FULL PAPERS

IBX-Mediated Conversion of Primary Alcohols and Aldehydes to *N*-Hydroxysuccinimide Esters

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Abstract: Recently, the use of the hypervalent iodine reagent 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) for the oxidation of primary alcohols and aldehydes to carboxylic acids was described. During the synthesis of these carboxylic acids the corresponding *N*-hydroxysuccinimide esters were formed as intermediate products, but their isolation as main reaction products was not successful. We report herein a simple and very efficient method to prepare these synthetically valuable active esters.

Keywords: alcohols; aldehydes; hypervalent iodine reagent; oxidation

Introduction

The use of hypervalent iodine reagents in organic synthesis has enjoyed an increasing popularity in the last 20 years.[1–7] They can be employed for a wide range of chemical transformations, especially as reagents for oxidations.[8–23] For these purposes, iodinanes like (diacetoxyiodo)benzene, [bis(trifluoroacetoxy)iodo]benzene, hydroxy(tosyloxy)(iodo)benzene (Koser's reagent), the Dess–Martin periodinane (DMP) and 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX; **1**) (Figure 1) are particularly suitable. The advantages of these reagents are their easy availability, mild reaction conditions and (with the exception of DMP) stability against moisture and oxygen. Moreover they can be regenerated.

Recently, the IBX-mediated oxidation of primary alcohols and aldehydes to carboxylic acids was described.[24] A plausible reaction mechanism is that aldehyde **II**, which was generated from a primary alcohol **I** and an excess of IBX, reacts with suitable *O*-nucleophiles (YO-H) to form intermediate **III** (not isolable). This intermediate is further oxidized to the corresponding active ester **IV**, which is subsequently hydrolysed to give the desired carboxylic acid **V** (Scheme 1).
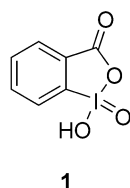
These active esters are valuable intermediates, for example, in peptide synthesis since their reaction with various amines could lead to the corresponding amides. However, although their intermediacy in the above-mentioned oxidations has been proven, they could only be isolated in low yields and as a mixture with the corresponding carboxylic acids.

Herein, we present a simple and efficient method for the preparation of various active esters (*N*-hydroxysuccinimide esters). Furthermore, we describe reaction conditions which allow the chemoselective oxidation of aldehydes in the presence of alcohols.
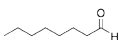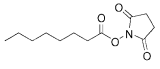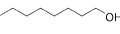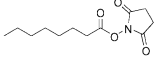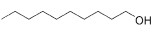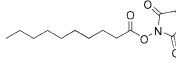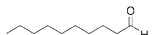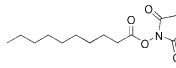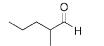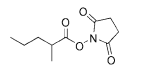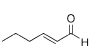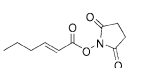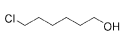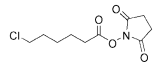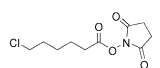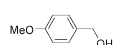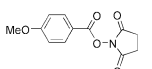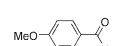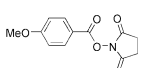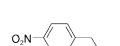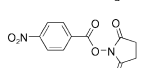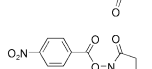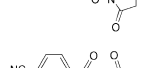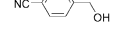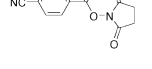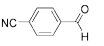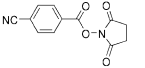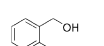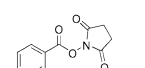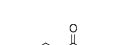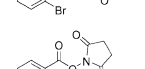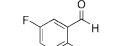
Results and Discussion

Under standard reaction conditions [1 equivalent of IBX and 1 equivalent of *N*-hydroxysuccinimide (NHS) in DMSO] octanal is oxidized to yield octanoic acid as the main product (yield 90%) accompanied by a small amount of the corresponding active ester (9%). Chang-

Figure 1. IBX.
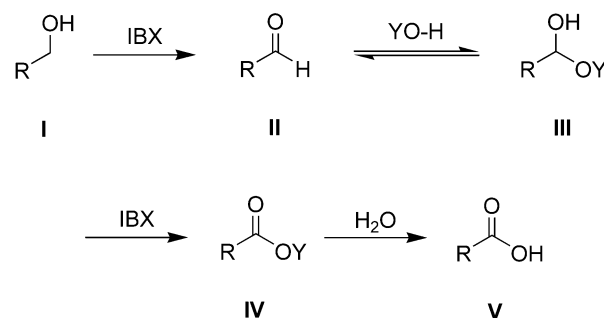
Scheme 1. Mechanism of the IBX-mediated oxidation of primary alcohols to carboxylic acids.

Table 1. IBX-mediated oxidation of primary alcohols and aldehydes to *N*-hydroxysuccinimide esters.

Entry	Substrate	Reaction time [h]	Product		Yield [%]
1	(aldehyde)	1	(NHS ester)	**3**	92
2	(alcohol)	3	(NHS ester)	**3**	90
3	(alcohol)	3	(NHS ester)	**4**	90
4	(aldehyde)	2	(NHS ester)	**4**	95
5	(aldehyde)	2	(NHS ester)	**5**	97
6	(aldehyde)	2	(NHS ester)	**6**	95
7	(Cl alcohol)	3	(NHS ester)	**7**	80
8	(Cl aldehyde)	2	(NHS ester)	**7**	82
9	(MeO alcohol)	3	(NHS ester)	**8**	62
10	(MeO aldehyde)	2	(NHS ester)	**8**	65
11	(O_2N alcohol)	3	(NHS ester)	**9**	53
12	(O_2N aldehyde)	2	(NHS ester)	**9**	55
13	(NC alcohol)	3	(NHS ester)	**10**	87
14	(NC aldehyde)	2	(NHS ester)	**10**	90
15	(Br alcohol)	3	(NHS ester)	**11**	60
16	(Br aldehyde)	2	(NHS ester)	**11**	60
17	(F, Br alcohol)	3	(NHS ester)	**12**	61
18	(F, Br aldehyde)	1	(NHS ester)	**12**	62
19	(amino-substituted aldehyde)	9	–		0
20	(amino-substituted aldehyde)	9	–		0

ing the solvent from DMSO to acetone improved considerably the profile of the reaction yielding after 4 h the active ester as the main product (yield 87%). Further improvement was achieved by carrying out the reaction in ethyl acetate with addition of 2 equivalents of NHS, whereby the active ester was formed in 92% yield within 1 h (Table 1, entry 1). Alcohols can be directly oxidized to the corresponding active esters by employing the above reaction conditions and using 2 equivalents of IBX. Thus, octanol was rapidly (3 h) oxidized in excellent yield (90%; Table 1, entry 2).

Employing the above simple experimental conditions, a series of aliphatic and aromatic aldehydes and primary alcohols was efficiently oxidized to the corresponding active esters (Table 1).

Other functional groups, such as isolated and conjugated double bonds, alkyl halides, electron-rich and -poor aromatic compounds were tolerated. However, it should be noted that this protocol was not successful in the case of amino-substituted aldehydes (Table 1, entries 19 and 20).

The observation that the successful oxidation of aldehydes benefits from the presence of 2 equivalents of NHS led us to speculate that an IBX-NHS adduct **VI** is the actual oxidizing agent (Scheme 2). Similar adducts have been proposed recently by Nicolaou.[21] Reaction of this putative intermediate with an aldehyde adduct of type **III** would finally afford the corresponding *N*-hydroxysuccinimide esters **IV**.

To test our hypothesis we suspended 1 equivalent of IBX and 1 equivalent of NHS in EtOAc. After refluxing for 2 h a clear yellow solution resulted. Upon removal of the solvent, a yellow solid was obtained, whose NMR spectra (600 MHz, $CDBr_3$) are in agreement with the structure of the proposed adduct **VI** (Figure 2).
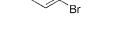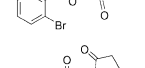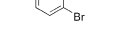
Inspection of the ^{1}H NMR spectra obtained at ambient temperature revealed additional signals in the range of 2.6 – 3.2 ppm that were initially attributed to impurities. However, these signals disappeared when the spectrum was recorded at 85 °C. This is a strong
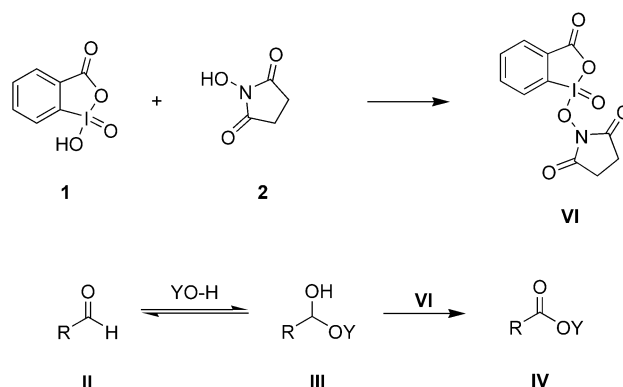
Scheme 2. Proposed mechanism of the IBX-mediated oxidation of aldehydes to *N*-hydroxysuccinimide esters.
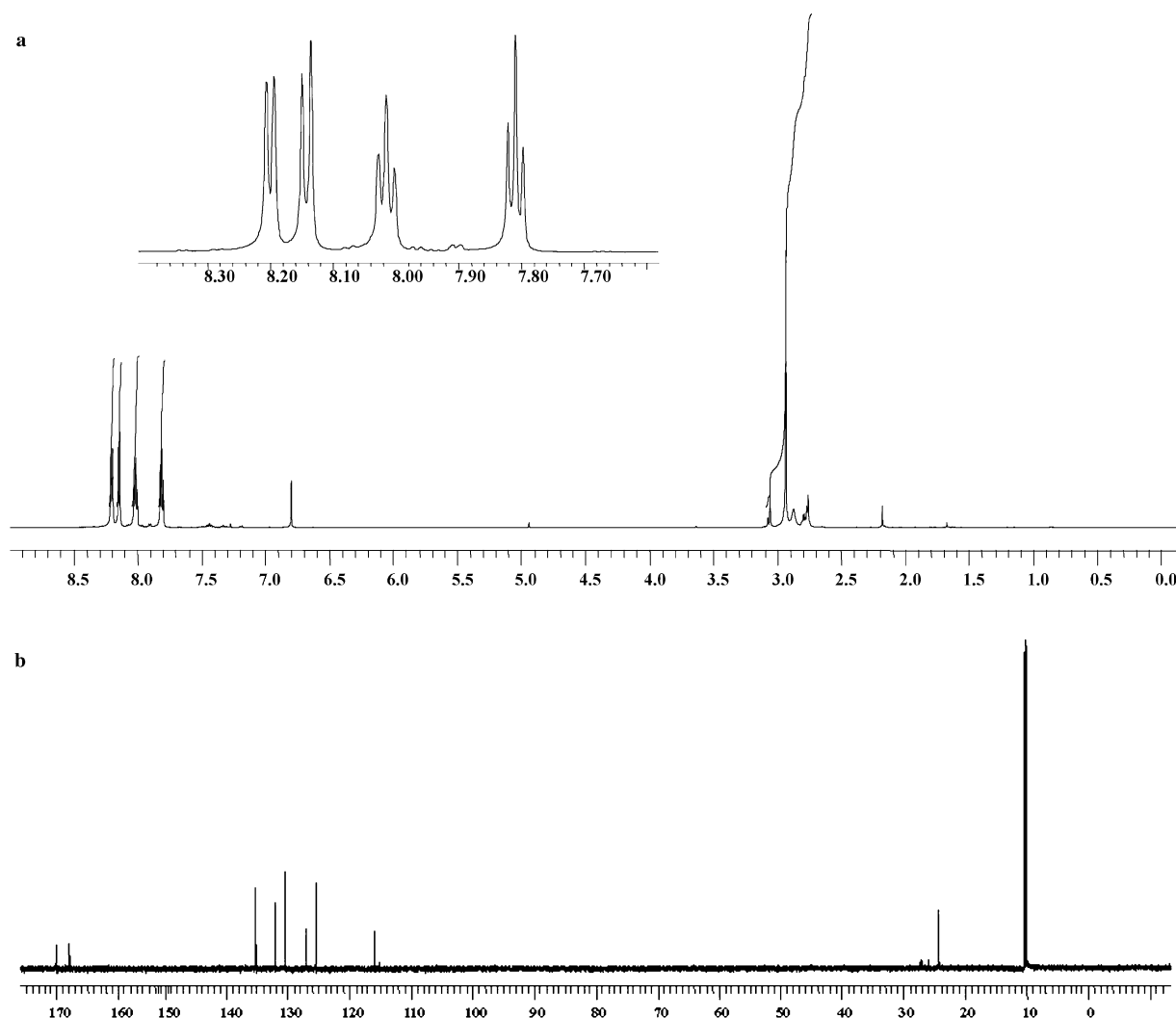
Figure 2. ^{1}H NMR (**a**) (600 MHz, CDBr$_3$) and ^{13}C NMR (**b**) spectra of **VI**.

indication that intermediate **VI** exists as a mixture of rotamers (Figure 3). To this end we were not able to further characterize the putative adduct **VI**. Currently we are trying to obtain crystals for an X-ray investigation.

Surprisingly enough, octanal is oxidized quantitatively within 1 h when treated with the solution obtained by reacting of IBX and NHS in EtOAc (see Experimental Section). In a separate experiment under the same reaction conditions, however, 1-octanol remained unaffected (Scheme 3). We attribute this result to the lower reactivity of the alcohol compared to the hydroxy group of **VII** (Scheme 3).

Conclusion

In the past, active esters, such as *N*-hydroxysuccinimide esters, were usually generated starting from the corresponding carboxylic acid or the acid chloride.

By comparison, the method presented herein allows us to convert primary alcohols and aldehydes into active esters. It is mild, easy to accomplish, efficient and fast. Aromatic and aliphatic aldehydes or primary alcohols containing functional groups such as isolated and conjugated double bonds, alkyl halides, electron-rich or -poor aromatic rings can be oxidized within 1–2 h (alcohols in 2.5–3 h) in good to excellent yields. Finally, use of the above-mentioned putative IBX-NHS-intermediate seems to allow the chemoselective oxidation of aldehydes in the presence of alcohols and we are currently investigating this in more depth.

Experimental Section

General Remarks

Reagents (except for IBX[10]) and solvents were commercially available and were used without further purification. ^{1}H and

Figure 3. ^{1}H NMR spectra (600 MHz, CDBr$_3$) measured at 25 °C (**a**) and at 85 °C (**b**).

^{13}C NMR spectra were recorded on a Varian VXR-Unity (200 and 300 MHz) in CDCl$_3$ with TMS as internal standard. The spectra at elevated temperature were recorded on a Bruker DRX-600 in CDBr$_3$. HRMS was obtained on a 7 T APEX II (for ESI) or a VG ZAB-HSQ (for EI). The reaction progress was monitored with a Varian SATURN 2200 GC/MS. Flash column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm).

Preparation of Active Esters

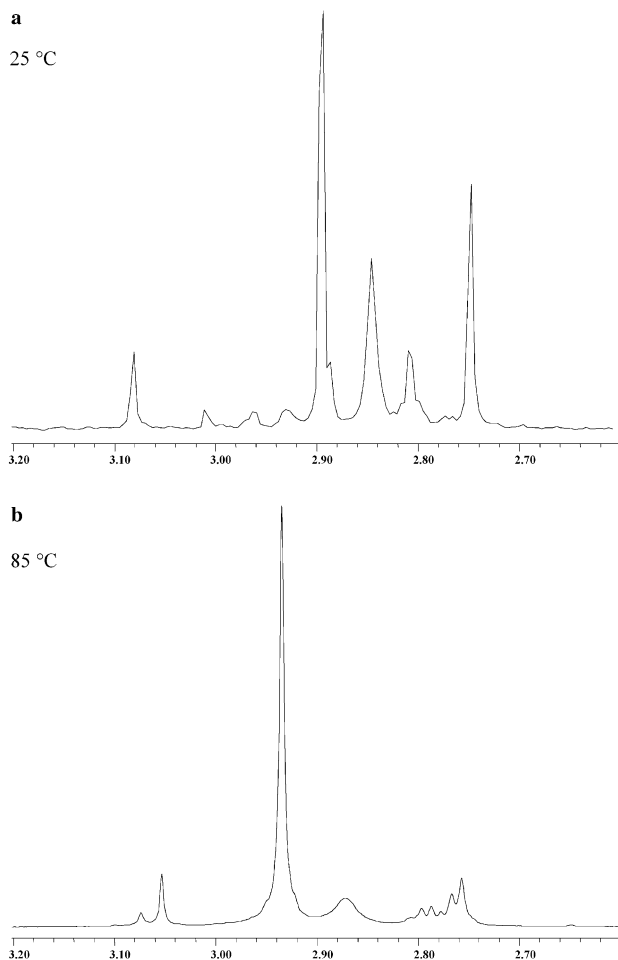A solution of the alcohol (1 equivalent, 2 mmol) in EtOAc (7 mL) was treated with IBX (2.2 equivalents, 4.4 mmol) (when starting from the aldehyde: 1.2 equivalent or 2.4 mmol IBX) and NHS (2.5 equivalents, 5 mmol). The reaction mixture was heated to reflux for 2–3 h depending on the alcohol (aldehydes: 1–2 h) until a yellow solution was formed. After cooling to ambient temperature, the solution was washed with saturated aqueous NaHCO$_3$ solution and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and analytically pure product was obtained by flash column chromatography.

Preparation of the Putative IBX-NHS Adduct

A suspension of IBX (1 mmol) and NHS (1 mmol) in EtOAc (5 mL) was refluxed for 2 h until a clear yellow solution was formed. The solvent was removed under reduced pressure and a pale yellow solid was obtained. This solid was used without further purification for the oxidations described in the text. For NMR spectroscopic investigations this solid was solved in CDCl$_3$ or CDBr$_3$.

2,5-Dioxopyrrolidin-1-yl octanoate (3): colourless crystals; mp 56 °C; $R_f = 0.13$ (hexane/EtOAc, 10:3); ^{1}H NMR (CDCl$_3$): $\delta = 0.86$ (t, 3H, $J = 6.6$ Hz), 1.27–1.76 (m, 12H), 2.82 (s, 4H); ^{13}C NMR (CDCl$_3$): $\delta = 14.0, 22.5, 24.5, 25.5, 28.7, 30.9, 31.5, 33.9, 169.2, 179.4$; HRESIMS: calcd. for (2M + Na)$^+$: 505.2520; found: 505.2531.

2,5-Dioxopyrrolidin-1-yl decanoate (4): colourless crystals; mp 67 °C; $R_f = 0.10$ (hexane/EtOAc, 10:3); ^{1}H NMR (CDCl$_3$): $\delta = 0.87$ (t, 3H, $J = 6.6$ Hz), 1.26–1.76 (m, 16H), 2.83 (s, 4H); ^{13}C NMR (CDCl$_3$): $\delta = 14.0, 22.5, 24.5, 24.6, 25.5, 28.7, 29.2, 30.9, 31.5, 33.9, 169.2, 175.2$; HRESIMS: calcd. for (2M + Na)$^+$: 561.3146; found: 561.3157.
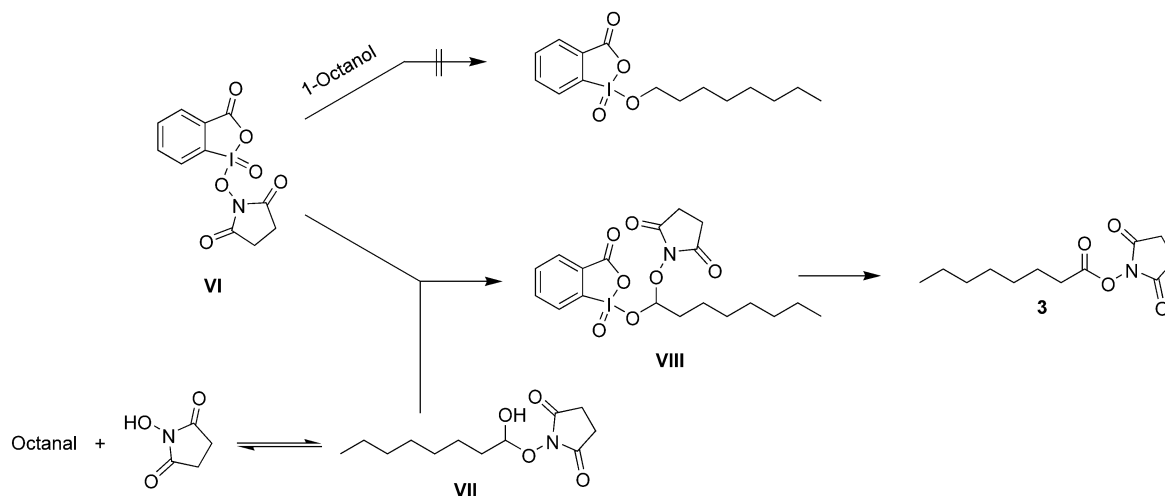
Scheme 3. Reaction of 1-octanol and octanal with **VI**.

2,5-Dioxopyrrolidin-1-yl 2-methylpentanoate (5): colourless oil; $R_f = 0.12$ (hexane/EtOAc, 10:3); ^{1}H NMR (CDCl$_3$): $\delta = 0.94$ (t, 3H, $J = 7.1$ Hz), 1.30 (d, 3H, $J = 7.1$ Hz), 1.34–1.60 (m, 4H), 1.74–1.84 (m, 1H), 2.83 (s, 4H); ^{13}C NMR (CDCl$_3$): $\delta = 13.8$, 16.8, 20.0, 25.6, 35.6, 36.8, 169.2, 171.8; HREIMS: calcd. for (M)$^+$: 213.1001; found: 213.0997.

2,5-Dioxopyrrolidin-1-yl 2-hexenoate (6): colourless oil; $R_f = 0.11$ (hexane/EtOAc, 10:3); ^{1}H NMR (CDCl$_3$): $\delta = 0.95$ (t, 3H, $J = 7.7$ Hz), 1.52 (q, 2H, $J = 7.7$ Hz), 2.27 (dq, 2H, $J = 7.7$ Hz, 2.0 Hz), 2.85 (s, 4H), 5.90 (dt, 1H, $J = 15.9$ Hz, 2.0 Hz), 7.25 (dt, 1H, $J = 15.9$ Hz, 7.1 Hz); ^{13}C NMR (CDCl$_3$): $\delta = 13.6$, 20.8, 25.6, 34.8, 115.4, 156.0, 161.3, 169.3; HREIMS: calcd. for (M)$^+$: 211.0844; found: 211.0836.

2,5-Dioxopyrrolidin-1-yl 6-chlorohexanoate (7): colourless solid; mp 147 °C; $R_f = 0.2$ (CHCl$_3$/MeOH, 30:1); ^{1}H NMR (CDCl$_3$): $\delta = 1.52$–1.58 (m, 2H), 1.70–1.83 (m, 4H), 2.60 (t, 2H, $J = 7.1$ Hz), 2.80 (s, 4H), 3.52 (t, 2H, $J = 6.6$ Hz); ^{13}C NMR (CDCl$_3$): $\delta = 21.7$, 23.7, 25.5, 25.9, 30.0, 30.6, 31.9, 44.5, 168.3, 169.1; HREIMS: calcd. for (M)$^+$: 247.0611; found: 247.0619.

2,5-Dioxopyrrolidin-1-yl 4-methoxybenzoate (8): yellow solid; mp 142 °C; $R_f = 0.41$ (CHCl$_3$/MeOH, 30:1); ^{1}H NMR (CDCl$_3$): $\delta = 2.89$ (s, 4H), 3.89 (s, 3H), 6.97 (d, 2H, $J = 6.6$ Hz), 8.09 (d, 2H, $J = 6.9$ Hz); ^{13}C NMR (CDCl$_3$): $\delta = 25.7$, 55.6, 114.2, 119.8, 131.5, 132.8, 164.9, 169.3; HRESIMS: calcd. for (2M + Na)$^+$: 521.1167; found: 521.1171.

2,5-Dioxopyrrolidin-1-yl 4-nitrobenzoate (9): yellow solid; mp 214 °C; $R_f = 0.29$ (CHCl$_3$/MeOH, 30:1); ^{1}H NMR (CDCl$_3$): $\delta = 2.94$ (s, 4H), 8.32 (d, 2H, $J = 9.3$ Hz), 8.37 (d, 2H, $J = 9.3$ Hz); ^{13}C NMR (CDCl$_3$): $\delta = 25.8$, 124.1, 130.7, 131.9, 151.7, 160.5, 168.9; HRESIMS: calcd. for (M + Na)$^+$: 287.0275; found: 287.0274.

2,5-Dioxopyrrolidin-1-yl 4-cyanobenzoate (10): yellow solid; mp 230 °C; $R_f = 0.37$ (CHCl$_3$/MeOH, 30:1); ^{1}H NMR (CDCl$_3$): $\delta = 2.93$ (s, 4H), 7.82 (d, 2H, $J = 8.8$ Hz), 8.24 (d, 2H, $J = 8.8$ Hz); ^{13}C NMR (CDCl$_3$): $\delta = 25.6$, 105.4, 117.3, 118.2, 126.9, 129.0, 130.9, 132.5, 160.5, 168.7; HRESIMS: calcd. for (M + Na)$^+$: 267.0382; found: 267.0382.

2,5-Dioxopyrrolidin-1-yl 2-bromobenzoate (11): yellow solid; mp 188 °C; $R_f = 0.6$ (CHCl$_3$/MeOH, 30:1); ^{1}H NMR (CDCl$_3$): $\delta = 2.90$ (s, 4H), 7.26–7.45 (m, 2H), 7.73–7.75 (m, 1H), 8.07–8.09 (m, 1H); ^{13}C NMR (CDCl$_3$): $\delta = 25.7$, 123.5, 126.5, 127.4, 132.5, 134.6, 135.0, 160.7, 169.0; HREIMS: calcd. for (M)$^+$: 296.964; found: 296.965.

2,5-Dioxopyrrolidin-1-yl 2-bromo-5-fluorobenzoate (12): yellow solid; mp 157 °C; $R_f = 0.49$ (CHCl$_3$/MeOH, 30:1); ^{1}H NMR (CDCl$_3$): $\delta = 2.89$ (s, 4H), 7.11 (d, 1H, $J = 8.6$ Hz), 7.74 (dd, 1H, $J = 2.6$ Hz, 8.6 Hz), 8.17 (d, 1H, $J = 2.6$ Hz); ^{13}C NMR (CDCl$_3$): $\delta = 25.6$, 116.9, 119.0, 119.5, 135.0, 139.4, 139.6, 164.1, 168.7; HRESIMS: calcd. for (2M + Na)$^+$: 654.8962; found: 654.8956.

Acknowledgements

References and Notes

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