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ARTICLE *in* TETRAHEDRON LETTERS · APRIL 2015

Impact Factor: 2.38 · DOI: 10.1016/j.tetlet.2015.04.031

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2-Oxopyridine-1-carboxylates, highly reactive carbamoylating agents of β-hydroxy α-aminoacids

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ARTICLE INFO

Article history:
Received 11 February 2015
Revised 2 April 2015
Accepted 8 April 2015
Available online xxxx

Keywords:
Di-2-pyridyl carbonate
2-Oxopyridine-1-carboxylate
Carbamoylation reaction
β-Hydroxy α-aminoacids

ABSTRACT

A reactivity study elucidating the mechanism and utility of di-2-pyridyl carbonate (2-DPC) as the activating agent for sterically-hindered alcohols is presented and discussed. Alcohol activation furnished isomeric mixtures of 2-pyridyl carbonates and 2-oxopyridine-1-carboxylates. A preliminary investigation of the reactivity of these two isomeric species in the carbamoylation reaction highlighted a higher reactivity of the 2-oxopyridine-1-carboxylates with respect to the corresponding 2-pyridyl isomers.

Introduction

Di-2-pyridyl carbonate[1] (2-DPC, **1**) has been reported as an efficient coupling reagent for the preparation of functionalized esters,[2] carboxamides,[3] peptides,[3,4] carbonates,[5] carbamates[5–7] and ureas.[5] This compound can be easily prepared from 2-hydroxypyridine and triphosgene in dichloromethane in the presence of triethylamine,[5,6,8] but is also commercially available.

In the preparation of carboxamides and peptides, 2-DPC has been used as a dehydrating agent that reacts with the carboxylic acid moiety, in the presence of a catalytic amount of 4-(dimethylamino) pyridine (DMAP), to afford the intermediate 2-pyridyl ester.[3] The subsequent addition of amines to the reaction mixture afforded the corresponding carboxamides in excellent yields. Notably, 2-DPC has been described to work efficiently also when highly hindered carboxylic acids were used.[3]

The versatility and efficiency of 2-DPC have been applied by Kim and coworkers in a convenient method for the preparation of active carbonates and ureas from alcohols and amines, respectively.[5] Active carbonates were conveniently prepared by reaction of alcohols with 2-DPC in the presence of a catalytic amount of DMAP [Scheme 1, reaction (a)].[5] On the other hand, when 2-DPC was reacted with amines the corresponding 2-pyridyl carbamates were obtained in high yields together with a small amount of the symmetrical ureas. The subsequent reaction of the 2-pyridyl carbamates with a catalytic amount of DMAP in aqueous tetrahydrofuran or with an equimolar amount of a different amine afforded the symmetrical or unsymmetrical ureas, respectively, in good to high yields [Scheme 1, reaction (b)].[5]

Gosh and co-workers[6] reported that the reaction of 2-DPC with diverse hindered secondary and tertiary alcohols afforded the corresponding mixed carbonates, which were efficiently transformed into carbamates in high yield under mild conditions.

Results and discussion

Recently, our group exploited the high versatility of 2-DPC as an activating agent for the conversion of different alcohols into key intermediates for the alkoxycarbonylation of α-amino β-lactones and β-hydroxy α-aminoacids.[9] In this Letter we report the study of the reaction of various alcohols **2** with 2-DPC, in the presence of a base (Scheme 2), furnishing an isomeric mixture of 2-pyridyl carbonates **3** and 2-oxopyridine-1-carboxylates **4**, which are reported as highly reactive species towards amino acids.[2,4,9,10] We have investigated the formation of compounds **3** and **4** and their reactivity in the carbamoylation of different β-hydroxy α-aminoacids.

The formation of 2-oxopyridine-1-carboxylates **4** was previously described both by Effenberger[4] and by Shiina.[3] Effenberger reported the isolation of *t*-butyl 2-oxopyridine-1-carboxylate (**4**, R = *t*-butyl) by fractional crystallization of **3** and **4**, obtained by the reaction of the isomeric mixture of 2-DPC and 2-pyridyl 2-oxopyridine-1-carboxylate with lithium *t*-butoxide. More recently, Shiina described the activation of cyclohexanol by

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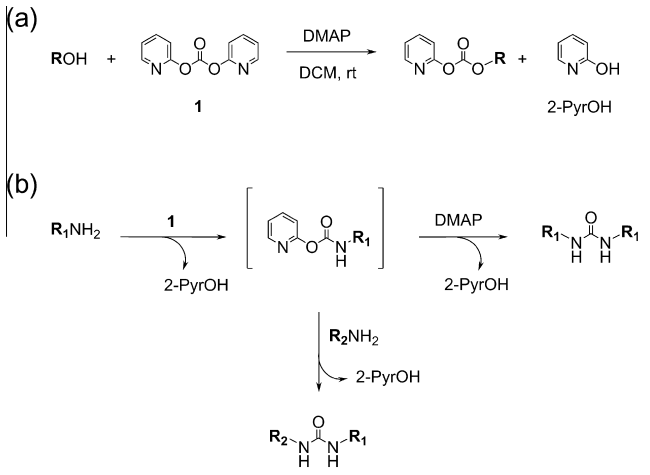
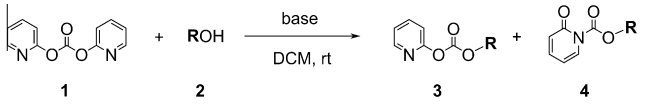
http://dx.doi.org/10.1016/j.tetlet.2015.04.031
0040-4039/



Scheme 1. Preparation of pyridyl carbonates (a) and ureas (b) using 2-DPC (**1**).



Scheme 2. Reaction of alcohol **2** with 2-DPC (**1**).

2-DPC affording a mixture of three different species: cyclohexyl 2-pyridyl carbonate (**3**, R = cyclohexyl), cyclohexyl 2-oxopyridine-1-carboxylate (**4**, R = cyclohexyl) and the symmetric dicyclohexyl carbonate in 52, 8 and 2% yield, respectively. However, no characterization and reactivity data were reported for cyclohexyl 2-oxopyridine-1-carboxylate due to instability under chromatographic conditions that prevented the isolation of the pure compound.[3]

Interestingly, Gosh and coworkers reported that mixed carbonates **3** obtained from 2-DPC often undergo rearrangement to the corresponding 2-oxopyridine-1-carboxylate derivatives **4** (in 5–10% amount) and that the latter isomers do not affect the final outcome of the subsequent reaction.[6] The mixtures of the isomeric *t*-butyl and (1-adamanthyl)-1methylethyl 2-pyridyl carbonate **3** [R = *t*-butyl and (1-adamanthyl)-1-methylethyl] and 2-oxopyridine-1-carboxylates **4** [R = *t*-butyl and (1-adamanthyl)-1-methylethyl] were indeed reported by Effenberger to react smoothly with natural aminoacids[4] to afford the corresponding *N*-*t*-butyl- and *N*-(1-adamanthyl)-1-methylethyl carbamates. In the alkoxycarbonylation of α-amino β-lactones and β-hydroxy α-aminoacids,[9] however, we often recovered 2-pyridyl carbonates from the reaction mixtures,[11] thus suggesting a different reactivity of isomers **3** and **4**.

We therefore set out to prepare, purify and isolate 2-pyridyl carbonates **3** and 2-oxopyridine-1-carboxylates **4** in order to evaluate their reactivity towards β-hydroxy α-aminoacids. Initial experiments starting from various alcohols were unsuccessful due to the limited stability of compounds **3** and **4** to chromatographic purification. In particular, as reported by Shiina[3] and our group,[9] the 2-oxopyridine-1-carboxylates **4** turned out to be unstable under silica purification conditions in contrast with the 2-pyridyl carbonates **3**.

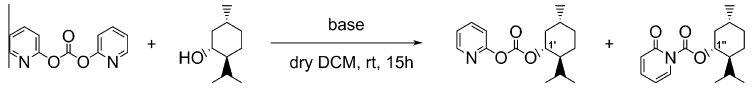
We turned therefore our attention to (+)-menthol (**2a**), since the isomer **3a** was previously described as a stable compound that could be isolated in analytically pure form.[6] In our hands, the reaction of alcohol **2a** with **1** in the presence of a base furnished both isomers, **3a** and **4a**. The 2-oxopyridine-1-carboxylate (**4a**) proved to be fairly stable, thus allowing its isolation and NMR characterization as a pure compound (Table S1).

The reaction of alcohols with 2-DPC has usually been carried out in dichloromethane in the presence of DMAP[5] or trimethylamine.[6] We started our study by evaluating the effect of the base in the formation of 2-pyridyl carbonate **3** and 2-oxopyridine-1-carboxylate **4** derivatives of (+)-menthol (**2a**), as the isomers **3a** and **4a** are stable under the reaction and purification conditions. Alcohol **2a** was therefore reacted at room temperature with a slight excess of 2-DPC (1.2 equiv) in dry dichloromethane for 15 h in the presence of a base, selected among the most common organic and inorganic bases (Table 1). The experimental results clearly revealed that the **3a**:**4a** ratio is affected by the base.

Overall, with bases having p*Ka* value ranging between 9 and 11, the formation of the two isomers was always observed even though in different ratios (entries 1–3 and 6). On the other hand, in the presence of a weak base such as pyridine (entry 5) as well as in the absence of a base (entry 8), the formation of the 2-oxopyridine-1-carboxylate (**4a**) did not occur. Moreover, DBU and HMDS (entries 4 and 7), the strongest bases in this selection, failed to generate any of the two isomers due to a rapid degradation of 2-DPC in the reaction mixture.

Considering the almost complete conversion of the starting alcohol (ca. 100%) and the relative abundance of both reactive species (**3a** and **4a**), the experimental conditions using a

Table 1
Effect of the base on the ratio between isomers **3a** and **4a** and the conversion of alcohol **2a**



1 2a 3a 4a

Entry	Base (1.5 equiv)	pKa[a]	Ratio **3a**:**4a**[b]	Conversion[c] **2a** (%)
1	Et_3N	10.75	72:28	94
2	DMAP (0.1 equiv)	9.2	60:40	>99
3	DMAP	9.2	60:40	94
4	DBU	12	—	—
5	Pyridine	5.21	>99:1	48
6	K_2CO_3	10.33	58:42	90
7	HMDS	26	—	—
8	—	—	>99:1	14

[a] The reported pKa values were taken from D.H. Ripin, D.A. Evans Tables (http://www.chem.wisc.edu/areas/reich/pkatable/index.htm).
[b] Ratio **3a**:**4a** after 15 h and reaction work-up. Ratio calculated from the intensity of the ^{1}H NMR signals of proton 1′ of **3a** and 1″of **4a**.
[c] Conversion calculated on the bases of ^{1}H NMR *CH*OH signal of **2a**.

catalytic amount of DMAP (0.1 equiv, entry 2, Table 1) were chosen to investigate in more detail the reaction of (+)-menthol with 2-DPC.

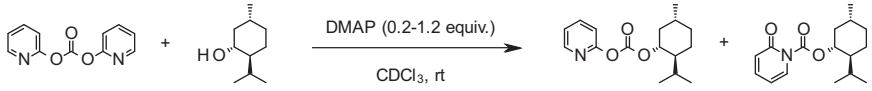
We first evaluated the time-dependency of the formation of compounds **3a** and **4a** after portion-wise addition of 2-DPC. To this purpose, alcohol **2a** was reacted with only 0.2 equiv of 2-DPC in the presence of a catalytic amount of DMAP and the **3a**:**4a** isomeric ratio was analysed by ^{1}H NMR at different time points. As shown in Table 2, while no product was detected after 5 min from addition of 2-DPC, the 2-pyridyl carbonate **3a** was observed as the only isomer after 15 min (entry 2, Table 2). Isomer **4a** was observed only after one hour (entry 3), and successive additions of 2-DPC (up to 1.2 overall equivalents) led only to a slight variation in the **3a**:**4a** ratio (entries 4–8). Full conversion of alcohol **2a** was achieved after nine hours, and a 69:31 ratio between **3a** and **4a** was observed at this time point (entry 9). Upon standing at room temperature up to 15 h, the **3a**:**4a** isomeric ratio adjusted to 60:40 (entry 10, Table 2), in agreement with the previously observed data (entry 2, Table 1). Interestingly, when the reaction was run for 15 h with 0.2 equiv of **1**, the **3a**:**4a** ratio and the alcohol conversion were similar to those reported in entry 3.

Based on these results, a rearrangement of the 2-pyridyl carbonate **3a** into the corresponding 2-oxopyridine-1-carboxylate **4a** can be hypothesized, as indicated by Gosh and co-workers.[6] This hypothesis was verified by analysing the reaction outcome starting from each isomer, **3a** or **4a**, in the presence of catalytic amount (0.1 equiv) of DMAP (Table 3). Although the same **3a**:**4a** final ratio was obtained after 15 h in both cases (entry 2), the two isomers displayed a remarkable difference in reactivity. Starting from the 2-oxopyridine-1-carboxylate **4a**, the 60:40 isomeric ratio was obtained after only 1 h (entry 1), while 15 h were necessary to afford the same ratio starting from the 2-pyridyl carbonate **3a** (entry 2). This finding clearly suggests a higher reactivity of the 2-oxopyridine-1-carboxylate species with respect to the 2-pyridyl carbonate isomer.

The interconversion of **3a** into **4a** and vice versa could be explained by the mechanism depicted in Scheme 3. The 2-pyridin-2-olate (**5**), generated by nucleophilic attack of DMAP onto the carbonyl group of **3a** or **4a**, could reasonably be considered as the key species which brings about the isomerization by reacting with intermediate **6** (Scheme 3). Once the anionic compound **5** is formed, the negatively charged nitrogen or oxygen could attack the carbonyl group of intermediate **6**, thus leading to the isomer of the starting compound or reforming the starting compound. Compound **5** could also react with either the 2-pyridyl carbonate **3a** or the 2-oxopyridine-1-carboxylate **4a** affording the other isomer.

Literature reports indicated that both isomers **3** and **4** are reactive species towards nitrogen nucleophiles,[2,4,9] and are therefore useful intermediates to obtain the corresponding carbamates. We previously exploited the reactivity of 2-pyridyl carbonate **3** and 2-oxopyridine 1-carboxylate **4** of various alcohols to prepare the corresponding carbamoyl derivatives of D-threonine as intermediates in the synthesis of β-lactones.[9] To further elucidate the reactivity of the two isomers in the carbamoylation reaction, D-threonine (**7**) was first reacted with the isomeric mixture of **3a**

Table 2
Time-dependency of the formation of isomers **3a** and **4a** from alcohol **2a**

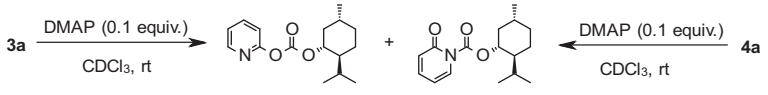


1 **2a** **3a** **4a**

Entry	Time (h)	**1** (equiv)	Ratio **3a**:**4a**[a]	Conversion **2a**[b] (%)
1	0.08	0.2	–	–
2	0.25	0.2	>99:1	9
3	1	0.2	83:17	20
4	2	0.4	74:26	32
5	3	0.6	73:27	53
6	4	0.8	70:30	73
7	5	1.0	71:29	86
8	6	1.2	68:32	91
9	7	1.2	69:31	>99
10	15	1.2	60:40	>99

[a] Ratio **3a**:**4a** calculated from the intensity of the ^{1}H NMR signals of proton 1′ of **3a** and 1″ of **4a** on the crude reaction.
[b] Conversion calculated on the bases on ^{1}H NMR *CH*OH signal of **2a**.

Table 3
Conversion of the isolated isomers **3a** and **4a** into the isomeric mixture

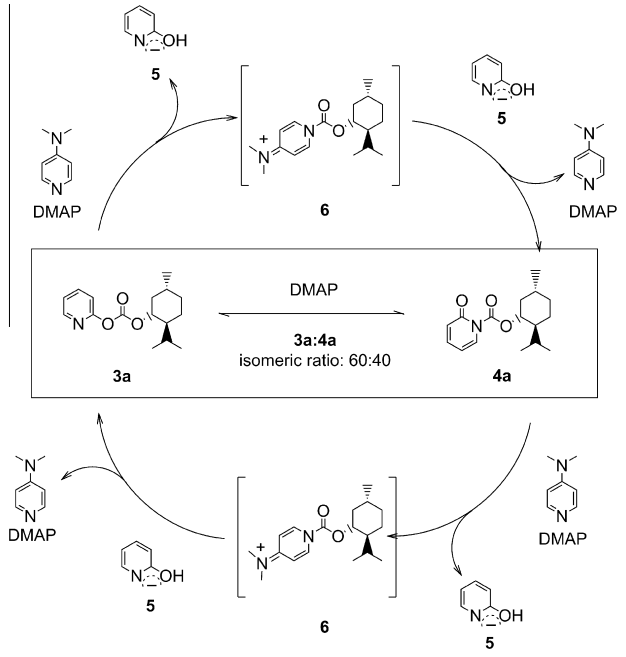


3a **4a**

Entry	Time (h)	Ratio **3a**:**4a**[a] (%)	
		From **3a**	From **4a**
1	1	80:20	60:40
2	15	60:40	60:40

[a] Ratio **3a**:**4a** calculated from the intensity of the ^{1}H NMR signals of proton 1′ of **3a** and 1″ of **4a** on the reaction crude.

Please cite this article in press as: Petracca, R.; et al. *Tetrahedron Lett.* (2015), http://dx.doi.org/10.1016/j.tetlet.2015.04.031



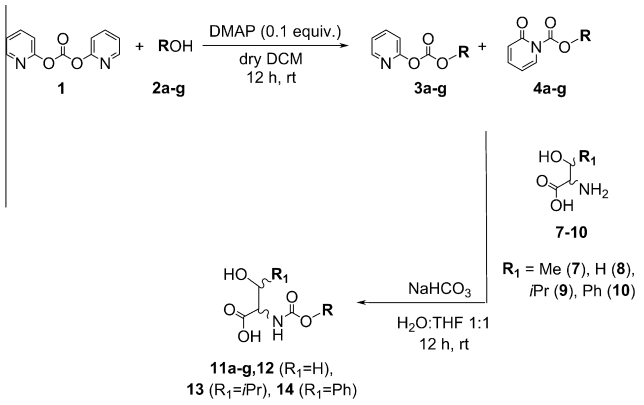
Scheme 3. Proposed mechanism for the interconversion of **3a** and **4a** in the presence of DMAP.

and **4a**, and then with each single isomer. Reaction of **7** with the mixture of **3a** and **4a** afforded the desired β-hydroxy acid derivative **11a** in moderate yield (53%, entry 1, Table 4). Surprisingly, when the pure isomers were reacted separately with **7**, the desired product **11a** was only obtained employing the 2-oxopyridine-1-carboxylate **4a.** The isomer **4a** reacted smoothly to afford the corresponding carbamoylated product **11a** in an excellent yield (98%), while the 2-pyridyl carbonate **3a** showed no reactivity under the same experimental conditions. This result is in agreement with the higher reactivity of 2-oxopyridine-1-carboxylate **4a** with respect to 2-pyridyl carbonate **3a** observed in the isomerization process.

The reactivity of the two isomers **3a** and **4a** towards other β-hydroxy α-aminoacids was then evaluated (Table 4). To this purpose, the isomeric mixture **3a** and **4a**, obtained by the usual procedure, was reacted with D-serine (**8**, entry 2), (2*S*,3*S*)-3-hydroxyleucine (**9**, entry 3) and DL-threo-3-phenylserine (**10**, entry 4), to afford the corresponding β-hydroxy acid derivatives **12**–**14**. The moderate yields observed in the reactions with those β-hydroxy α-aminoacids, displaying a different substitution at the β-position, are in agreement with the results obtained with D-threonine. Most likely, the very low or lack of reactivity of the 2-pyridyl carbonate **3a** under our experimental conditions[12] is responsible for the moderate yields of compounds **12**–**14**.

We then moved to study the reactivity of different primary, secondary and tertiary alcohols with 2-DPC and the reaction of the corresponding mixtures of isomers **3** and **4** with D-threonine (**7**) to afford the carbamic acid esters **11b**–**g** (Table 4). The alcohols **2b**–**g** were activated with **1** and catalytic DMAP (0.1 equiv) affording the 2-pyridyl carbonates **3b**–**g** and 2-oxopyridine-1-carboxylates **4b**–**g** in good to excellent yields (Table 4). Interestingly, the isomeric ratio **3**:**4** turned out to be independent from the starting alcohol **2b**–**g**, providing in all cases a value similar to that observed in the reaction between alcohol **2a** and **1** (entry 1, Table 4). The obtained 2-pyridyl carbonates **3b**–**g** and 2-oxopyridine-1-carboxylates **4b**–**g** were not purified to avoid any degradation and used as a mixture directly in the following coupling reaction with **7**, affording the corresponding β-hydroxy α-substituted acids **11b**–**g**

Table 4
Synthesis and isolated yields of α-substituted-β-hydroxy-acids **11a**–**g**, **12**–**14**



Entry	2	R^1	Ratio[a] **3a–g**:**4a–g**	Yield[b] (%) **3a–g**, **4a–g**	Yield[c] (%) **11a–g**, **12–14**
1	**a**	Me	62:38	Quant.[d]	53
2	**a**	H	62:38	Quant.[d]	59
3	**a**	*i*Pr	62:38	Quant.[d]	51
4	**a**	Ph	62:38	Quant.[d]	57
5	**b**	Me	61:39	81	91
6	**e**	Me	63:37	Quant.[d]	99
7	**c**	Me	63:37	91	85
8	**d**	Me	63:37	98	81
9	**f**	Me	65:35	51	44
10	**g**	Me	63:37	72	34

[a] Ratio **3a**–**g**:**4a**–**g** calculated from the intensity of the ^{1}H NMR signals of proton 1′ of **3a** and 1″ of **4a** after work-up.
[b] Yield of the isolated products as mixtures of **3a**–**g** and **4a**–**g** after reaction work-up.
[c] Yield of isolated product.
[d] Quant. = quantitative (>99%).

in satisfactory yields (Table 4). Although primary and secondary alcohols (entries 5–8) led to derivatives **11b**–**e** in moderate to high yields, in the case of tertiary alcohols (entries 9 and 10) the isolated yields were significantly lower, in line with the result obtained with alcohol **2a**.

The low reactivity of isomers **3f** and **3g** towards **7** was confirmed by UPLC-MS and ^{1}H NMR analyses, which detected the corresponding isomer **3** together with carbamate **11** in the crude reactions. This result confirmed the higher reactivity of the sterically-hindered 2-oxopyridine-1-carboxylates **4f**–**g** with respect to 2-pyridyl carbonates **3f**–**g**, as observed with compounds **4a** and

3a. On the other hand, the high yields of carbamoylated β-hydroxy α-aminoacids **11b**–**e** suggest a comparable reactivity of 2-pyridyl carbonates and 2-oxopyridine-1-carboxylates deriving from primary alcohols.

The reactivity of the isomeric mixture of **3** and **4** was also exploited for the carbamoylation of un-natural β-hydroxy α-aminoacids to afford intermediates in the synthesis of differently β-substituted α-amino β-lactones.[13] In general, the β-alkyl substitution as either ethyl, *i*-propyl or *t*-butyl group, on the starting α-aminoacid had only a marginal effect on the reaction outcomes, since the desired products were obtained in similar good to high yields.

Conclusion

In conclusion, we studied the reaction of representative primary, secondary and tertiary alcohols with 2-DPC in the presence of a base. All alcohols reacted with 2-DPC furnishing an isomeric mixture of 2-pyridyl carbonates **3** and 2-oxopyridine-1-carboxylates **4**. The stability of isomers **3a** and **4a** allowed us to perform a complete spectroscopic characterization of these two species, to study the effect of the base on the **3a**:**4a** ratio, and to uncover a time-dependent formation of the 2-oxopyridine-1-carboxylate **4a** and the 2-pyridyl carbonate **3a** during the reaction. Furthermore, a preliminary investigation of the reactivity of **3a** and **4a** in the carbamoylation reaction of different β-hydroxy α-aminoacids indicated a higher reactivity of the 2-oxopyridine-1-carboxylates **4** deriving from sterically-hindered alcohols as compared to the 2-pyridyl carbonates **3**.

Di-2-pyridyl carbonate confirmed therefore as a suitable activating agent for sterically-hindered alcohols in the synthesis of carbamates of β-hydroxy α-aminoacids through the highly reactive intermediate 2-oxopyridine-1-carboxylates **4**.

Acknowledgments

The authors wish to thank Dr. Esther Torrente De Haro for the fruitful discussion during the characterization of the final compounds and the preparation of this manuscript.

Supplementary data

Supplementary data (detailed experimental procedures, analytical and spectroscopical data of intermediate and final compounds, and full NMR characterization of isomers **3a** and **4a**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.04.031.

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