 1H NH), 6.13 (s, 2H), 4.16 (q, 4H, J = 7.1 Hz), 3.83 (s, 6H), 3.80 (s, 3H), 1.25 (t, 3H, J = 7.1 Hz), 1.17 (br t, 3H, J = 7.1 Hz).

^{13}C NMR (14 MHz, $CDCl_3$): 160.6(2C), 156.5, 155.4, 112.5, 90.7, 62.1, 61.2, 55.7(2C), 55.1, 14.1(2C).

Anal. Calcd. For $C_{15}H_{22}N_2O_7$: C, 52.61; H, 6.48; N 8.19. Found: C, 52.85; H; 6.73, N, 8.24.

3.1.3. Diethyl 1-(2,4-dimethoxyphenyl)hydrazine-1, 2-dicarboxylate (**3c**)

According to the general procedure using 3.45 g (25 mmol, 10 eq) of 1,3-dimethoxybenzene, 0.57 g (1.83 mmol, 73% yield) of **3c** was isolated as a colorless viscous oil.

^{1}H NMR (60 MHz, $CDCl_3$): 7.49 with 7.33 (br s, 1H, NH), 7.20 (br s, 1H), 6.55-6.35(m, 2H), 4.18 (br q, 4H, J = 7.1 Hz), 3.80 (s, 6H), 1.25 (t, 3H, J = 7.1 Hz), 1.21 (br t, 3H, J = 7.1 Hz).

^{13}C NMR (14 MHz, $CDCl_3$): 160.6(2C), 156.2, 155.8, 130.2, 123.6, 104.1, 99.2, 62.6, 61.7, 55.5(2C), 14.4(2C).

HRMS (EI) m/z$[M+Na]^+$ calculated for $C_{14}H_{20}N_2NaO_6$: 335.1214. Found 335.1214.

3.1.4. Diethyl 1-(2,3,4,5,6-pentamethylphenyl)hydrazine-1, 2-dicarboxylate (**3d**)

According to the general procedure using 0.37 g (2.5 mmol, 1 eq) of 1,2,3,4,5-pentamethylbenzene, 0.73 g (2.27 mmol, 91% yield) of **3d** was isolated as a white solid; mp 179-181 ℃.

^{1}H NMR (60 MHz, $CDCl_3$):6.96 and 6.81 (br s, 1H, NH), 4.21 (q, 2H, J = 7.1 Hz), 4.17 (q, 2H, J = 7.1 Hz), 2.26 (s, 6H), 2.20 (s, 9H), 1.25 (t, 3H, J = 7.1 Hz), 1.20 (t, 3H, J = 7.1 Hz).

^{13}C NMR (14 MHz, $CDCl_3$): 156.5, 156.2, 136.9, 135.4, 133.5, 131.7, 62.8, 61.9, 16.9, 16.7, 15.7, 17.7, 14.4.

Anal. Calcd. For $C_{17}H_{26}N_2O_4$: C, 63.32; H, 8.13; N 8.69. Found: C, 63.24; H, 8.36; N, 8.62.

3.1.5. Diethyl 1-(2,3,5,6-tetramethylphenyl)hydrazine-1, 2-dicarboxylate (**3e**)

According to the general procedure using 1.68 g (12.5 mmol, 5 eq) of durene, 0.65 g (2.11 mmol, 85% yield) of **3e** was isolated as a white solid; mp 185-186 ℃.

^{1}H NMR (400 MHz, $CDCl_3$): 7.32 (br s, 1H, NH), 6.96 (br s, 1H) 4.20 (q, 2H, J = 7.1 Hz), 4.16 (q, 2H, J = 7.1 Hz), 2.22 (s, 12H), 1.23 (t, 3H, J = 7.1 Hz), 1.19 (t, 3H, J = 7.1 Hz).

^{13}C NMR (14 MHz, $CDCl_3$): 156.3(2C), 138.9, 134.6, 132.1, 131.5, 62.8, 61.9, 20.0, 14.7, 14.6, 14.4.

Anal. Calcd. For $C_{16}H_{24}N_2O_4$: C, 62.30; H, 7.85; N 9.09. Found: C, 62.70; H, 8.02; N, 9.05

3.1.6. Diethyl 1-(2,4,6-trimethylphenyl)hydrazine-1, 2-dicarboxylate (**3f**)

According to the general procedure using 1.50 g (12.5 mmol, 5 eq) of mesitylene, 0.69 g (2.35 mmol, 94% yield) of **3f** was isolated as a white solid; mp 159-160 ℃ (lit.[12c] 159-161 ℃).

^{1}H NMR (60 MHz, $CDCl_3$): 7.52 and 7.23 (br s, 1H, NH) 6.87 (br s, 2H), 4.14 (q, 2H, J = 7.1 Hz), 4.10 (q, 2H, J = 7.1 Hz), 2.34 (s, 6H), 2.26, s (3H), 1.22 (t, 3H, J = 7.1 Hz), 1.18 (t, 3H, J = 7.1 Hz).

^{13}C NMR (14 MHz, $CDCl_3$): 156.47 (2C), 137.9, 136.1, 136.0, 129.3, 62.9, 61.9, 20.9, 18.2, 14.5, 14.4.

3.1.7. Diethyl 1-(2,4-dimethylphenyl)hydrazine-1, 2-dicarboxylate (**3g**)

According to the general procedure using 0.43 g (25 mmol, 10 eq) of m-xylene, 0.62 g (2.21 mmol, 89% yield) of **3g** was isolated as a white solid.; mp 83-84 ℃ (lit.[12d]81-82 ℃).

^{1}H NMR (60 MHz, $CDCl_3$): 7.4-6.9 (m, 4H), 4.15 (q, 2H, J = 7.1 Hz), 3.13 (q, 2H, J = 7.1 Hz), 2.31 (s, 3H), 2.26 (s, 3H), 1.25 (t, 3H, J = 7.1 Hz), 1.22 (t, 3H, J = 7.1 Hz).

^{13}C NMR (14 MHz, $CDCl_3$): 156.5, 155.7, 138.0, 137.6, 135.2, 131.1, 127.4, 127.0, 62.5, 61.6, 20.7, 17.3, 14.2(2C).

Anal. Calcd. For $C_{15}H_{22}N_2O_7$: C, 59.97; H, 7.19; N 10.00. Found: C, 60.27; H, 7.49; N, 9.97.

3.1.8. Diethyl 1-(4-methylphenyl)hydrazine-1, 2-dicarboxylate (**3h**)

According to the general procedure using 10 mL of toluene as solvent and heating the reaction mixture to 60 ℃ for 24 h, 0.28 g (1.05 mmol, 42% yield) of **3h** was isolated as a colorless viscous oil.

^{1}H NMR (60 MHz, $CDCl_3$): δ (mixture of isomers) 7.8 and 7.66 (br s, 1H, NH), 7.39-7.00 (m, 4H), 4.15 (q, 2H, *J* = 7.1 Hz), 4.12 (q, 2H, *J* = 7.1 Hz), 2.30 (s, 3H), 1.23 (t, 6H, *J* = 7.1

Hz).

^{13}C NMR of *para* isomer (14 MHz, $CDCl_3$): δ 156.6 (2C), 139.3, 136.2, 129.2, 124.4, 62.8, 62.1, 20.9, 14.4(2C).

^{13}C NMR of *ortho* isomer (14 MHz, $CDCl_3$): δ 155.2(2C), 140.4, 135.6, 130.7, 128.2, 127.7, 126.6, 62.8, 62.1, 17.7, 14.4 (2C).

HRMS (EI) *m/z*$[M+Na]^+$ calculated for $C_{13}H_{18}N_2NaO_4$: 289.1159. Found 289.1160.

3.1.9. Diethyl 1-(naphthalen-2-yl)hydrazine-1, 2-dicarboxylate (**3i**)

According to the general procedure using 1.60 g (12.5 mmol, 5 eq) of naphthalene, 0.49 g (1.63 mmol, 65% yield) of **3i** was isolated as a white solid; 137 -138 ℃[10].

^{1}H NMR (60 MHz, $CDCl_3$): δ 8.07-7.26 (m, 8H), 4.15 (q, 4H, J = 7.1 Hz), 1.25 (t, 3H, J = 7.1 Hz), 1.13 (br t, 3H, J = 7.1 Hz).

^{13}C NMR (14 MHz, $CDCl_3$): δ 156.7, 156.1, 138.0, 134.5, 130.2, 128.9, 128.4, 126.9, 126.3, 126.0, 125.7, 122.8, 63.1, 62.2, 14.5(2C).

Anal. Calcd. For $C_{16}H_{18}N_2O_4$: C, 63.55; H, 6.00; N 9.27. Found: C, 63.71; H, 6.25; N, 9.19.

3.1.10. Diisopropyl 1-(4-methoxyphenyl)hydrazine-1, 2-dicarboxylate (**4**)

According to the general procedure using 0.54 g (5 mmol, 2 eq) of anisole and 0.51 g (2.5 mmol) of diisopropylazodic arboxylate, 0.70 g (2.26 mmol, 90% yield) of **4** was isolated as a colorless viscous oil. Spectral data were in accord with literature values[4c,e].

4. Conclusions

In summary, the reaction of DEAD with sufficiently activated aromatic compounds provides a general, highyield method for the synthesis of monoarylhydrazides. The optimized method requires only 25 mol% of the inexpensive and readily available Lewis acid catalyst BF_3•$O(Et)_2$. The greatest limitation is the requirement for aromatic rings at least as electronically activated as toluene.

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