Isoprene-Mediated Lithiation of 1-Alkylimidazoles: Chiral Induction of the Alkyl Substituent

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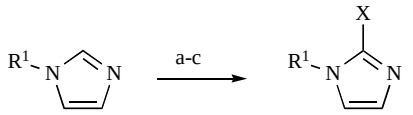
Abstract: The isoprene-mediated lithiation of imidazoles bearing a secondary alkyl substituent at the nitrogen (**7**, **8** and **13**) and the subsequent nucleophilic addition to different electrophiles allows the preparation of the corresponding 2-functionalized imidazoles **10**, **11** and **14**. The presence of a stereogenic center in the alkyl substituent induces diastereoselection during the nucleophilic addition step with a prochiral electrophile (i.e. pivalaldehyde), producing the expected imidazole derivative with excellent overall yield, but low de (up to 26%).

Keywords: Isoprene-mediated lithiation, imidazole derivatives, nucleophilic addition, lithium.

1. INTRODUCTION

About half of the registered chemical compounds contain a heterocyclic moiety. Imidazoles, and azoles in general, are an important family of those heterocyclic compounds with a broad interest due to their bioactive properties [1]. Consequently, the synthesis of imidazole derivatives constitutes a wide field of interest in synthetic organic and medicinal research [2]. Imidazole derivatives can be obtained by different routes, the employment of metalated imidazole derivatives being one of them [3].



1 (R^1 = Me)
2 (R^1 = Ph)
3 [R^1 = $CH(OEt)_2$]

4 (77-99%, R^1 = Me)
5 (64-89%, R^1 = Ph)
6 (48-93%, R^1 = H)

Scheme 1. Reagents and conditions: (a) Li, isoprene, THF, 25 ºC; (b) Electrophile, THF, 25 ºC; (c) H_2O (or HCl 0.1 M for compound 3).

Lithium metal is a widely used lithiation agent for the preparation of organolithium reagents. Additionally, the use of an arene as catalyst has been extensively employed as a very practical methodology [4]. A variety of functionalized organolithium intermediates has been prepared, employing metal lithium as lithiating agent, by means of this methodology [5]. More recently, we have reported the use of a diene (i.e. isoprene) as a promoting lithiation agent in the generation of lithio-imidazole derivatives. Thus, isoprene-mediated lithiation of different imidazole derivatives, such as *N*-methyl- (**1**) [6], *N*-phenyl- (**2**) [7] and *N*-(diethoxy-methyl)imidazole (**3**) [8] has been reported (Scheme **1**). Albeit the generation of 2-lithioimidazole derivatives bearing methyl or primary alkyl groups in the nitrogen has been extensively studied, the preparation of this type of organolithium intermediates with a secondary alkyl moiety has not been yet reported. Herein, we describe the use of the isoprene-mediated lithiation methodology in the preparation and reactivity of *N*-cyclohexyl- and *N*-(1-methylheptyl)-2-lithioimidazole. Additionally, it has been considered the influence of a stereogenic center in the alkyl substituent [using 1-(1-cyclohexylethyl)imidazole] during the nucleophilic addition reaction to a prochiral electrophile [9].

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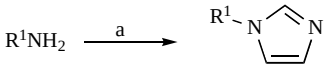
2. RESULTS AND DISCUSSION

N-Cyclohexyl- (**7**) and *N*-(1-methylheptyl)imidazole (**8**) were respectively obtained from cyclohexylamine and 2-octylamine, in their reaction with formaldehyde, glyoxal and ammonia. Thus, an equimolecular mixture of the four components was heated at 75 ºC in a mixture of water/methanol during 3 hours producing imidazoles **7** and **8** in good isolated yields (Scheme **2**) [10].



7 (80%, R^1 = cyclohexyl)
8 (75%, R^1 = 1-methylheptyl)

Scheme 2. Reagents and conditions: (a) NH_3 (25% aq.), $[(CHO)_2]_3 \cdot (H_2O)_2$, CH_2O (36% aq.), H_2O/MeOH, 75 ºC.

Imidazole derivatives **7** and **8** were treated with lithium powder in the presence of isoprene [11] at room temperature, producing the corresponding organolithium intermediates **9** which underwent nucleophilic addition to different aldehydes and ketones giving, after hydrolysis, the corresponding 2-functionalized imidazoles **10** and **11** (Table **1**) [12]. The final products **11** were obtained as diastereo-isomeric mixtures, when the reactions were performed with prochiral electrophiles, due to the presence of a stereogenic center in the *N*-substituent of compound **8** (Table **1**, entries

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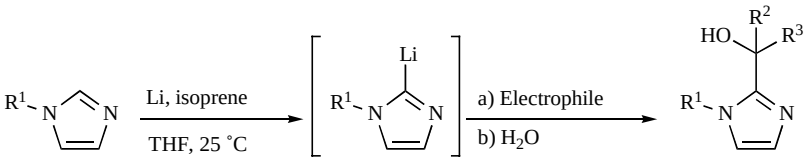
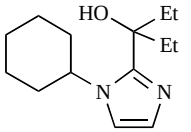
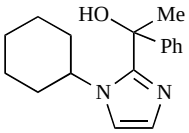
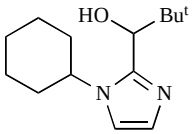
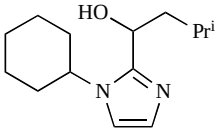
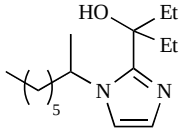
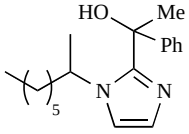
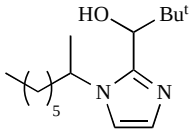
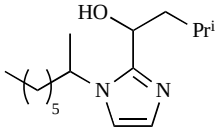
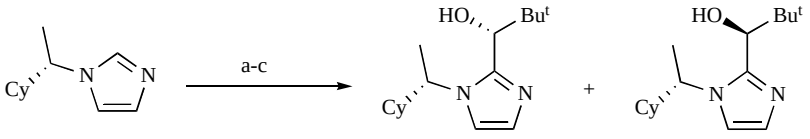
Table 1. Isoprene-Mediated Lithiation of Imidazoles 7 and 8[a]



7-8 **9** **10-11**

Entry	Substrate	Electrophile	Product		
			No.	Structure	Yield (%)
1	**7**	Et_2CO	**10a**		82
2	**7**	PhCOMe	**10b**		53
3	**7**	Bu^tCHO	**10c**		65
4	**7**	Pr^iCH_2CHO	**10d**		75
5	**8**	Et_2CO	**11a**		65
6	**8**	PhCOMe	**11b**		82[b]
7	**8**	Bu^tCHO	**11c**		94[c]
8	**8**	Pr^iCH_2CHO	**11d**		72[b]

[a]Reactions performed with the corresponding imidazole (2 mmol), lithium (6 mmol), isoprene (4 mmol) in THF (5 mL), and then the electrophile (2.2 mmol).
[b]This compound was obtained as a mixture of diastereoisomers (0% de, ^{1}H-NMR).
[c]This compound was obtained as a mixture of diastereoisomers (9% de, ^{1}H-NMR).



13 **14**

90% yield (26% de)

Scheme 3. Reagents and conditions: (a) Li, isoprene, THF, 25 ºC; (b) Bu^{t}CHO, THF, 25 ºC; (c) H_2O.

6-8, footnotes b and c). Although, compounds **11b** and **11d** resulted as a 1:1 mixture of diastereoisomers, compound **11c** was obtained with a slight diastereoisomeric excess.

The selectivity of the nucleophilic addition process seems to be controlled by the stereogenic center in the *N*-substituent. Thus, we prepared (*R*)-1-(1-imidazolyl)-1-phenylethane (**12**) and (*S*)-1-cyclohexyl-1-(1-imidazolyl) ethane (**13**) starting from the corresponding chiral amines by means of the methodology described above (in Scheme **2**) [10,13]. Lithiation of compound **12** did not give the expected 2-lithioimidazole derivative under any of the reaction conditions employed, because the reductive cleavage of the benzylic substituent occurred in the presence of the mixture lithium/isoprene [14]. However, the lithiation of imidazole **13** employing the same methodology described previously and the nucleophilic addition to pivalaldehyde gave compound **14** as a diastereoisomeric mixture in good overall yield (Scheme **3**) [15].

CONCLUSIONS

In conclusion, we have reported here that the lithium/isoprene methodology is applicable to successfully generate 2-lithio-*N*-alkylimidazole derivatives bearing secondary alkyl groups, although higher amounts of isoprene are needed in comparison with the lithiation of 1-methylimidazole. Additionally, the reaction of the chiral organolithium intermediates with a prochiral electrophile (i.e. pivalaldehyde) gives the corresponding functionalized imidazoles with a certain degree of diastereoselection, when a stereogenic center is linked to the *N*-substituent.

ACKNOWLEDGEMENTS

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[9] A part of this study was preliminary presented: Torregrosa, R.; Pastor, I. M.; Yus, M. Isoprene-mediated lithiation of chiral *N*-alkylimidazoles. *ECSOC-11*, **2007**, communication [a005] (http://www.mdpi.org/ecsoc-11).

[10] General procedure for preparation of imidazoles: A solution of the corresponding amine (10 mmol) and ammonia (25% aq., 10 mmol, 0.75 mL) in MeOH (4 mL) and a solution of glyoxal (trimer dihydrate, 10 mmol, 0.70 g) and formaldehyde (36% aq., 10 mmol, 0.77 mL) in MeOH (4 mL) and water (4 mL) were slowly and simultaneously added to a round bottom flask with MeOH (7 mL) heated to 50 ºC. After the addition was finished, the reaction mixture was heated to 75 ºC during 3 h. The reaction mixture was cooled down, diethyl ether and water were added in equal portions until two phases were observed and the aqueous phase was extracted with Et_2O (3×10 mL). All the organic phases were dried over anhydrous magnesium sulphate. The solvents were evaporated under reduced pressure and the corresponding imidazoles were

purified by column chromatography (silica gel, mixtures of hexane and ethyl acetate).

[11] Different amounts of isoprene have been used depending on the substrate, see ref. 6-8. For these cases it was observed and improvement of the yield in the final product by increasing the isoprene amount up to 200% molar, so this amount has been employed for all the reactions.

[12] General procedure for the isoprene-mediated lithiation: The corresponding imidazole (2 mmol) was added to a suspension of lithium powder (6 mmol, 0.042 g) and isoprene (4 mmol, 0.404 mL) in THF (5 mL) at room temperature. The mixture was stirred for 1 hour and then the corresponding electrophile (2.2 mmol) was added, continuing the stirring during 45 min at the same temperature. The reaction mixture was hydrolyzed with water (10 mL), extracted with ethyl acetate (3×10 mL), and the resulting organic phase was dried over anhydrous magnesium sulfate. After removing the solvent under reduced pressure (15 Torr), the resulting crude was purified by column chromatography (silica gel, mixtures of hexane and ethyl acetate) or by recrystallization.

[13] Imidazoles **12** and **13** were respectively isolated with 70% and 44% yield after column chromatography (silica gel, hexane/ethyl acetate mixtures).

[14] The *N*-benzyl substituent is not stable under isoprene-mediated lithiation reaction: for the stability of *N*-substituted imidazoles under these conditions see ref. 8.

[15] *1-[1-(1-Cyclohexylethyl)-1H-imidazol-2-yl]-2,2-dimethylpropan-1-ol* (**14**). [Diastereoisomer 1]: Colorless solid; m.p. 72–74 ºC; $[\alpha]_D^{20}$ = +3.6 (*c* 2.4, CH_2Cl_2); t_r 15.33; R_f 0.35 (hexane/EtOAc 2:1); ν(KBr) 3660–3019 (OH); δ_H (400 MHz, $CDCl_3$): 0.84–0.92, 0.98, 1.07, 1.20–1.26, 1.42–1.44, 1.65, 1.76–1.80, 1.84–1.88 [1H, 10H, 3H, 1H, 4H, 2H, 1H and 1H, 8m, 5×CH_2 and CH, CH_3CH and C$(CH_3)_3$], 3.42 (1H, br s, OH), 3.88–3.92 (1H, m, C*H*CH_3), 4.36 (1H, s, C*H*OH), 6.85, 7.03 (1H and 1H, 2s, NCHCHN); δ_C (100 MHz, $CDCl_3$): 18.8 (*C*H_3CH), 25.6 [3C, C(*C*$H_3)_3$], 25.8, 25.9, 25.9, 29.3, 30.0 (5×CH_2), 37.0 [*C*$(CH_3)_3$], 45.3 (CH), 56.7 (*C*HCH_3), 73.2 (CHOH), 115.5, 127.3 (NCHCHN), 149.1 (NCN); *m/z* 265 (M^++1, 1%), 264 (4), 208 (12), 207 (76), 97 (100), 69 (20). HRMS calculated for $C_{16}H_{28}N_2O$ 264.2202, found 264.2210. [Diastereoisomer 2]: Colorless solid; m.p. 30–35 ºC; $[\alpha]_D^{20}$ = +10.5 (*c* 2.9, CH_2Cl_2); t_r 15.44; R_f 0.29 (hexane/EtOAc 2:1); ν(KBr) 3800–3024 (OH); δ_H (400 MHz, $CDCl_3$): 0.82–0.91, 1.07, 1.14, 1.26, 1.33–1.34, 1.46–1.49, 1.68, 1.81–1.84, 1.91–1.94 [1H, 10H, 2H, 1H, 3H, 1H, 3H, 1H and 1H, 9m, 5×CH_2 y CH, CH_3CH and C$(CH_3)_3$], 2.58 (1H, br s, OH), 4.00–4.07 (1H, m, C*H*CH_3), 4,37 (1H, s, C*H*OH), 6.87, 7.02 (1H and 1H, 2s, NCHCHN); δ_C (100 MHz, $CDCl_3$): 20.7 (*C*H_3CH), 26.0, 26.1, 26.1, 30.0, 30.4 (5×CH_2), 26.2 [3C, C(*C*$H_3)_3$], 36.5 [*C*$(CH_3)_3$], 43.7 (CH), 56.9 (*C*HCH_3), 73.6 (CHOH), 115.7, 127.5 (NCHCHN), 148.4 (NCN); *m/z* 264 (M^+, 4%), 208 (12), 207 (69), 99 (10), 97 (100), 69 (24), 55 (10). HRMS calculated for $C_{16}H_{28}N_2O$ 264.2202, found 264.2192.