Steric effects on the sydnones reactivity. New sydnones and pyrazoles

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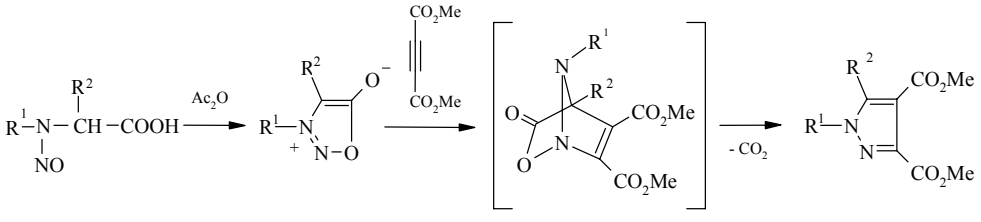
Abstract

The sydnones **7a,b** and **8a-c** gave the corresponding pyrazoles **9a-e** by 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate (DMAD). The highly sterically hindered 3-(4,6-dibromo-2-methylphenyl)-4-iodosydnone (**8d**) failed to react with DMAD on heating in boiling xylene. The iodination of sterically hindered sydnone **7b** required more drastic reaction conditions than the sydnone **7a**.

Keywords: Sydnones, pyrazoles, steric effect, 1,3-dipolar cycloaddition

Introduction

Among the mesoionic compounds sydnones **2** are the best studied and thoroughly known.[1-5] Sydnones can readily prepared by cyclodehydration of *N*-substituted-*N*-nitroso-aminoacids **1** with reagents such as acetic anhydride. The resulting compounds contain a mesoionic aromatic system which can be depicted with polar resonance structures. Sydnones undergo smooth cycloaddition with acetylenes to give pyrazoles **4** in high yield.[6-9] The reaction involves a 1,3-dipolar cycloaddition of the sydnones, behaving like a cyclic azomethine imine, to the corresponding acetylene followed by carbon dioxide evolution and aromatization (Scheme 1).



1 **2** **3** **4**

Scheme 1

The present work describes the synthesis of new halogenated sydnones and their cycloaddition reaction to form pyrazoles. The halogen atoms are present in the benzene and/or heterocycle ring. The influence of steric effects on reactivity of sydnones is also discussed.

Results and Discussion

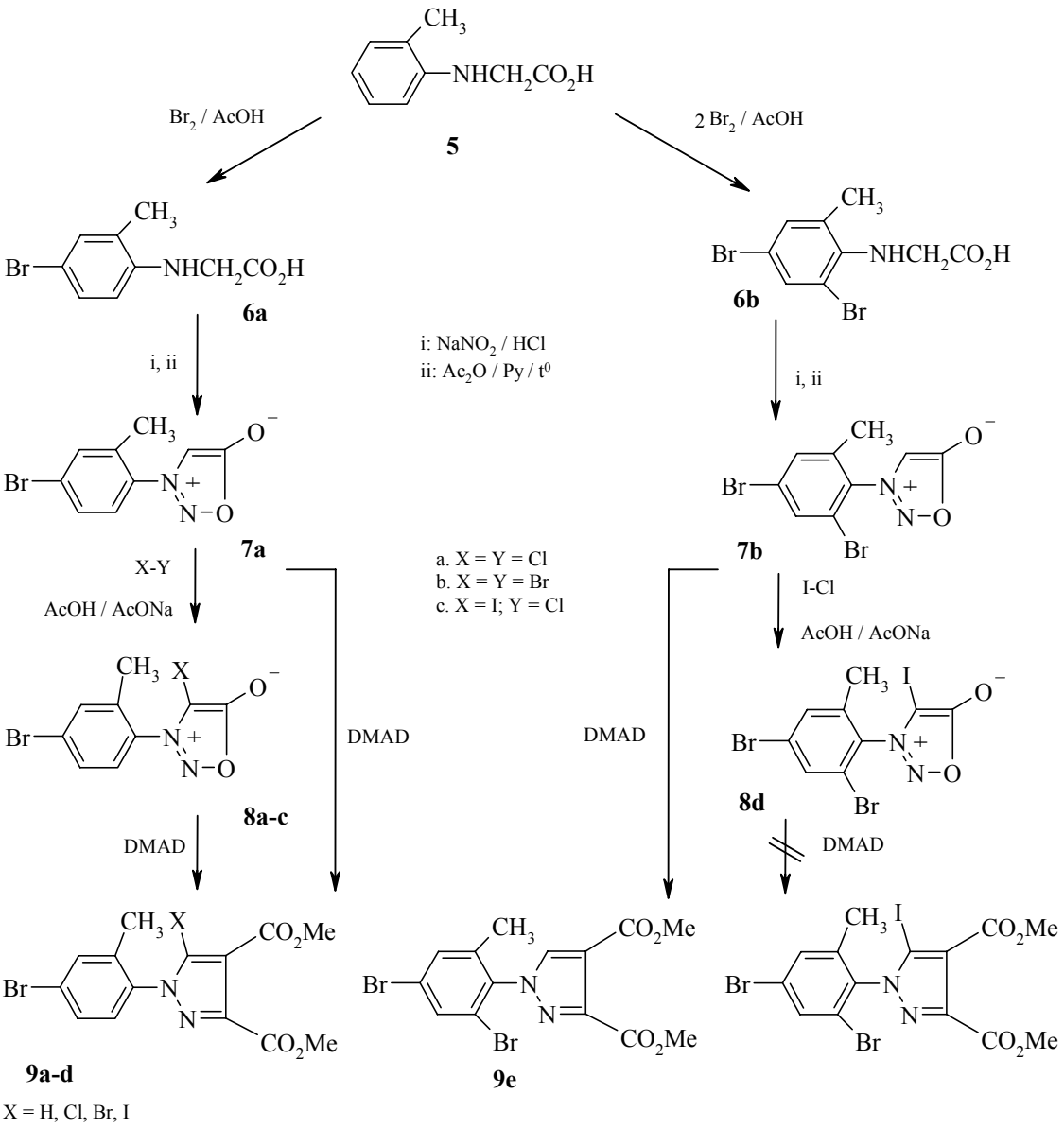
The starting material, *N*-(2-methylphenyl)glycine (**5**), was obtained by a method described for *N*-(2-ethylphenyl)glycine.[10] Monobromination of **5** with bromine/acetic acid gave *N*-(4-bromo-2-methylphenyl)glycine (**6a**) which was identically with the compound described in literatutre.[11] When two equivalents of bromine were used *N*-(4,6-dibromo-2-methylphenyl)glycine (**6b**) was obtained (Scheme 2). The 4-unsubstituted sydnones **7a** and **7b** were prepared in good yields by known procedure[1-6] from the corresponding *N*-arylglycines **6a** and **6b** (Scheme 2). The chemical shift of the 4-H proton of sydnones **7a** and **7b** in DMSO-d_6 appears as being unusually high (δ = 7.47 and 7.51 ppm) as compared to those measured in other solvent as $CDCl_3$ (δ = 6.48 ppm). A plausible explanation is the formation of hydrogen bonds between DMSO and 4-CH group. This is supported by a ^{13}C-NMR study of sydnones which confirm the tendency of 4-CH group to form hydrogen bonds.[12]

The chlorination and bromination of the sydnone **7a** were performed with chlorine- and bromine-acetic acid to give 4-chlorosydnone **8a**, respectively 4-bromosydnone **8b** in good yields (Scheme 2).

Recently[13] we obtained good results in the direct iodination of sydnone ring by using the reagent iodine monochloride/acetic acid. By using this method the sydnones **7a** and **7b** could be iodinated with this reagent in the presence of an equivalent of sodium acetate added to neutralize the hydrochloride acid formed in the reaction. Two new 4-iodosydnones **8c** and **8d** were obtained by this method.

The iodination of the sydnone **7b** required large excess of iodine monochloride and a reaction time of 10 hrs., whereas the iodination of the sydnone **7a** was complete in 1 hr. with only a slightly excess of iodination reagent. This was explained by steric hindering at the electrophilic center, C-4 in the sydnone ring.

The ^{13}C-NMR spectra of 4-iodosydnones showed a strong negative increment at C-4 ($\Delta\delta$ = 44.4, respectively 44.9 ppm). A shielding effect of 3-aryl group on C-4 was also apparent, provided that the aromatic ring was not strongly deviated from coplanarity by *ortho* substituents. A weak influence on polarization of the carbonyl group could also be observed with bromine and chlorine as 4-substituents. The transformation of sydnones **7a,b** and **8a-c** into halogenated pyrazoles **9a-e** was performed by 1,3-dipolar cycloaddition reaction with DMAD.



Scheme 2

The 4-chloro- and 4-bromosydnones were found by Dickopp[14] to be unstable in non-polar solvents such that the corresponding pyrazoles were obtained in ethylene glycol upon reaction with excess DMAD. In our hands, 4-halogenosydnones **8a** and **8b** proved to be quite stable in xylene at reflux temperature and their reaction with a small excess of DMAD (1.2 molar ratio) led to the corresponding 5-halogenopyrazoles in yield of over 80%.In addition, 1-(4-Bromo-2-methylphenyl)-3,4-dicarboethoxy-5-iodopyrazole (**9f**) was obtained by 1,3-dipolar cycloaddition between 4-iodosydnone **8c** and diethyl acetylenedicarboxylate. By this method, six new pyrazoles **9a-f** were obtained.

The ^{13}C-NMR spectra of 5-iodopyrazoles **9e** and **9f** showed about the same negative increments ($\Delta\delta$ = 45.6 and 45.8 ppm) for the signal of C-5 as in the case of the corresponding 4-iodosydnones **8c** and **8d**. For the 4-iodopyrazoles[15] negative increments of $\Delta\delta$ = 41.5-42.2 were measured.

The highly hindered 3-(4,6-dibromo-2-methylphenyl)-4-iodosydnone (**8d**) failed to react with DMAD (Scheme 2) or diethyl acetylenedicarboxylate for three days in boiling xylene. This finding could be explained by steric hinderance. The *ortho* substituents at benzene ring and the bulky iodine atom at C-4 in the sydnone ring does not allow the formation of the transition state the between sydnone **8d** and acetylenic dipolarophiles.

Experimental Section

General Procedures. ^{1}H- and ^{13}C-NMR spectra were recorded with a Varian Gemini instrument at 300 and 75 MHz, chemical shifts being expressed in δ values relative to TMS as internal standard. All mps were taken with a micro-Boetius apparatus and are uncorrected.

***N*-(4-Bromo-2-methylphenyl)glycine (6a).** A solution of 11.2 g (70 mmol) of bromine in 10 mL of glacial acetic acid was dropped under stirring to a suspension of 11.5 g (70 mmol) of *N*-(2-chlorophenyl)glycine (**5**)[10] in 40 mL of glacial acetic acid. Stirring was continued for 30 min. The reaction mixture was poured into water and the precipitate was filtered by suction. Yield 83%; mp 139-142 °C (Lit.[11] yield 82%; mp 142-145 °C); ^{1}H-NMR ($CDCl_3$+TFA) δ 7.54 (d, 1H, 2.2, 3'-H); 7.49 (dd, 1H, 8.5, 2.2, 5'-H); 7.31 (d, 1H, 8.5, 6'-H); 4.29 (s, 2H, CH_2); 2.45 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$+TFA) δ 168.9 (CO); 135.6 (3'-C); 132.8 (1'-C); 131.7 (2'-C); 131.5 (5'-C); 124.8 (4'-C); 124.0 (6'-C); 51.5 (CH_2); 16.2 (CH_3).

General procedure for sydnones 7a and 7b

To a solution of 2 g NaOH in 30 mL of water were added 20 mmol N-arylglycine **6a,b** and 1.4 g (21 mmol) of $NaNO_2$. In the cooled solution 10 mL of HCl were dropped under stiring, the temperature maintened under 5 °C. The nitroso derivatives which separated as oils were extracted twice with CH_2Cl_2. The organic layer was dried on $CaCl_2$ and then the solvent was evaporated off. The residue was treated with 30 mL of acetic anhydride and 2 mL of pyridine and evaporated under reduced pressure on the water bath. The crude products **7a** and **7b** were recrystallized from ethanol as clourless crystals.

3-(4-Bromo-2-methylphenyl)sydnone (7a).[16] ^{1}H-NMR ($CDCl_3$) δ 7.62 (d, 1H, 2.2, 3'-H); 7.57 (dd, 1H, 8.4, 2.2, 5'-H); 7.32 (d, 1H, 8.4, 6'-H); 6.47 (s, 1H, 4-H); 2.33 (s, 3H, CH_3); ^{1}H-NMR (DMSO-d_6) δ 7.80 (d, 1H, 2.1, 3'-H); 7.68 (dd, 1H, 8.5, 2.1, 5'-H); 7.60 (d, 1H, 8.5, 6'-H); 7.47 (s, 1H, 4-H); 2.25 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 168.6 (CO); 135.3 (3'-C); 135.0 (1'-C); 133.0 (2'-C); 130.7 (5'-C); 126.8 (4'-C); 126.5 (6'-C); 96.9 (4-C); 17.1 (CH_3).

3-(4,6-Dibromo-2-methylphenyl)sydnone (7b). Yield 77%; mp 189-190˚C; ^{1}H-NMR ($CDCl_3$) δ 7.81 (d, 1H, 2.1, 5'-H); 7.57 (d, 1H, 2.1, 3'-H); 6.48 (s, 1H, 4-H); 2.29 (s, 3H, CH_3); ^{1}H-NMR (DMSO-d_6) δ 8.05 (d, 1H, 2.1, 5'-H); 7.84 (d, 1H, 2.1, 3'-H); 7.51 (s, 1H, 4-H); 2.21 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 168.6 (CO); 138.3 (1'-C); 135.3 and 134.1 (3'-C and 5'-C); 132.5 (2'-C); 126.8 (4'-C); 120.4 (6'-C); 97.3 (4-C); 17.2 (CH_3). Anal. Calcd for $C_9H_6Br_2N_2O_2$: C, 32.36; H, 1.81; Br, 47.84; N, 8.38. Found: C, 32.61; H, 2.11; Br, 48.18; N, 8.67.

3-(4-Bromo-2-methylphenyl)-4-chlorosydnone (8a). To a suspension of 2.5 g (10 mmol) sydnone **7a** and 1 g dry sodium acetate in 15 mL glacial acetic acid was added dropwise with stirring and cooling 0.71 g (10 mmol) of chlorine dissolved in 15 mL glacial acetic acid. After 20 min. the reaction mixture was poured into water and the precipitate filtered by suction. Yield 75%; mp 131-3˚C; ^{1}H-NMR ($CDCl_3$) δ 7.67 (d, 1H, 2.2, 3'-H); 7.61 (dd, 1H, 8.4, 2.2, 5'-H); 7.31 (d, 1H, 8.4, 6'-H); 2.27 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 163.4 (CO); 136.1 (1'-C); 134.9 (3'-C); 133.3 (2'-C); 130.8 (5'-C); 127.4 (6'-C); 127.1 (4'-C); 99.6 (4-C); 16.7 (CH_3). Anal. Calcd for $C_9H_6BrClN_2O_2$: N, 9.67. Found: N, 9.91.

4-Bromo-3-(4-bromo-2-methylphenyl)sydnone (8b). The method used was the same as that described above but with bromine in place of chlorine. Yield 77%; mp 142-4˚C; ^{1}H-NMR (DMSO-d_6) δ 7.85 (d, 1H, 2.3, 3'-H); 7.74 (dd, 1H, 8.2, 2.3, 5'-H); 7.64 (d, 1H, 8.5, 6'-H); 2.18 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) δ 165.5 (CO); 136.9 (1'-C); 134.7 (3'-C); 132.2 (2'-C); 131.0 (5'-C); 128.9 (6'-C); 126.5 (4'-C); 87.6 (4-C); 16.3 (CH_3). Anal. Calcd for $C_9H_6Br_2N_2O_2$: C, 32.36; H, 1.81; Br, 47.84; N, 8.38. Found: C, 32.64; H; 2.15; Br, 48.19; N, 8.67.

3-(4-Bromo-2-methylphenyl)-4-iodosydnone (8c). A solution of 22 mmol (1.1 mL) of iodine monochloride in 10 mL of glacial acetic acid was added dropwise to a stirred mixture of 5.1 g (20 mmol) of sydnone 7a and 2.2 g (25 mmol) of dry sodium acetate and of 20 ml glacial acetic acid. Stirring was continued for 1 hr at 50˚C, after which the 4-iodosydnone was precipitated by the addition of water. The product was filtered off and throughly washed with water. Yield 82%; mp 197-8˚C (from ethanol); ^{1}H-NMR ($CDCl_3$) δ 7.65 (d, 1H, 2.2, 3'-H); 7.61 (dd, 1H, 8.4, 2.2, 5'-H); 7.21 (d, 1H, 8.4, 6'-H); 2.21 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 168.4 (CO); 136.3 (1'-C); 134.8 (3'-C); 133.3 (2'-C); 130.8 (5'-C); 127.6 (6'-C); 126.9 (4'-C); 52.3 (4-C); 16.9 (CH_3). Anal. Calcd for $C_9H_6BrIN_2O_2$: N, 7.35. Found: N, 7.62.

3-(4,6-Dibromo-2-methylphenyl)-4-iodosydnone (8d). The method used was the same as that described above but with an excess of iodine monochloride (4 molar ratio) and stirring for 10 hrs at 55-60˚C. Yield 80%; mp 237-239 ˚C (from AcOH); ^{1}H-NMR ($CDCl_3$) δ 7.83 (d, 1H, 2.2, 5'-H); 7.59 (d, 1H, 2.2, 3'-H); 2.20 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 168.4 (CO); 138.7 (1'-C); 134.2 and 133.6 (3'-C and 5'-C); 132.5 (2'-C); 127.3 (4'-C); 121.2 (6'-C); 52.4 (4-C); 17.6 (CH_3). Anal. Calcd for $C_9H_5BrIN_2O_2$: N, 6.09. Found: N, 6.39.

General procedure for pyrazoles 9a-e

A mixture of 10 mmol sydnone (**7a,b** and **8a-c**) and 1.55 g (12 mmol) of DMAD was refluxed in 30 mL xylene for 8 hrs. After removal of the solvent in vacuo, the pyrazoles **9a-e** were crystallized from ethanol as clourless crystals.

1-(4-Bromo-2-methylphenyl)-3,4-dicarbomethoxypyrazole (9a). Yield 83%; mp 93-95 ˚C; ^{1}H-NMR ($CDCl_3$) δ 8.06 (s, 1H, 5-H); 7.50 (d, 1H, 2.1, 3'-H); 7.45 (d, 1H, 8.4, 2.1, 5'-H); 7.22 (d, 1H, 8.4, 6'-H); 3.98 and 3.88 (2s, 6H, OCH_3); 2.23 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 161.9 and 161.8 (2CO); 144.4 (3-C); 137.5 (1'-C); 136.0 (2'-C); 135.6 (5-C); 134.3 (3'-C); 130.0 (5'-C); 127.7 (6'-C); 123.7 (4'-C); 115.9 (4-C); 52.8 and 52.1 (OCH_3); 17.8 (CH_3). Anal. Calcd for $C_{14}H_{13}BrN_2O_4$: C, 47.59; H, 3.68; Br, 22.66; N, 7.93. Found: C, 47.90; H, 3.97; Br, 22.97; N, 8.24.

1-(4-Bromo-2-methylphenyl)-3,4-dicarbomethoxypyrazole-5-chloropyrazole (9b). Yield 81%; mp 123-4 ˚C; ^{1}H-NMR ($CDCl_3$) δ 7.54 (d, 1H, 2.2, 3'-H); 7.48 (dd, 1H, 8.4, 2.2, 5'-H); 7.15 (d, 1H, 8.4, 6'-H); 3.96 and 3.93 (2s, 6H, OCH_3); 2.09 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) 161.3 (2CO); 144.3 (3-C); 138.2 (1'-C); 134.9 (2'-C); 134.1 (3'-C); 132.6 (5-C); 130.1 (5'-C); 129.3 (6'-C); 124.8 (4'-C); 112.6 (4-C); 52.8 and 52.5 (OCH_3); 17.2 (CH_3). Anal. Calcd for $C_{14}H_{12}BrClN_2O_4$: N, 7.23. Found: N, 7.50.

5-Bromo-1-(4-bromo-2-methylphenyl)-3,4-dicarbomethoxypyrazole (9c). Yield 88%; mp 128-130 ˚C; ^{1}H-NMR ($CDCl_3$) δ 7.54 (d, 1H, 2.1, 3'-H); 7.48 (dd, 1H, 8.4, 2.1, 5'-H); 7.14 (d, 1H, 8.4, 6'-H); 3.96 and 3.93 (2s, 6H, OCH_3); 2.07 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 161.5 and 161.1 (2CO); 144.7 (3-C); 138.2 (1'-C); 135.8 (2'-C); 133.9 (3'-C); 129.9(5'-C); 129.3 (6'-C); 124.6 (4'-C); 119.4 (4-C); 115.7 (5-C); 52.7 and 52.3 (OCH_3); 17.1 (CH_3). Anal. Calcd for $C_{14}H_{12}Br_2N_2O_4$: C, 38.92; H, 2.79; Br, 36.99; N, 6.48. Found: C, 39.21; H, 3.04; Br, 37.33 ; N, 6.79.

1-(4-Bromo-2-methylphenyl)-3,4-dicarbomethoxy-5-iodopyrazole (9d). Yield 79%; mp 107-8 ˚C; ^{1}H-NMR ($CDCl_3$) δ 7.53 (d, 1H, 2.1, 3'-H); 7.48 (dd, 1H, 8.4, 2.1, 5'-H); 7.11 (d, 1H, 8.4, 6'-H); 3.95 and 3.93 (2s, 6H, OCH_3); 2.03 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 162.1 and 161.3 (2CO); 145.5 (3-C); 138.4 (1'-C); 137.5 (2'-C); 134.0 (3'-C); 130.0 (5'-C); 129.7 (6'-C); 124.7 (4'-C); 121.0 (4-C); 90.8 (5-C); 52.8 and 52.4 (OCH_3); 17.4 (CH_3). Anal. Calcd for $C_{14}H_{12}BrIN_2O_4$: N, 5.85. Found: N, 6.11.

1-(4,6-Dibromo-2-methylphenyl)-3,4-dicarbomethoxypyrazole (9e). Yield 92%; mp 153-4 ˚C; ^{1}H-NMR ($CDCl_3$) δ 7.97 (s, 1H, 5-H); 7.67 (d, 1H, 2.2, 5'-H); 7.42 (d, 1H, 2.1, 3'-H); 3.94 and 3.85 (2s, 6H, OCH_3); 2.06 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 161.6 and 161.5 (2CO); 144.5 (3-C); 139.9 (1'-C); 136.7 (2'-C); 136.4 (5-C); 133.2 (5'-C); 132.9 (3'-C); 124.4 (4'-C); 122.6 (6'-C); 115.9 (4-C); 52.6 and 52.0 (OCH_3); 17.8 (CH_3). Anal. Calcd for $C_{14}H_{12}Br_2N_2O_4$: C, 38.92; H, 2.80; Br, 36.99; N, 6.48. Found: C, 40.37; H, 3.11; Br, 37.29 ; N, 6.77.

1-(4-Bromo-2-methylphenyl)-3,4-dicarboethoxy-5-iodopyrazole (9f). The method used was the same described for **9d** but with diethyl acetylenedicarboxylate in place of DMAD. Yield 82%; mp 86-8 ˚C (from ethanol); ^{1}H-NMR ($CDCl_3$) δ 7.49 (d, 1H, 2.2, 3'-H); 7.43 (dd, 1H, 8.4, 2.2, 5'-H); 7.08 (d, 1H, 8.4, 6'-H); 4.38 and 34.37 (2q, 4H, 7.1, CH_2); 2.00 (s, 3H, CH_3); 1.36 and 1.35 (2t, 6H, 7.1, $CH_2\mathbf{CH_3}$); ^{13}C-NMR ($CDCl_3$) δ 161.5 and 161.0 (2CO); 145.8 (3-C); 138.3 (1'-C); 137.4 (2'-C); 133.8 (3'-C); 129.8 and 129.7 (6'-C and 5'-C); 124.5 (4'-C); 120.7 (4-C); 90.3 (5-C); 61.8 and 61.4 (OCH_3); 17.3 (CH_3); 14.0 and 13.9 ($CH_2\mathbf{CH_3}$). Anal. Calcd for $C_{16}H_{16}BrIN_2O_4$: N, 5.52. Found: N, 5.80.

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