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β-Dimethylphenylsilylethyl esters: a linker for solid-phase chemistry

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Abstract

Preparation of a β-dimethylphenylsilylethyl (BMPSE) ester linker from 2% divinylbenzene–styrene copolymer by lithiation, chlorodimethylvinylsilane silylation, hydroboration/oxidation (giving **9**), and *O*-acylation is reported. The resulting polymer-bound BMPSE esters were employed in a reaction sequence consisting of RCHO→RCH=NOH→isoxazoline/isoxazole (giving **12**). © 2000 Elsevier Science Ltd. All rights reserved.

Choosing the correct linker is a crucial step in solid-phase organic synthesis. Alternative methods[1] for attachment/detachment of substrates from solid-supports have resulted in the construction of an impressive range of compound classes.[2] A survey of the literature indicates an increasing popularity of trialkylsilyl groups in solid-phase linker applications.[3] This application breadth reflects solution-phase developments where silyl-based linkers are: (1) readily introduced at many functional groups; (2) compatible with many organic transformations; (3) compatible with other protecting group strategies; and (4) easily and chemoselectively cleaved. That said, trialkylsilyl protection of carboxylic acids is rare owing to hydrolytic lability. With TMSE [2-(trimethylsilyl)ethyl] esters, independently introduced by Sieber[4a] and Gerlach[4b] for the protection of the carboxyl functionality, requisite stability is achieved by positioning the silicon atom β to the carboxylate giving TMSE-esters that are broadly applied, uniquely stable, and can be readily deprotected with trifluoroacetic acid.

The focus of the present report is the development of a polymer-anchored β-dimethylphenylsilylethyl (BMPSE) ester protecting group and its application in the synthesis of carboxylic acid and ester substituted isoxazolines. An early report of the solid-phase synthesis of this type of isoxazoline by Cheng and Mjalli[5] used Wang resin. We report here that the BMPSE ester linker is readily introduced, compatible with all synthetic steps required for this isoxazoline synthesis, and labile under both TFA and TBAF cleavage conditions.

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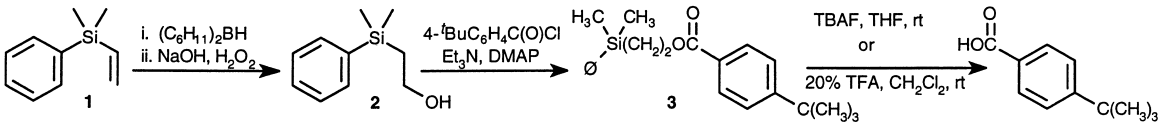
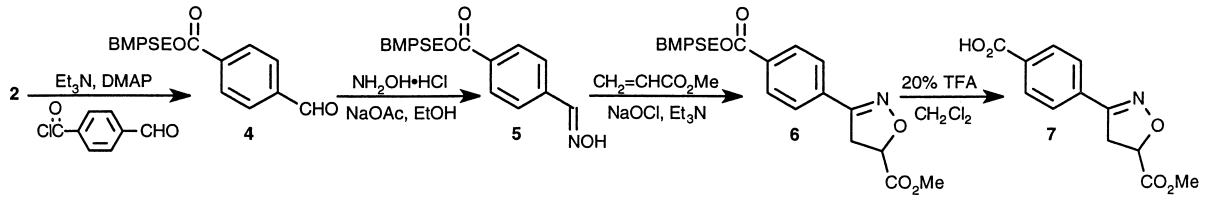
To determine the feasibility of a solid-phase BMPSE linker, we first established resin-compatible conditions for the derivatization of a vinyl silane moiety for ester formation as well as conditions under which the silicon–carbon bond could be cleaved under mild conditions. Toward this end, a solution-phase model study beginning with dimethylphenylvinylsilane was initiated for the synthesis of aryl-substituted isoxazolines.[6] The results of this solution-phase study are outlined in Scheme 1. Hydroboration/oxidation of commercially available dimethylphenylvinylsilane was carried out using dicyclohexylborane as the hydroborating agent. This generally regioselective reagent[7] added with complete selectivity to vinyl silane **1** giving alcohol **2** upon oxidative work-up. Esterification of **2** with 4-*t*butylbenzoyl chloride gave silyl ethyl ester **3**. Tetrabutylammonium fluoride (TBAF) treatment in THF (rt) delivered 4-*t*butylbenzoic acid in 43% yield (unoptimized). Likewise, treating **3** with 20% trifluoroacetic acid (TFA) in CH_2Cl_2 delivered 4-*t*butylbenzoic acid in 56% yield (unoptimized).



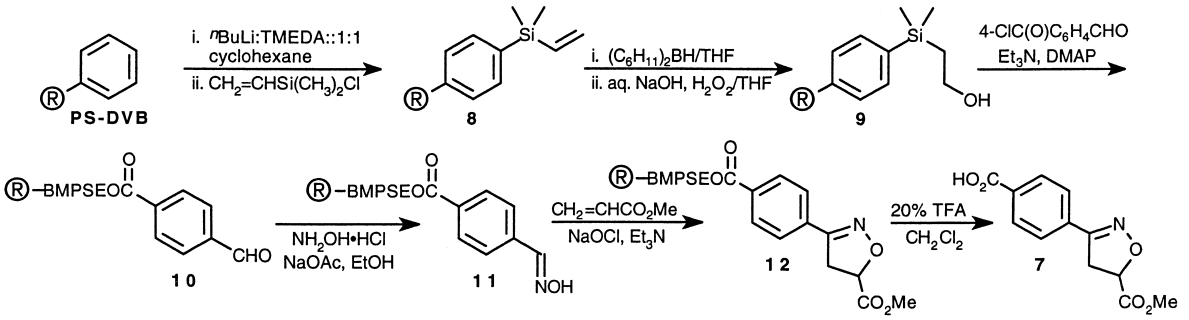
Scheme 1.

With these protocols in hand, treatment of silyl ethanol **2** with 4-formyl benzoyl chloride under neutral conditions afforded the expected silyl ethyl ester **4** (Scheme 2). Reaction of **4** with hydroxylamine and sodium acetate in EtOH at room temperature afforded **5** in quantitative yield.[8] This aldoxime was added dropwise over 15 min to a mixture of methyl acrylate (1 equiv.) and catalytic Et_3N in CH_2Cl_2 plus an aqueous sodium hypochlorite[9] solution. As demonstrated by Martin and Dupre,[10] sterically hindered nitrile oxides undergo highly regioselective cycloaddition with *cis*-disubstituted olefins. This bias is based on the size of the olefin substituents with the nitrile betaine oxygen adding to the more hindered site and, in the present example, gave only **6** (^{1}H NMR of crude reaction). Selective cleavage of the silyl ethyl ester in the presence of the methyl ester in **6** with either TBAF in THF or 20% TFA in CH_2Cl_2 gave the desired desilylated product in 75 and 72% yield, respectively.



Scheme 2.

Attention was next focused on development of the polymer-supported analog of this strategy (Scheme 3). Following the method developed by Chalk,[11] commercial 2% cross-linked polystyrene-divinylbenzene copolymer (®) was lithiated at 65°C with the complex formed from *n*butyllithium and TMEDA (1:1) in cyclohexane. The resulting polymer-bound aryllithium[12] was quenched in situ with chlorodimethyl–vinylsilane in benzene (FTIR: 1250 and 835 cm^{-1} for



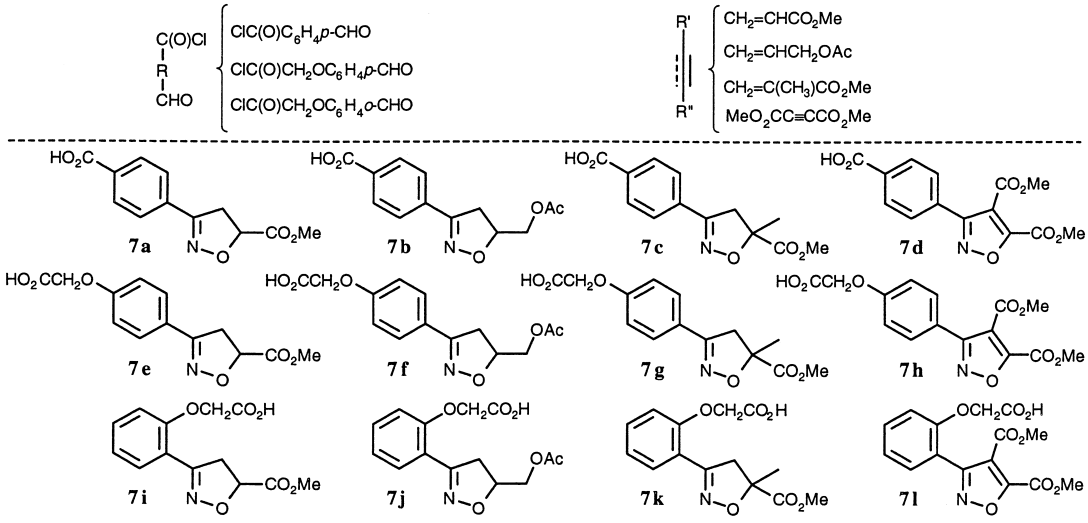
Scheme 3. See Reference 13

SiMe). The extent of polymer lithiation was determined by CO_2 quench and subsequent acid-base titration; loading generally falls in the range of 0.9–1.02 mmol/g resin. The most reliable method for monitoring the progress of this and all subsequent solid-phase transformations was by recording FTIR spectra of the crushed resin.

Hydroboration of resin **8** and oxidative work-up with basic peroxide provided the silyl ethanol resin **9** which was esterified with 4-formylbenzoyl chloride to afford polymer **10** as evidenced by both aldehyde and ester group absorptions in the IR spectrum (1690 and 1736 cm^{-1}, respectively). Reaction of **10** with hydroxylamine in the presence of sodium acetate in EtOH at room temperature afforded the aldoxime resin **11** which was suspended in THF and treated with excess bleach (Clorox, 10 equiv.) and methyl acrylate to form the corresponding nitrile oxide. Concomitant 1,3-dipolar cycloaddition gave resin-bound Δ^2-isoxazoline **12**.

An important advantage of the solid-phase **11**→**12** process over the solution-phase **5**→**6** reaction is the ease of separation and isolation of the targeted cyclic isoxazoline; resin washing in the former versus aqueous work-up and chromatography in the latter. Again, protodesilylation

Table 1
Library application of the solid-phase BMPSE ester linker[14]



was smoothly accomplished by treatment of resin **12** with CF_3COOH/CH_2Cl_2 to give isoxazoline **7** in ≈95% purity and 60% overall yield from lithiated PS-DVB.

Reaction rates for the solid- and solution-phase reactions were comparable. Moreover, both 1,3-dipolar cycloaddition protocols were highly regioselective. Encouraged by these observations, we applied this solid-phase DMPSE ester technology to the preparation of a library of aryl-substituted isoxazolines. By employing three different formyl carboxylic acid chlorides and four different dipolarophiles, a library of 12 isoxazolines was obtained (see Table 1).

In conclusion, a β-dimethylphenylsilylethyl (DMPSE) ester linker has been developed for solid-phase organic synthesis and used in the preparation of a library of aryl-substituted isoxazolines. Protolytic cleavage of the coupled products from the resin proceeds under mild conditions and generally in high yield.

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8. Hydroxylamine hydrochloride (0.090 g, 1.3 mmol) and sodium acetate (0.14 g, 1.7 mmol) were added to ethanolic (10 mL) **4** (0.31 g, 1 mmol) and the solution was stirred at room temperature overnight. The solvent was removed (rotoevaporation) and the crude product was triturated into CH_2Cl_2. Purification by filtration afforded an almost pure oxime (99% yield) which was used in the next reaction without further purification. For analytical purposes, the oxime was purified by column chromatography to give **5** as a colorless oil in 86% yield (0.28 g): ^{1}H NMR ($CDCl_3$) δ 8.18 (s, 1H), 7.96 (d, 2H, J=6.0 Hz), 7.61 (d, 2H, J=6.0 Hz), 7.56–7.35 (m, 5H), 4.44 (t, 2H, J=8.0 Hz), 2.70 (s, 1H), 1.41 (t, 2H, J=8.0 Hz), 0.37 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.2, 149.3, 136.1–126.5 (m), 63.2,

16.6, –2.9; IR 3383, 1704, 1679, 1112, 768 cm^{-1}. Anal. calcd for $C_{18}H_{21}NSiO_3$: C, 66.02; H, 6.46; N, 4.28. Found: C, 65.65; H, 6.50; N, 4.15.

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13. Solid-phase preparation of isoxazolines (**7**; via **10**→**11**→**12**). A solution of acid chloride (1.0 mmol) in dry CH_2Cl_2 (2.0 mL) was added dropwise to a cold mixture (0°C) of polymeric alcohol **9** (0.200 g) swollen in CH_2Cl_2 (7.0 mL) and containing triethylamine (0.28 mL, 2.0 mmol) and DMAP (0.0012 g, 0.01 mmol). The mixture was shaken at room temperature overnight, filtered and washed with CH_2Cl_2, water, THF and MeOH to afford the corresponding polymeric ester aldehyde **10**. To this resin was added EtOH (5.0 mL), hydroxylamine hydrochloride (0.069 g, 1.0 mmol) and sodium acetate (0.106 g, 1.3 mmol) and the mixture was shaken at room temperature for 2 days. The polymer was filtered and washed with EtOH, water, THF and MeOH affording polymeric oxime **11**. This oxime was swollen in CH_2Cl_2 (5.0 mL) and treated dropwise over 15 min with a cold solution (0°C) of dipolarophile (1.0 mmol), triethylamine (0.001 g, 0.01 mmol), 5.25% aqueous sodium hypochlorite (2.64 mL, 0.140 g NaOCl, 1.8 mmol) and dichloromethane (2.0 mL). The mixture was shaken at room temperature overnight and the resin filtered and washed with CH_2Cl_2, water, THF:water (3:1), THF and MeOH to give **12**. Substrate cleavage was accomplished by treating **12** with a freshly prepared TFA:CH_2Cl_2 (1:4) solution (3 h at reflux temperature; ethylene release is observed). Filtration, resin washing with MeOH (3×), and solvent removed gave the targeted isoxazolines or isoxazoles in 50–75% yield which were purified by crystallization affording the expected isoxazolines **7** (spectroscopic data given below).
14. Compound **7a**: 72% yield (0.159 g); m.p. 196–197°C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 8.05 (d, 2H, J = 9.0 Hz), 7.69 (d, 2H, J = 9.0 Hz), 5.18 (dd, 1H, J = 10.5 Hz , J = 8.0 Hz), 3.78 (s, 3H), 3.64 (d, 1H, J = 8.0 Hz), 3.63 (d, 1H, J = 10.5 Hz); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 177.6, 167.7, 155.4, 132.0, 131.9, 130.1, 126.6, 78.2, 52.8, 38.5; IR 2960, 1759, 1687, 1429, 1290 cm^{-1}. Anal. calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 58.10; H, 4.76; N, 5.75. Compound **7b**: 70% yield (37 mg); m.p. 207–208°C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 8.02 (d, 2H, J = 9.1 Hz), 7.75 (d, 2H, J = 9.1 Hz), 5.02–4.94 (m, 1H), 4.90–4.16 (m, 2H), 3.46 (dd, 1H, J = 16.8 Hz, J = 10.9 Hz), 3.16 (d, 1H, J = 16.8 Hz, J = 8.4 Hz), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 171.3, 163.4, 155.7, 133.2, 130.3, 127.0, 126.6, 78.7, 64.8, 36.9, 20.7; IR 2936, 1738, 1680, 1426, 1232 cm^{-1}. Anal. calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.19; H, 4.90; N, 5.17. Compound **7c**: 51% yield (27 mg); m.p. 159–160 (dec.)°C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 8.09 (d, 2H, J = 1.5 Hz), 7.73 (d, 2H, J = 1.5 Hz), 3.90 (d, 1H, J = 16.9 Hz), 3.80 (s, 3H), 3.23 (d, 1H, J = 16.9 Hz), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 172.3, 160.1, 155.6, 133.5, 133.4, 130.6, 126.7, 86.7, 53.1, 44.4, 23.5; IR 2954, 1738, 1680, 1427, 1290 cm^{-1}. Anal. calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.01; H, 5.28; N, 4.97. Compound **7d**: 69% yield (40 mg); m.p. 156–157°C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 8.14 (d, 2H, J = 6.0 Hz), 7.75 (d, 2H, J = 6.0 Hz), 4.00 (s, 3H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 168.4, 160.6, 159.8, 159.5, 156.3, 132.0, 131.2, 130.3, 128.2, 115.8, 53.5, 53.2; IR 2960, 1724, 1687, 1430, 1265 cm^{-1}. Anal. calcd for $C_{14}H_{11}NO_7$: C, 55.09; H, 3.63; N, 4.59. Found: C, 55.30; H, 4.01; N, 4.19. Compound **7e**: 75% yield (40 mg); m.p. 114–115°C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.55 (d, 2H, J = 9.0 Hz), 6.90 (d, 2H, J = 9.0 Hz), 5.11 (t, 1H, J = 8.9 Hz), 4.59 (s, 2H), 3.75 (s, 3H), 3.56 (d, 2H, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 170.9, 170.8, 159.5, 155.5, 128.5, 121.7, 114.8, 77.6, 65.0, 52.8, 39.0; IR 2911, 1724, 1435, 1245 cm^{-1}. Anal. calcd for $C_{13}H_{13}NO_6$: C, 55.92; H, 4.69; N, 5.02. Found: C, 55.88; H, 4.69; N, 4.82. Compound **7f**: 67% yield (39 mg); m.p. 134–135°C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.57 (d, 2H, J = 9.0 Hz), 6.90 (d, 2H, J = 9.0 Hz), 4.96–4.87 (m, 1H), 4.63 (s, 2H), 4.25–4.13 (m, 2H), 3.40 (dd, 1H, J = 16.7 Hz, J = 10.8 Hz), 3.10 (dd, 1H, J = 16.7 Hz, J = 7.21 Hz), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 171.1, 170.9, 159.2, 155.8, 128.2, 122.2, 114.7, 77.8, 64.8, 63.9, 37.2, 20.5; IR 2923, 1710, 1362, 1235 cm^{-1}. Anal. calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 56.99; H, 5.08; N, 4.66. Compound **7g**: 70% yield (41 mg); m.p. 119–120°C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.60 (d, 2H, J = 9.0 Hz), 6.93 (d, 2H, J = 9.0 Hz), 4.67 (s, 2H), 3.80 (d, 1H, J = 18.0 Hz), 3.79 (s, 3H), 3.18 (d, 1H, J = 18.0 Hz), 1.70 (s, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 172.7, 170.1, 159.3, 155.9, 128.3, 122.3, 114.8, 85.9, 58.0, 53.0, 44.9, 23.5; IR 2969, 1732, 1709, 1426, 1247 cm^{-1}. Anal. calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.52; H, 5.21; N, 4.58. Compound **7h**: 69% yield (46 mg); m.p. 90–91°C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.63 (d, 2H, J = 9.0 Hz), 6.99 (d, 2H, J = 9.0 Hz), 4.67 (s, 2H), 3.99 (s, 3H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 171.1, 169.7, 161.9, 160.6, 159.5, 156.5, 126.7, 120.2, 115.0, 114.9, 64.8, 53.4, 53.2; IR 2954, 1726, 1421, 1229 cm^{-1}. Anal. calcd for $C_{15}H_{13}NO_8$: C, 53.74; H, 3.91; N, 4.18. Found: C, 54.05; H, 3.89; N, 3.82. Compound **7i**: 50% yield (27 mg); m.p. 148–149°C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.36–6.80 (m, 4H), 5.10–5.03 (m, 1H), 4.60 (s, 2H), 3.75–3.61 (m, 5H); ^{13}C NMR ($CDCl_3$/

CD_3OD) δ 171.1, 168.6, 155.5 (2), 131.7, 129.9, 122.0, 118.3, 112.0, 78.1, 65.4, 65.3, 41.5; IR 2917, 1711, 1235 cm^{-1}. Anal. calcd for $C_{13}H_{13}NO_6$: C, 55.92; H, 4.69; N, 5.02. Found: C, 55.66; H, 4.34; N, 4.97. Compound **7j**: 51% yield (30 mg); m.p. 65–66°C; ^1H NMR ($CDCl_3/CD_3OD$) δ 7.26–6.78 (m, 4H), 4.63–4.62 (m, 1H), 4.33 (s, 2H), 4.04-3.93 (m, 2H), 3.31 (dd, 1H, $J = 16.8$ Hz, $J = 10.7$ Hz), 3.02 (dd, 1H, $J = 16.8$ Hz, $J = 7.1$ Hz), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 171.3, 156.4, 156.1, 155,5, 131.8, 130.1, 120.7, 119.1, 114.0, 77.4, 68.2, 63.1, 39.7, 20.8; IR 2940, 1737, 1615, 1226 cm^{-1}. Anal. calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.33; H, 5.07; N, 4.70. Compound **7k**: 57% yield (33 mg); ^1H NMR ($CDCl_3/CD_3OD$) δ 7.28–6.74 (m, 4H), 4.33 (s, 2H), 3.78 (d, 1H, $J = 17.6$ Hz), 3.61 (s, 3H), 3.21 (d, 1H, $J = 17.6$ Hz), 1.48 (s, 3H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 173.0, 156.4 (2), 156.0, 131.6, 131.0, 121.0, 120.9, 113.8, 85.0, 68.3, 52.8, 47.1, 23.2; IR 2967, 1731, 1709, 1246 cm^{-1}. Anal. calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.63; H, 5.10; N, 4.66. **7l**: 51% yield (34 mg); m.p. 174–175°C; ^1H NMR ($CDCl_3/CD_3OD$) δ 7.63–6.79 (m, 4H), 4.75 (s, 5H), 4.71 (s, 3H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 169.7, 168.3, 159.4, 159.3, 156.0, 134.2, 133.9, 133.8, 121.6, 121.8, 115.9, 112.2, 91.5, 65.5, 65.3; IR 2912, 1737, 1709, 1248 cm^{-1}. Anal. calcd for $C_{15}H_{13}NO_8$: C, 53.74; H, 3.91; N, 4.18. Found: C, 54.01; H, 3.70; N, 4.29.