Lewis Acid Mediated Selective Monohydrolysis of Geminal Diesters: Synthesis of Functionalized Malonic Acid Half Esters

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Abstract: Geminal diesters, *N*-alkyl/aryl-2,2-bis(ethoxycarbonyl)vinylamines, were found to undergo selective hydrolysis in the presence of $BF_3{\cdot}OEt_2$ at room temperature to give the corresponding half esters. Neighboring group participation by nitrogen in the hydrolysis was observed. This method is useful for the preparation of highly functionalized malonic acid half esters.

Key words: Lewis acid, boron trifluoride, geminal diesters, hydrolysis, esters

Ester hydrolysis remains an crucial functional group transformation[1] in multistep syntheses of several natural products, pharmaceuticals, fine chemicals, and novel organic materials. It can also be considered as a deprotection step to unmask a carboxyl group. Partial hydrolysis of diesters produces half esters or hemi-esters that could be classified, depending upon the position of the ester and acid group, as geminal, vicinal, vinylic, and aromatic half esters. Half esters of malonates, which fall under the class of geminal half esters, are important building blocks that are useful in the synthesis of substituted α-amino acids,[2] doubly homologated esters,[3] tricarbonyl compounds,[4] alcohols,[5] β-amino esters, and β-hydroxy esters.[6]

Half esters can be synthesized by various methods already known in the literature, and each of these methods has its own merits and demerits. The well-known saponification[7] approach involves use of strong bases such as NaOH or KOH, which may seriously affect sensitive functional groups. Enzyme hydrolysis[8] depends on the availability of suitable enzymes, the stereochemistry varies depending upon the substrate, and usually requires a long reaction time. Preparation of cyclic anhydrides[9] is a prerequisite for Lewis acid[10] or Lewis base[11] mediated ring opening of anhydrides. Methods involving multistep protection and deprotection[12] as well as transesterification[13] with alcohols has also been used. Geminal half esters are synthesized especially by hydrolysis of geminal diesters using base[7] or enzyme.[8] The development of simple and efficient methods for the synthesis of geminal half esters using Lewis acid catalysts is of practical importance because this could avoid the use of expensive enzymes and base, which could affect base-sensitive functional groups.

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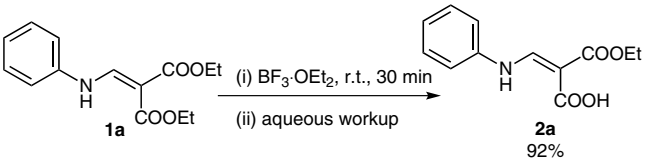
We recently demonstrated that the bis-ethoxycarbonylvinyl (BECV) group undergoes cleavage on reaction with ethylenediamine, a base, and it could be used as a versatile amine protecting group for selective functional group transformations.[14] In this direction, we examined the reaction of the BECV amine group in the presence of a Lewis acid and found that one of the geminal diester groups in diethyl 2-phenylaminomethylene malonate (**1a**), undergoes selective hydrolysis to give highly functionalized malonic acid half ester **2a** in very high yield (Scheme 1).



Scheme 1 $BF_3{\cdot}OEt_2$ mediated monohydrolysis of **1a**

Notably, $BF_3{\cdot}OEt_2$ does not hydrolyze geminal diesters with no neighboring heteroatom[15,16] nor does it hydrolyze a monoester, even in the presence of an α- or β-nitrogen atom.[17] Lewis acid mediated ester hydrolysis is an uncommon reaction and only a few examples are known, for example, in the case of $BF_3{\cdot}OEt_2$ mediated hydrolysis of the ethyl ester vicinal to a carbonyl group,[18] the *tert*-butyl ester in a coumarin ring,[19] and the $ZnBr_2$ or LiBr mediated selective hydrolysis of remote dissimilar diesters.[20,21] To the best of our knowledge, there are no reports on Lewis acid mediated monohydrolysis of geminal diesters to give geminal half esters. This observation prompted us to make a thorough further study.

Different Lewis acids were examined for the mono hydrolysis of compound **1a** to generate **2a**; the results are summarized in Table1. $AlCl_3$ did not catalyze the hydrolysis in 1,2-dichloroethane (DCE) at room temperature (ca. 32 °C), even using more than stoichiometric quantities (2.5 equiv), and the product **2a** was obtained in high yield only at reflux (entry 7). However, with $BF_3{\cdot}OEt_2$ (1 equiv) the reaction took place at room temperature. Among the different solvents examined, $CHCl_3$ gave high yield of the product, whereas use of solvents such as MeCN, $MeNO_2$, tetrahydrofuran (THF), and *N*,*N*-dimethylformamide (DMF) led to either low yield or no reaction. Lewis acids such as $ZnCl_2$, $SnCl_4$, $Yb(OTf)_3$, $FeCl_3$, or $CuSO_4$ were ineffective for the hydrolysis. Based on these results it was

decided to use the mild reaction conditions, $BF_3{\cdot}OEt_2$ (1 equiv) in $CHCl_3$ at room temperature, for further study.

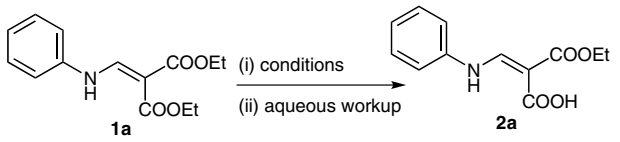
To check the versatility of this hydrolysis reaction and the stereoelectronic influence of substituents on the aromatic ring, a range of *N*-aryl-2,2-bis(ethoxycarbonyl)vinylamine derivatives (**1a**–**n**) were prepared[14] and subjected to the hydrolysis reaction under standardized reaction conditions; the results are summarized in Table 2.

With electron-donating (Me, OMe and OBn) substituents on the phenyl ring (**1b**–**f**) the rate of hydrolysis was fast compared to unsubstituted aniline (**1a**). The presence of a methoxy substituent at the *ortho*, *meta* or *para* position (Table 2, entries 3–5) did not change the reaction rate. This observation suggests that the substituent effect is mainly electronic and not steric in nature. Inductively electron-withdrawing (Cl, NO_2, and COMe) substituents in compounds **1g**–**m** led to slower reactions. The naphthyl derivative **1n** behaved in a similar way to substrates that contained a phenyl ring with an electron-withdrawing substituent. Monoesters were obtained in high yield with almost all the substrates. Functional groups such as ether, ketone, and nitro groups remained unaffected under the hydrolysis conditions.

The versatility of this monohydrolysis reaction was checked on aliphatic substrates by using compounds **3**–**5**. 2-(Benzylaminomethylene)malonic acid diethyl ester (**3**) reacted with $BF_3{\cdot}OEt_2$ within 30 minutes to give the mono ester **3a** in very high yield. The diamino tetra ester **4**, on treatment with $BF_3{\cdot}OEt_2$, gave mono hydrolysis product **4a** in 40% yield. In addition, an unidentified solid mass that was insoluble in polar organic solvents such as dimethyl sulfoxide (DMSO) and water was obtained.[22] Interestingly, the tetra ester **5** gave symmetric bis-half ester **5a** in high yield, which is highly functionalized and contains several potential chelating functional groups (Scheme 2).

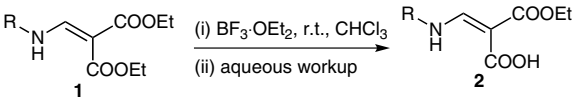
Chemical intramolecular reactions resemble intracomplex reactions of enzymes, hence the study of neighboring group participation in organic reactions has gained a lot of

Table 1 Optimization of the Lewis Acid Mediated Selective Monohydrolysis of **1a**



Entry	Lewis acid	Equiv	Solvent	Temp (°C)	Time (h)	Yield (%)
1	$AlCl_3$	0.1	$CHCl_3$	r.t.	24	0
2	$AlCl_3$	1.0	$CHCl_3$	r.t.	24	0
3	$AlCl_3$	2.5	$CHCl_3$	r.t.	24	0
4	$AlCl_3$	1.0	$(CH_2)_2Cl_2$	r.t.	24	0
5	$AlCl_3$	1.0	$CHCl_3$	reflux	1.0	52
6	$AlCl_3$	2.5	$CHCl_3$	reflux	1.0	60
7	$AlCl_3$	1.0	$(CH_2)_2Cl_2$	reflux	1.0	72
8	$AlCl_3$	2.0	$(CH_2)_2Cl_2$	reflux	1.0	81
9	$SnCl_4$	1.0	$(CH_2)_2Cl_2$	r.t.	1.0	0
10	$SnCl_4$	2.0	$(CH_2)_2Cl_2$	reflux	1.0	0
11	$FeCl_3$	0.5	$CHCl_3$	reflux	1.0	0
12	$FeCl_3$	1.5	$CHCl_3$	r.t.	3.0	0
13	$CuSO_4$	2.0	$CHCl_3$	reflux	3.0	0
14	$ZnCl_2$	2.0	$CHCl_3$	reflux	3.0	0
15	$Yb(OTf)_3$	0.1	$CHCl_3$	reflux	3.0	0
16	$BF_3{\cdot}OEt_2$	1.0	$CHCl_3$	r.t.	0.30	92
17	$BF_3{\cdot}OE_2$	0.5	$CHCl_3$	r.t.	0.25	51
18	$BF_3{\cdot}OEt_2$	0.1	$CHCl_3$	r.t.	0.25	trace
19	$BF_3{\cdot}OEt_2$	1.0	toluene	r.t.	0.30	80
20	$BF_3{\cdot}OEt_2$	1.0	MeCN	r.t.	0.30	70
21	$BF_3{\cdot}OEt_2$	1.0	THF	r.t.	4.0	45
22	$BF_3{\cdot}OEt_2$	1.0	none	r.t.	0.30	76
23	$BF_3{\cdot}OEt_2$	1.0	DMF	r.t.	4.0	0
24	$BF_3{\cdot}OEt_2$	2.0	DMF	r.t.	0.30	trace

Table 2 Stereoelectronic Influence of Aromatic Substituents on $BF_3{\cdot}OEt_2$ Mediated Monohydrolysis of *N*-Aryl-2,2-bis(ethoxycarbonyl)vinylamine Derivatives



Entry	R	1	Time (h)	Yield (%)
1	Ph	**1a**	0.30	92
2	4-MeC_6H_4	**1b**	0.20	90
3	4-$MeOC_6H_4$	**1c**	0.25	90
4	2-$MeOC_6H_4$	**1d**	0.25	89
5	3-$MeOC_6H_4$	**1e**	0.25	89
6	4-$BnOC_6H_4$	**1f**	0.25	91
7	4-ClC_6H_4	**1g**	2.0	81
8	2-ClC_6H_4	**1h**	2.15	80
9	3-ClC_6H_4	**1i**	2.15	78
10	4-$O_2NC_6H_4$	**1j**	2.20	83
11	2-$O_2NC_6H_4$	**1k**	2.30	83
12	3-$O_2NC_6H_4$	**1l**	2.20	85
13	4-$MeC(O)C_6H_4$	**1m**	2.30	86
14	1-naphthyl	**1n**	2.30	85

significance. NaOH mediated acetalysis of 4-(acetoxyphenyl)imidazole,[23] and LiBr[21] mediated ester hydrolysis are a few examples wherein nitrogen is known to participate as a neighboring group. We examined the compatibility of other ester groups in the $BF_3{\cdot}OEt_2$ mediated ester hydrolysis. Compounds **6**–**10**,[14] on treatment with $BF_3{\cdot}OEt_2$, gave the corresponding half esters **6a**–**10a** as exclusive products in very good yield. In compound **6**, the bond distance between the nitrogen and the vinyl ester as well as the aromatic ester was nearly the same. Similarly, the aliphatic ester group lies very close to the reactive site in compounds **8**–**10**. In all these cases, only the geminal diester underwent hydrolysis and second ester group remained unaffected (Scheme 3).

Single crystals of compounds **6a** and **8a** were obtained as prisms and needles, respectively, using hexane–EtOAc (8:2, v/v) as solvent.[24] From the crystal structure it was found that the carboxylic acid and the vinyl amine lie on the same side of the double bond, giving rise to *E* configuration for the product. This is further proof of the highly selective nature of the ester hydrolysis reaction (Figure 1).

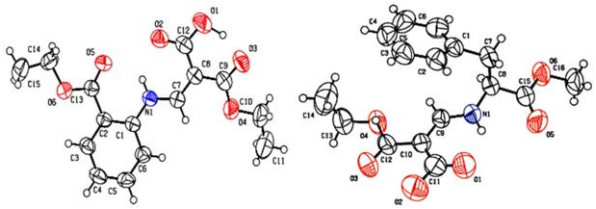
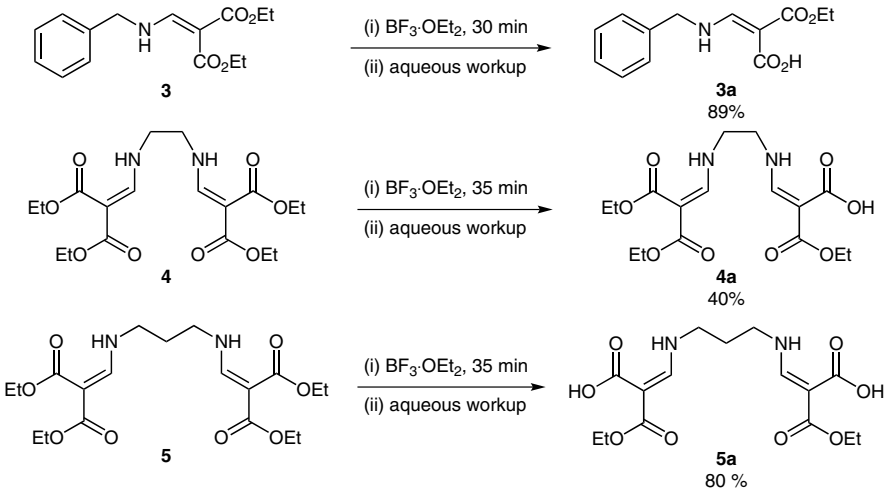


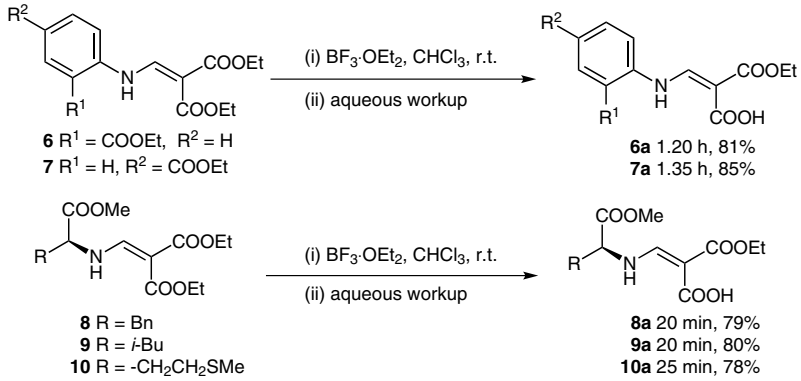
Figure 1 (a) ORTEP diagram for compound **6a**; (b) ORTEP diagram for compound **8a**

Our attempts to convert compound **1a** into the corresponding *N*-Cbz-protected amino acid through Curtius rearrangement using triphenyl phosphoryl azide[2] or ethylchloroformate and sodium azide[11,12] failed to give the desired product and the starting material was recovered as such. However, acid **2a** could be successfully converted into the corresponding amide **2b** by treatment with 4-methoxyaniline in the presence of EDC, HOBt, and DIPEA at room temperature (Scheme 4). Similarly, a series of amide derivatives were prepared successfully. These results, along with the biological activity of these compounds, will form a separate communication.[25]

To establish the role of the intramolecular nitrogen atom, geminal diesters **11**–**14** and diesters **15** and **16** were sub-



Scheme 2 $BF_3{\cdot}OEt_2$ mediated monohydrolysis of *N*-alkyl-2,2-bis(ethoxycarbonyl)vinylamines



Scheme 3 Monohydrolysis of *N*-aryl-2,2-bis(ethoxycarbonyl)vinylamines containing similar ester groups

jected to hydrolysis under the same reaction conditions. None of these esters underwent hydrolysis. These observations led us to the conclusion that the presence of a neighboring NH group adjacent to the geminal diester is essential for this hydrolysis reaction (Figure 2).

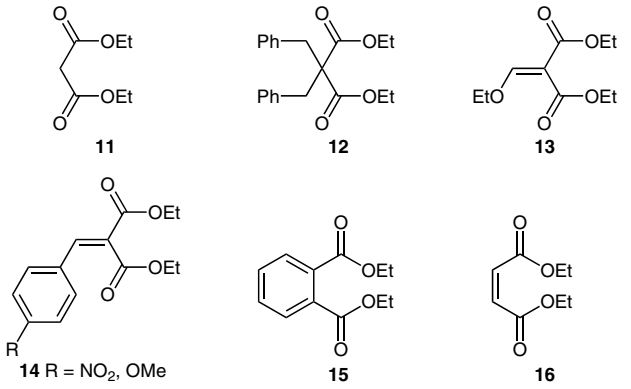
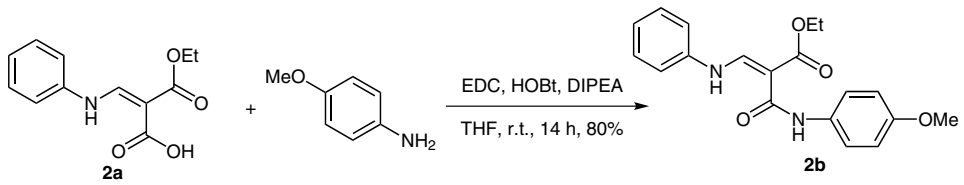


Figure 2 Diesters which failed to undergo $BF_3{\cdot}OEt_2$-mediated monoester hydrolysis

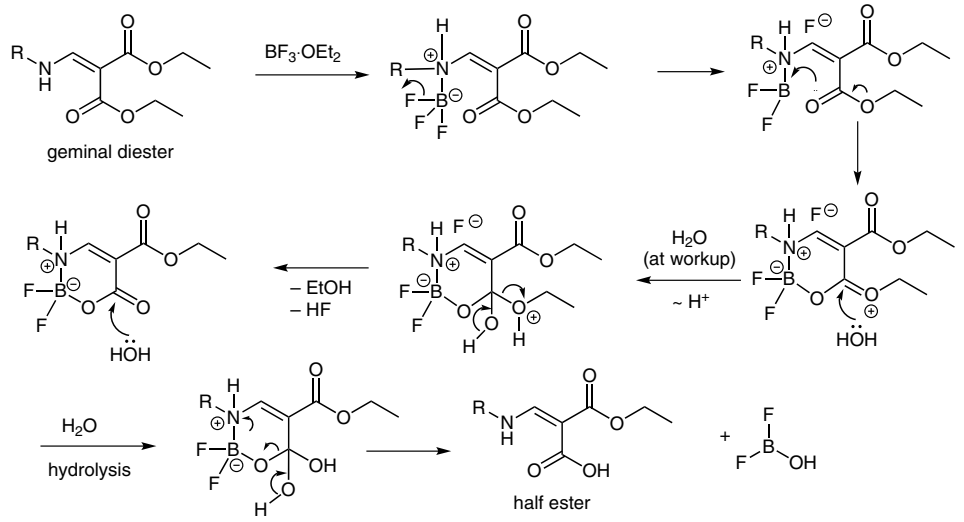
To investigate the mechanism, the reaction of compound **1** with $BF_3{\cdot}OEt_2$ was monitored in situ by ^1H NMR spectroscopic analysis at 25 °C, during an interval of 30 minutes over a period of 120 minutes.[26] During the course of the reaction the intensity of the vinylic NH and CH protons, appearing at δ = 10.80 and 8.55 ppm, respectively, decreased gradually with a concomitant increase in intensity of new peaks appearing at δ = 11.08 and 8.68 ppm, and the reaction reached completion after 120 minutes. This experiment shows that the NH protons remain intact but resonate at a new shift value. With less than one equivalent of $BF_3{\cdot}OEt_2$ the reaction did not reach completion and the acid proton peak (δ = 12.94 ppm) appeared only after quenching with water. This indicates that a complex is formed between stoichiometric quantities of reactants. Based on these observations a suitable mechanism was proposed (Scheme 5).

Thus, $BF_3{\cdot}OEt_2$ might preferentially coordinate to the more nucleophilic nitrogen and adjacent carbonyl, instead of to two carbonyl groups,[27,28] to form an ionic complex[26] that, on hydrolysis, gives rise to the half ester. This would be an intramolecular activation of the carbonyl group in which a six-membered intermediate is involved.

In conclusion, geminal diesters were found to undergo selective hydrolysis upon treatment with Lewis acids such as $BF_3{\cdot}OEt_2$ and $AlCl_3$ for the first time.[29] Neighboring group participation of nitrogen in the selective hydrolysis was established. This hydrolysis reaction is specific to the geminal diester and other ester groups remain unaffected. This new method is useful for the synthesis of highly functionalized malonic acid half esters, starting from the geminal diester. The reaction conditions are mild, and functional groups such as alkyl ether, aryl ether, thioether, ester, and ketones remain unaffected and no racemization or isomerization was observed.[26] This chemoselective, Lewis acid mediated hydrolysis of geminal diesters should be of general utility for the synthesis of highly substituted malonate derivatives.



Scheme 4 Synthesis of the amide derivative



Scheme 5 Plausible mechanism of the reaction

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(24) Compound **6a** and **8a** both belong to a monoclinic system with space group $P2_1/n$ and $P2_1$, respectively. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre [CCDC-832627 (**6a**) and 832624 (**8a**)]. The crystal information file (CIF) can be obtained free of charge from www.ccdc.cam.ac.uk/products/csd/request/.
(25) Half esters of substituted aniline were coupled with some substituted aniline and amino acid methyl esters to obtain novel amide derivatives such as (*E*)-ethyl 2-(2-bromophenylcarbamoyl)-3-(phenylamino)acrylate and found to show good antibacterial (e.g., *E. coli*) and antifungal (e.g., *C. albicans*) activity.
(26) For details on racemization, isomerization and in situ NMR studies see the Supporting Information.
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(29) **General procedure for BF_3·OEt_2-mediated hydrolysis of diethyl 2-[(aryl/alkyl-amino)methylene]malonate**: To a solution of diethyl 2-[(aryl/alkyl-amino)methylene]-malonate (1.0 equiv) in chloroform (3 × w/v), BF_3·OEt_2 (1.0 equiv) was added and the mixture was stirred at r.t. under a nitrogen atmosphere (the reaction was monitored by TLC). Upon completion, the reaction mixture was quenched with water (1 × w/v) and extracted with chloroform (3 × 5 mL). The combined organic layer was dried (anhyd. Na_2SO_4) and evaporated in a rotary evaporator. The crude product was passed through a short column (silica gel) using a suitable eluent to obtain the corresponding product in 40–92% yield. **Preparation of 2-(*p*-tolylaminomethylene)malonic acid monoethyl ester (2b)**: The reaction was carried out according to the general procedure using diethyl 2-(*p*-tolylaminomethylene)malonate[1] (**1b**; 500 mg, 1.8 mmol), and BF_3·OEt_2 (453 μL, 1.8 mmol) in chloroform (1.5 mL) at r.t. for 20 min. The title compound **2b** (0.40 g, 90%) was obtained as a white solid after passing through a short silica gel column (hexane–EtOAc, 9:1). Mp 92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.2 Hz, 3 H), 2.33 (s, 3 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 7.06 (d, *J* = 8.4 Hz, 2 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 8.44 (d, *J* = 13.6 Hz, 1 H), 11.62 (d, *J* = 13.2 Hz, 1 H), 13.0 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 20.7, 61.3, 89.0, 177.7, 130.3, 135.9, 136.0, 151.6, 169.9, 170.7; IR (KBr): 3183, 2978, 2688, 1696, 1630, 1512, 1473, 1407, 1268, 1205, 1089, 1017, 887, 831, 811 cm^{-1}; MS: *m*/*z* calcd. for $C_{13}H_{15}NO_4$: 249.10; found: 250.2 [M + 1]; Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.62; H, 6.08; N, 5.60.

