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Isoprene-mediated lithiation of chiral *N*-alkylimidazoles

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Abstract- The isoprene-mediated lithiation of different chiral *N*-alkylimidazoles (**2a** and **2b**) and the following reaction with pivalaldehyde leads to the corresponding imidazolylpropanol derivatives **4** and **5** with excellent overall yield, but low de (up to 26%).

Introduction

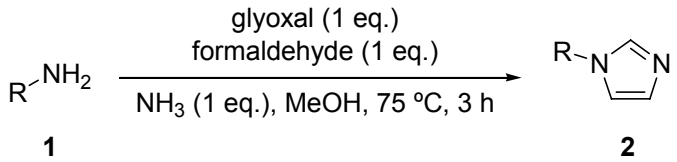
Imidazole derivatives are compounds of great importance due to their presence in biological active molecules.[1] One way of obtaining these compounds is by reaction of metallated imidazole intermediates, prepared by hydrogen-metal or halogen-metal exchange using lithium reagents or Grignard reagents, with an amply range of electrophilic reagents.[2]
Lithium metal is commonly used as lithiation agent, although due to its low reactivity under some reaction conditions it could need activation. This activation can be done by compounds acting as electron carriers, so the use of an arene in substoichiometric amount has shown to be a very efficient protocol for this procedure. Thus the arene-promoted lithiation of different substrates has been one of our topic research.[3] A variety of functionalised organolithium intermediates have been prepared, employing metal lithium as lithiating agent, by means of this methodology.[3-6] More recently, we have reported the use of a diene (i.e. isoprene) as a promoting lithiation agent, being employed for the generation of lithio-imidazole derivatives. After the good results obtained in the isoprene-mediated lithiation of different imidazole derivatives, such as *N*-methyl-,[7] *N*-phenyl-[8] and *N*-(diethoxymethyl)imidazole,[9] we thought of preparing organolithium derivatives of imidazoles bearing a nitrogen substituent with a esterogenic center in the C_α and studying their electrophilic substitution reaction with prochiral electrophiles.

Results and discussion

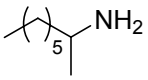
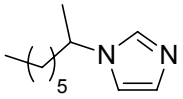
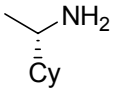
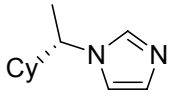
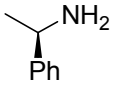
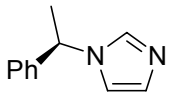
Compounds **2** were prepared by a heterocyclic ring formation starting from acyclic precursors. Thus, the corresponding amine **1**, ammonia (water solution), glyoxal and formaldehyde (water solution) were heated up at 75 ºC in methanol during 3 h (Table 1).

Keywords: Lithium; Isoprene-mediated lithiation; Imidazole; Chiral.

Table 1. Preparation of *N*-alkylimidazoles **2**.[a]



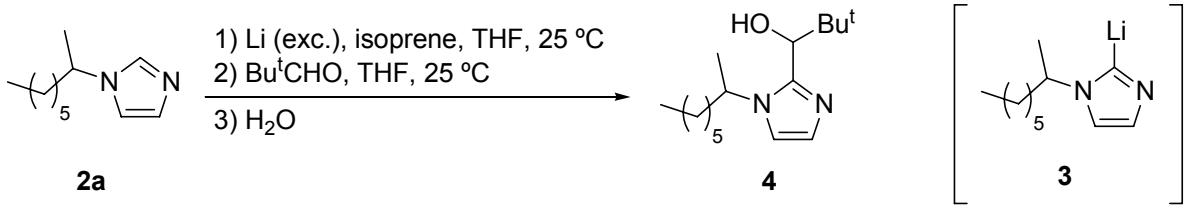
1 **2**

Entry	RNH_2	Product **2**[b]		
		no.	Structure	Yield (%)[c]
1		**2a**		75
2		**2b**		44
3[d]		**2c**		70

[a] Reaction performed using: RNH_2 (1 eq.), ammonia (aq. 25%, 1 eq.), glyoxal (1 eq.) and formaldehyde (aq. 36%, 1 eq.). [b] All products were obtained with >95% purity (CG and ^{1}H-NMR). [c] Yield of pure compound **2** after chromatography column (silica gel, hexane/EtOAc). [d] Cy = cyclohexyl.

The racemic 1-(1-methylheptyl)-1*H*-imidazole (**2a**) was treated with a slightly excess of lithium metal in the presences of isoprene at room temperature in order to generate the corresponding organolithium intermediate **3**, which was subsequently reacted with pivalaldehyde giving after quenching with water the corresponding product **4**. The product **4** was only detected in traces in the reaction mixture when 20 mol% of isoprene was used (Table 2, entry 1). Increasing the isoprene amount used during the lithiation step we detected an improvement in the yield of product **4** up to 94% when an excess of isoprene was employed (200 mol%) (Table 2). However, the observed diastereoselectivity for compound **4** was low (9%, CG–MS).

Table 2. Isoprene amount during the lithiation step.



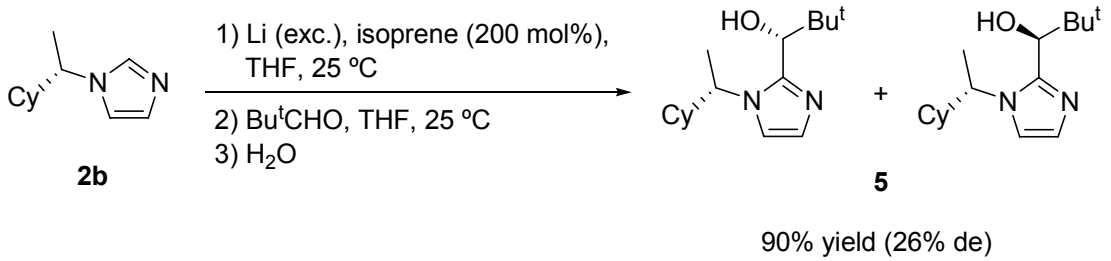
2a **4** **3**

Entry	Isoprene (mol%)[a]	Yield (%)[b,c]
1	20	traces
2	50	30
3	100	70
4	200	94

[a] Isoprene mol% refer to starting material **2a**. [b] All products were obtained with >95% purity (CG and ^{1}H-NMR). [c] Yield of pure compound **4** after chromatography column (silica gel, hexane/EtOAc).

The lithiation–S_E reaction was then performed following the same methodology using (1*S*)-1-cyclohexyl-1-(1*H*-1-imidazolyl)ethane (**2b**) and pivalaldehyde (as electrophile). The diastereomeric

mixture of compounds **5** was isolated with good overall yield (90%) (Scheme 1), but the diastereomeric excess obtained was just 26% (^{1}H-NMR).



Scheme 1. Lithiation and electrophilic substitution using imidazole **2b**.

Finally, we carried out the same reaction using the imidazole **2c** as starting material. The expected product was not obtained in this case due to the instability of the starting imidazole under the reaction conditions.[9] Thus, ethylbenzene was detected in the reaction crude, which resulted from cleavage of the group bonded to the nitrogen.

Conclusions

In conclusion, we have reported here that the lithium/isoprene methodology is applicable to successfully generate 2-lithio-*N*-alkylimidazole derivatives bearing chiral substituents. The reaction of that organolithium intermediates with a prochiral electrophile (i.e. pivalaldehyde) gave the corresponding functionalised imidazoles with excellent yield but with poor estereoselectivity (up to 26% de).

Experimental part

For general experimental information, see reference 7. All reagents used for the preparation of substrates **2** were commercially available (Acros, Aldrich) and were used without further purification. Lithium powder was commercially available (MEDALCHEMY S. L.).

*General procedure for preparation of imidazoles **2**.*

A solution of the corresponding amine (10 mmol) and ammonia (aq. solution 25%, 10 mmol, 0.75 mL) in MeOH (4 mL) and a solution of glyoxal (trimer dihydrate, 10 mmol, 0.70 g) and formaldehyde (aq. solution 36%, 10 mmol, 0.77 mL) in MeOH (4 mL) and water (4 mL) were slowly and simultaneously added ro 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 products **2** were purified by column chromatography (silica gel, mixtures of hexane and ethyl acetate).

1-(1-Methylheptyl)-1H-imidazole (**2a**): Yellow oil; t_r 12.13; R_f 0.10 (hexane/EtOAc 1:1); ν (film) 3105 (C=CH); δ_H (300 MHz, $CDCl_3$): 0.86 (3H, t, J = 6.7 Hz, CH_3CH$_2$), 1.12–1.24 [8H, m, (CH_2)$_4$CH$_3$], 1.46 (3H, d, J = 6.7 Hz, CH_3CH), 1.68–1.75 (2H, m, CH_2CH), 4.06–4.18 (1H, m, CHCH$_3$), 6.93, 7.06 (1H and 1H, 2s, NCHCHN), 7.50 (1H, s, NCHN); δ_C (75 MHz, $CDCl_3$): 14.2, 22.4 (2×CH$_3$), 22.7, 26.2, 29.0, 31.8, 38.0 (5×CH$_2$), 53.9 (*C*HCH$_3$), 116.6, 129.5 (NCHCHN), 136.0 (NCHN); *m/z* 181 (M^++1, 4%), 180 (27), 179 (11), 165 (39), 153 (50), 138 (13), 137 (30), 124 (11), 111 (11), 110 (23), 109 (14), 97 (15), 96 (100), 95 (69), 81 (16), 69 (63), 68 (31), 57 (13), 55 (14).

1-[(1S)-1-Cyclohexylethyl]-1H-imidazole (**2b**): Yellow oil; t_r 12.87; $[\alpha]_D^{20}$ = +28.5 (*c* 1.6, CH_2Cl_2); R_f 0.51 (EtOAc/MeOH 9:1); ν (film) 3108 (C=CH); δ_H (300 MHz, $CDCl_3$): 0.75–0.90, 0.93–1.02,

1.06–1.26, 1.32–1.36 (1H, 1H, 3H and 1H, 4m, 3×CH_2), 1.45 (3H, d, J = 7.0 Hz, CH_3), 1.50–1.55, 1.66–1.70, 1.75–1.80 (1H, 2H and 2H, 3m, 2×CH_2 and CH), 3.80–3.89 (1H, m, C*H*CH_3), 6.90, 7.05 (1H and 1H, 2s, NCHCHN), 7.46 (1H, s, NCHN); δ_C (75 MHz, $CDCl_3$): 18.7 (CH_3), 25.6, 25.7, 25.9, 29.2, 29.6 (5×CH_2), 44.2 (CH), 58.5 (*C*HCH_3), 116.9, 128.7 (NCHCHN), 136.1 (NCHN); *m/z* 179 (M^++1, 5%), 178 (38), 163 (26), 152 (11), 151 (99), 136 (16), 96 (84), 95 (100), 81 (26), 69 (66), 68 (20), 67 (14), 55 (29). HRMS calculated for $C_{11}H_{18}N_2$ 178.1470, found 178.1483.

1-[(1R)-1-Phenylethyl]-1H-imidazole (**2c**): Yellow oil; t_r 12.68; $[\alpha]_D^{20}$ = +5.0 (*c* 1.9, $CHCl_3$); R_f 0.32 (EtOAc); ν (film) 3109 (C=CH); δ_H (300 MHz, $CDCl_3$): 1.82 (3H, d, J = 7.0 Hz, CH_3), 5.32 (1H, q, J = 7.0 Hz, C*H*CH_3), 6.91, 7.06 (1H and 1H, 2s, NCHCHN), 7.11–7.14, 7.27–7.35 (2H and 3H, 2m, ArH), 7.57 (1H, s, NCHN); δ_C (75 MHz, $CDCl_3$): 21.7 (CH_3), 56.2 (*C*HCH_3), 117.6, 125.7, 127.7, 128.6, 129.0, 135.7 (8C, ArCH, NCHCHN and NCHN), 141.3 (ArC); *m/z* 173 (M^++1, 4%), 172 (28), 105 (100), 104 (15), 103 (12), 79 (12), 77 (16).

*Lithiation and reaction with pivalaldehyde of imidazoles **2**.*

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 45 min and then the pivalaldehyde (2.2 mmol, 0.250 mL) 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 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).

2,2-Dimethyl-1-[1-(1-methylheptyl)-1H-imidazol-2-yl]-propan-1-ol (**4**)

[Diastereoisomer 1]: Colorless solid; m.p. 69–71 ºC; t_r 14.11; R_f 0.26 (hexane/EtOAc 1:1); ν (film) 3701–3005 (OH); δ_H (300 MHz, $CDCl_3$): 0.85 (3H, t, J = 6.9 Hz, C*H*$_3$CH$_2$), 0.99 [9H, s, C(CH$_3$)$_3$], 1.22 [8H, m, (C*H*$_2$)$_4$CH$_3$], 1.44 (3H, d, J = 6.6 Hz, C*H*$_3$CH), 1.64–1.66 (2H, m, C*H*$_2$CH), 3.08 (1H, br s, OH), 4.17–4.29 (1H, m, CH), 4.37 (1H, s, C*H*OH), 6.89, 7.05 (1H and 1H, 2s, NCHCHN); δ_C (75 MHz, $CDCl_3$): 14.0, 21.5 (2×CH_3), 22.5, 25.9, 28.9, 31.5, 38.8 (5×CH_2), 25.7 [3C, C(*C*H$_3$)$_3$], 36.9 [*C*(CH$_3$)$_3$], 51.8 (CH), 73.4 (CHOH), 115.0, 127.7 (NCHCHN), 148.7 (NCN); *m/z* 267 (M^++1, 2%), 266 (4), 210 (13), 209 (82), 179 (15), 98 (10), 97 (100). HRMS calculated for $C_{16}H_{30}N_2O$ 266.2358, found 266.2338.

[Diastereoisomer 2]: Colorless solid; m.p. 79–81 ºC; t_r 14.19; R_f 0.20 (hexane/EtOAc 1:1); ν (film) 3706–2999 (OH); δ_H (300 MHz, $CDCl_3$): 0.88 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$), 1.02 [9H, s, C(CH$_3$)$_3$], 1.27–1.35 [11H, m, (C*H*$_2$)$_4$CH$_3$ and C*H*$_3$CH], 1.76–1.78 (2H, m, C*H*$_2$CH), 2.90 (1H, br s, OH), 4.22–4.33 (1H, m, CH), 4.38 (1H, s, C*H*OH), 6.89, 7.03 (1H and 1H, 2s, NCHCHN); δ_C (75 MHz, $CDCl_3$): 14.0, 22.8 (2×CH_3), 22.5, 26.5, 29.1, 31.5, 36.9 (5×CH_2), 25.9 [3C, C(*C*H$_3$)$_3$], 36.7 [*C*(CH$_3$)$_3$], 51.8 (CH), 73.5 (CHOH), 115.1, 127.6 (NCHCHN), 148.2 (NCN); *m/z* 267 (M^++1, 1%), 266 (3), 210 (10), 209 (64), 179 (15), 98 (10), 97 (100), 69 (10). HRMS calculated for $C_{16}H_{30}N_2O$ 266.2358, found 266.2348.

1-[1-(1-Cyclohexylethyl)-1H-imidazol-2-yl]-2,2-dimethylpropan-1-ol (**5**)

[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, C*H*$_3$CH 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$_3$CH), 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.

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References and notes

1. Grimmett, M. R. *Imidazole and Benzimidazole Synthesis*; Academic Press: London, 1997.
2. (a) Iddon, B. *Heterocycles* **1985**, *23*, 417-443; (b) Iddon, B.; Ngochindo, R. I. *Heterocycles* **1994**, *38*, 2487-2568; (c) Grimmett, M. R. *Sci. Synth.* **2002**, *12*, 325-528.
3. For reviews, see: (a) Yus, M. *Chem. Soc. Rev.* **1996**, *25*, 155-161; (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225-237; (c) Yus, M. *Synlett* **2001**, 1197-1205; (d) Yus, M.; Ramón, D. J. *Lat. J. Chem.* **2002**, 79-92; (e) Yus, M. In *The Chemistry of Organolithium Compounds;* Rappoport, Z.; Mareck, I. Eds.; J. Wiley & Sons: Chichester, 2004; Chapter 11.
4. For reviews in the preparation of organolithium starting from halogenated substrates, see: (a) Nájera, C.; Yus, M. *Trends Org. Chem.* **1991**, *2*, 155-181; (b) Najera, C.; Yus, M. *Org. Prep. Proced. Int.* **1995**, *27*, 383-456; (c) Nájera, C.; Yus, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 67-96; (d) Nájera, C.; Sansano, J. M.; Yus, M. *Tetrahedron* **2003**, *59*, 9255-9303; (e) Nájera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867-926; (f) Chinchilla, R.; Nájera, C.; Yus, M. *Tetrahedron* **2005**, *61*, 3139-3176.
5. For a review in the preparation of organolithium starting from non-halogenated substrates, see: Guijarro, D.; Yus, M. *Recent Res. Dev. Org. Chem.* **1998**, *2*, 713-744.
6. For reviews in the preparation of organolithium starting from heterocyclic substrates, see: (a) Yus, M.; Foubelo, F. *Rev. Heteroatom. Chem.* **1997**, *17*, 73-107; (b) Yus, M.; Foubelo, F. *Targets in Heterocyclic Systems* **2002**, *6*, 136-171; (c) Yus, M. *Pure Appl. Chem.* **2003**, *75*, 1453-1475.
7. Torregrosa, R.; Pastor, I. M.; Yus, M. *Tetrahedron* **2005**, *61*, 11148-11155.
8. Torregrosa, R.; Pastor, I. M.; Yus, M. *ARKIVOC* **2008**, in press.
9. Torregrosa, R.; Pastor, I. M.; Yus, M. *Tetrahedron* **2007**, *63*, 947-952.