

# Isoprene-promoted lithiation of 1-phenylimidazole

Rosario Torregrosa, Isidro M. Pastor, and Miguel Yus\*

*Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apartado 99, E-03080 Alicante, Spain*

*E-mail: [yus@ua.es](mailto:yus@ua.es)*

**This paper is dedicated to Professor Guy Quéguiner on the occasion of his 70<sup>th</sup> anniversary**

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## Abstract

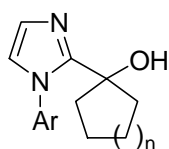
The reaction of 1-phenylimidazole (**1**) with an excess of lithium powder (1:3 molar ratio) and isoprene (1:2 molar ratio) in THF at room temperature leads to a solution of the corresponding 2-lithio-1-phenylimidazole intermediate (**2**), which by treatment with different carbonyl compounds [*t*-BuCHO, PhCHO, Et<sub>2</sub>CO, (CH<sub>2</sub>)<sub>5</sub>CO, (*c*-C<sub>3</sub>H<sub>5</sub>)<sub>2</sub>CO, Ph<sub>2</sub>CO] or benzylideneaniline and final hydrolysis with water yields the expected 2-functionalized 1-phenylimidazoles (**3**), with no products resulting from a possible *ortho*-lithiation at the aromatic ring.

**Keywords:** Isoprene-promoted lithiation, 2-substituted 1-phenylimidazoles, electrophilic substitution, deprotonation, 1-phenylimidazole

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## Introduction

In a recent paper<sup>1</sup> Erker *et al.* showed that 2-hydroxyalkyl-1-arylimidazoles of the type **I** are inhibitors of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) which are involved in cancer and pain development,<sup>2</sup> their activity being determined by the nature of the aryl substituent. On the other hand, porphyrins containing 2-imidazolylcarbinol moieties have been described<sup>3</sup> as being tripodal ligands as copper atom (Cu<sub>B</sub>) site mimics of cytochrome *c* oxidase (CcO), a terminal enzyme of the respiratory chains of mitochondria and aerobic bacteria.<sup>4</sup>

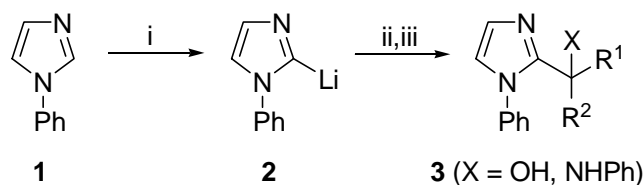


**I** (n = 1-3)

The normal way to prepare compounds of type **1** is the deprotonation of the *N*-substituted imidazoles at the most acidic 2-position using a strong base such as *n*-butyllithium in an ethereal solvent followed by condensation of the corresponding lithium intermediate with a carbonyl compound.<sup>5</sup> However, this old procedure gives variable yields depending on the structure of the electrophile,<sup>5</sup> and when carbonyl compounds are used the yields are moderate (< 40%).<sup>1</sup> One problem associated with the lithiation of the starting 1-substituted imidazoles arise when an aryl group is present as a substituent: in this case a competing lithiation at the *ortho* position of the aryl ring can also take place,<sup>6</sup> especially when an excess of the lithiating agent is used.<sup>5</sup> In the last few years we have been studying the arene-promoted lithiation of different substrates using a catalytic amount of the electron transfer agent.<sup>7</sup> This methodology allowed us to prepare very reactive functionalized organolithium intermediates<sup>8</sup> (mainly by chlorine–lithium exchange<sup>9</sup> but also by using non-halogenated materials<sup>10</sup> or by reductive ring opening of different heterocycles<sup>11</sup>), or polyolithiated synthons,<sup>12</sup> or to activate other transition metals<sup>13</sup> generating the corresponding nanoparticles.<sup>14</sup> Recently, we have found that not only arenes can be used as electron carriers, but that dienes such as isoprene are also effective agents in facilitating the transfer of one electron from the metal to the substrate.<sup>15</sup> In this paper we describe the application of this last methodology (an isoprene-promoted lithiation) to the regioselective lithiation of 1-phenylimidazole at the 2- position, and subsequent reaction with carbonyl compounds or their imine derivatives, so avoiding a possible *ortho*-lithiation in the phenyl ring.

## Results and Discussion

The reaction of commercially available 1-phenylimidazole (**1**) with an excess of lithium powder (1: 3 molar ratio) and isoprene (1: 2 molar ratio) in THF at room temperature led after one hour to a solution of the corresponding 2-lithio-1-phenylimidazole (**2**), which was then treated with 3-pentanone (1: 1.1 molar ratio) to yield, after hydrolysis with water, the expected 1-phenyl-2-substituted imidazole **3c** with 87% isolated yield (Scheme 1 and Table 1, entry 4). The above-described conditions were the optimal ones, since the use of a lower amount of isoprene resulted in lower yields (Table 1).



**Scheme 1.** (i) Li (1:3 molar ratio), isoprene (1:2 molar ratio), THF, RT, 1h; (ii) Electrophile (1:1.1 molar ratio) [*t*-BuCHO, PhCHO, Et<sub>2</sub>CO, (CH<sub>2</sub>)<sub>5</sub>CO, (*c*-C<sub>3</sub>H<sub>5</sub>)<sub>2</sub>CO, Ph<sub>2</sub>CO or PhN=CHPh]; (iii) H<sub>2</sub>O.

**Table 1.** Influence of the amount of isoprene in the preparation of compound **3c**

Entry	Isoprene (equiv.) <sup>a</sup>	Yield. (%) <sup>b</sup>
1	0.2	43
2	0.5	56
3	1	67
4	2	87

<sup>a</sup> Isoprene/1-phenylimidazole molar ratio. <sup>b</sup> Isolated yield of pure compound **3c** (>95% by GLC and/or 300 MHz <sup>1</sup>H NMR) after column chromatography (silica gel, hexane/ethyl acetate).

Once the best conditions were established, the reaction with other electrophiles was studied [*t*-BuCHO, PhCHO, (CH<sub>2</sub>)<sub>5</sub>CO, (*c*-C<sub>3</sub>H<sub>5</sub>)<sub>2</sub>CO, Ph<sub>2</sub>CO or PhN=CHPh; 1:1.1 molar ratio], so the expected compounds **3** were isolated following the same protocol (Scheme 1 and Table 2). In no case were products resulting from an *ortho*-lithiation at the phenyl ring detected. As Table 2 shows, the reaction worked well for aldehydes and ketones (R<sup>1</sup>R<sup>2</sup>CO; Table 2, entries 1–6), as well as for one imine, benzylideneaniline (Table 2, entry 7).

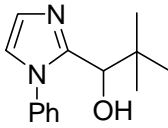
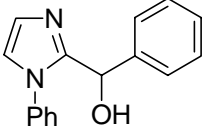
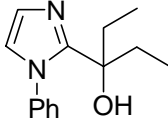
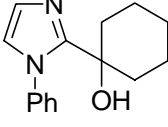
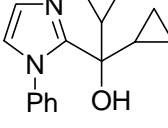
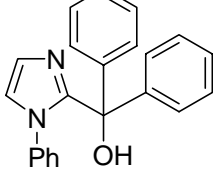
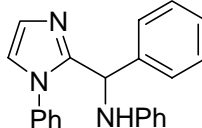
In conclusion, we describe here a new lithiation methodology that permits the generation of 2-lithio-1-phenylimidazole without any contamination of the possible 1-(1-imidazolyl)-2-lithiobenzene resulting from an *ortho*-lithiation at the phenyl group. The reaction of this intermediate with different carbonyl compounds or benzylideneaniline affords 2-functionalized 1-phenylimidazoles, compounds which shown interesting biological activities.

## Experimental Section

**General Procedures.** All lithiation reactions were carried out under argon atmosphere in oven-dried glassware. All commercially available reagents (Acros, Aldrich, Fluka) were used without further purification, except for liquid electrophiles, which were used freshly distilled. Commercially available anhydrous THF (99.9%, water content ≤0.006%, Fluka) was used as solvent in all the lithiation reactions. Melting points were obtained with a MPA100 Optimelt SRS apparatus. IR spectra were measured with a Nicolet Impact 400 D-FT Spectrometer. NMR spectra were recorded on a Bruker Avance 300 and Bruker Avance 400 (300 and 400 MHz for <sup>1</sup>H NMR, and 75 and 100 MHz for <sup>13</sup>C NMR) using, except otherwise stated, CDCl<sub>3</sub> as solvent and TMS as internal standard; chemical shifts are given in δ (ppm) and coupling constants (*J*) in Hz. Mass spectra (EI) were obtained at 70 eV on an Agilent 5973 spectrometer, fragment ions in *m/z* with relative intensities (%) in parentheses, and High Resolution Mass Spectra (HRMS) analyses were carried out on a Finnigan MAT95S spectrometer, when indicated the samples were inserted in the Direct Insertion Probe (DIP) mode. The purity of volatile materials and the chromatographic analyses (GLC) were determined with an Agilent 6890N instrument equipped with a flame ionization detector and a 30 m capillary column (0.25 mm diameter, 0.25 μm film

thickness), using nitrogen (2 mL/min) as carrier gas,  $T_{\text{injector}} = 275\text{ }^{\circ}\text{C}$ ,  $T_{\text{column}} = 60\text{ }^{\circ}\text{C}$  (3 min) and 60–270  $^{\circ}\text{C}$  (15  $^{\circ}\text{C}/\text{min}$ ); retention times ( $t_r$ ) are given in minutes under these conditions. Thin layer chromatography was carried out on TLC plastic sheets with silica gel 60 F<sub>254</sub> (Merck). Lithium powder was commercially available (Medalchemistry S. L.).

**Table 2.** Preparation of compounds **3**

Entry	Electrophile	Product <b>3</b> <sup>a</sup>		
		No.	Structure	Yield (%) <sup>b</sup>
1	<i>t</i> -BuCHO	<b>3a</b>		67
2	PhCHO	<b>3b</b>		68
3	Et <sub>2</sub> CO	<b>3c</b>		87
4	(CH <sub>2</sub> ) <sub>5</sub> CO	<b>3d</b>		64
5	( <i>c</i> -C <sub>3</sub> H <sub>5</sub> ) <sub>2</sub> CO	<b>3e</b>		89
6	Ph <sub>2</sub> CO	<b>3f</b>		78
7	PhCHNPh	<b>3g</b>		66

<sup>a</sup> All products **3** were >95% pure (GLC and/or 300 MHz <sup>1</sup>H NMR). <sup>b</sup> Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material (**1**).

**Preparation of compounds 3. General procedure.** To a green suspension of lithium powder (21 mg, 3 mmol) and isoprene (200  $\mu$ L, 2 mmol) in THF (3 mL) was added dropwise 1-phenylimidazole (**1**) (130  $\mu$ L, 1 mmol) at RT. After 1h of stirring the corresponding electrophile (1.1 mmol) was added and the resulting mixture was stirred for 45 min further. The mixture was hydrolyzed with water (5 mL) and extracted with ethyl acetate (3 $\times$ 10 mL). The organic layers were dried over MgSO<sub>4</sub> and evaporated under vacuum to give a residue, which was purified by column chromatography and/or recrystallization to yield the title compounds **3**. Yields are included in Table 2; physical, analytical and spectroscopic data follow.

**2,2-Dimethyl-1-(1-phenyl-1H-imidazol-2-yl)propan-1-ol (3a).** Colorless solid; mp 93–95 °C;  $t_r$  14.71;  $R_f$  0.22 (hexane/EtOAc, 1:1);  $\nu$ (KBr) 3700–3020  $\text{cm}^{-1}$  (OH);  $\delta_H$  (300 MHz, CDCl<sub>3</sub>): 0.83 [9H, s, C(CH<sub>3</sub>)<sub>3</sub>], 3.39 (1H, br s, OH), 4.37 (1H, s, CHOH), 6.99, 7.13 (1H and 1H, 2s, NCHCHN), 7.31–7.33, 7.43–7.51 (2H and 3H, 2m, ArH);  $\delta_C$  (75 MHz, CDCl<sub>3</sub>): 25.6 [3C, C(CH<sub>3</sub>)<sub>3</sub>], 36.9 [C(CH<sub>3</sub>)<sub>3</sub>], 72.8 (CHOH), 121.0, 126.4, 127.6, 128.5, 129.5 (7C, ArCH and NCHCHN), 137.6 (ArC), 148.9 (NCN).  $m/z$  230 ( $M^+$ , 3%), 174 (25), 173 (100), 145 (12). HRMS:  $M^+$ , found 230.1401, C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O requires 230.1401.

**Phenyl-(1-phenyl-1H-imidazol-2-yl)methanol (3b).** Yellow oil;  $R_f$  0.13 (hexane/EtOAc, 1:1);  $\nu$ (film) 3675–2968  $\text{cm}^{-1}$  (OH);  $\delta_H$  (400 MHz, CDCl<sub>3</sub>): 4.72 (1H, br s, OH), 5.71 (1H, s, CHOH), 7.00, 7.10–7.14, 7.19–7.21, 7.33–7.38 (1H, 5H, 3H and 3H, respectively, s and 3m, respectively, NCHCHN and ArH);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>): 68.8 (CHOH), 121.8, 126.2, 126.9, 127.6, 127.7, 128.3, 128.6, 129.3 (12C, ArCH and NCHCHN), 137.0, 141.3 (ArC), 149.3 (NCN).  $m/z$  (DIP) 252 ( $M^{+2}$ , 2%), 251 (16), 250 (100), 249 (71), 233 (18), 232 (13), 231 (24), 173 (45), 167 (35), 157 (23), 145 (20), 144 (16), 117 (30), 105 (11), 90 (11), 79 (12), 77 (42), 51 (11). HRMS (DIP):  $M^+$ , found 250.1142, C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O requires 250.1106.

**3-(1-Phenyl-1H-imidazol-2-yl)pentan-3-ol (3c).** Colorless solid; mp 91–93 °C;  $t_r$  13.70;  $R_f$  0.32 (hexane/EtOAc 1:1);  $\nu$ (KBr) 3638–3013  $\text{cm}^{-1}$  (OH).  $\delta_H$  (300 MHz, CDCl<sub>3</sub>): 0.75 (6H, t,  $J = 7.3$  Hz, 2 $\times$ CH<sub>3</sub>), 1.40–1.67 (4H, m, 2 $\times$ CH<sub>2</sub>), 4.37 (1H, br s, OH), 6.94, 7.03 (1H and 1H, 2s, NCHCHN), 7.29–7.32, 7.43–7.50 (2H and 3H, 2m, ArH).  $\delta_C$  (75 MHz, CDCl<sub>3</sub>): 7.9 (2C, 2 $\times$ CH<sub>3</sub>), 33.4 (2C, 2 $\times$ CH<sub>2</sub>), 75.8 (COH), 124.2, 125.6, 127.2, 129.0, 129.3 (7C, ArCH and NCHCHN), 138.5 (ArC), 151.3 (NCN).  $m/z$  230 ( $M^+$ , 0.5%), 202 (15), 201 (100), 197 (11), 145 (52), 117 (10), 77 (10). HRMS:  $M^+$ , found 230.1382, C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O requires 230.1419.

**1-(1-Phenyl-1H-imidazol-2-yl)cyclohexanol (3d).** Colorless solid; mp 114–116 °C;  $t_r$  15.31;  $R_f$  0.19 (hexane/EtOAc 1:1);  $\nu$ (KBr) 3735–3000  $\text{cm}^{-1}$  (OH).  $\delta_H$  (300 MHz, CDCl<sub>3</sub>): 1.06–1.23, 1.43–1.88 (1H and 9H, 2m, 5 $\times$ CH<sub>2</sub>), 2.66 (1H, br s, OH), 6.91, 7.03 (1H and 1H, 2s, NCHCHN), 7.37–7.48 (5H, m, ArH).  $\delta_C$  (75 MHz, CDCl<sub>3</sub>): 21.8, 25.2, 37.4 (5C, 5 $\times$ CH<sub>2</sub>), 71.9 (COH), 124.0, 126.1, 127.7, 128.9, 129.0 (7C, ArCH and NCHCHN), 139.4 (ArC), 152.8 (NCN);  $m/z$  243 ( $M^+ + 1$ , 4%), 242 (22), 225 (14), 224 (15), 223 (19), 213 (18), 200 (27), 199 (100), 195 (11), 187 (27), 185 (25), 172 (13), 171 (52), 158 (34), 157 (19), 145 (34), 144 (13), 117 (23), 91 (13), 90 (10), 77 (21). HRMS:  $M^+$ , found 242.1435, C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O requires 242.1419.

**Dicyclopropyl-(1-phenyl-1*H*-imidazol-2-yl)methanol (3e).** Colorless solid; mp 128–130 °C;  $R_f$  0.44 (hexane/EtOAc 1:1);  $\nu$ (KBr) 3685–3042  $\text{cm}^{-1}$  (OH).  $\delta_H$  (400 MHz,  $\text{CDCl}_3$ ): 0.10–0.26, 0.31–0.37, 0.50–0.56, 0.79–0.86 (4H, 2H, 2H and 2H, 4m, 4 $\times$ CH<sub>2</sub> and 2 $\times$ CH cyclopropyl ring), 4.09 (1H, br s, OH), 6.94, 6.98 (1H and 1H, 2s, NCHCHN), 7.40–7.48 (5H, m, ArH).  $\delta_C$  (75 MHz,  $\text{CDCl}_3$ ): -0.3, 1.6 (4C, 4 $\times$ CH<sub>2</sub>), 19.5 (2C, 2 $\times$ CH cyclopropyl ring), 70.0 (COH), 124.2, 125.1, 128.1, 128.8, 129.2 (7C, ArCH and NCHCHN), 138.8 (ArC), 154.4 (NCN);  $m/z$  (DIP) 254 ( $M^+$ , 3%), 225 (10), 218 (17), 214 (15), 213 (100), 211 (15), 197 (19), 185 (11), 171 (19), 157 (10), 145 (38), 144 (17), 117 (15), 77 (14), 70 (13), 69 (20), 57 (10), 44 (15), 41 (14). HRMS (DIP):  $M^+$ , found 254.1438,  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$  requires 254.1419.

**Diphenyl-(1-phenyl-1*H*-imidazol-2-yl)methanol (3f).** Colorless oil;  $R_f$  0.42 (hexane/EtOAc, 1:1);  $\nu$ (film) 3625–2840  $\text{cm}^{-1}$  (OH);  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ): 4.24 (1H, s, OH), 6.77–6.80, 6.95–6.96, 7.05–7.22 (2H, 1H and 14H, respectively, 3m, NCHCHN and ArH);  $\delta_C$  (75 MHz,  $\text{CDCl}_3$ ): 79.0 (COH), 124.2, 126.4, 127.2, 127.5, 127.7, 127.9, 128.2, 128.5 (17C, ArCH and NCHCHN), 138.3, 144.6 (3C, ArC), 151.4 (NCN).  $m/z$  (DIP) 328 ( $M^+$ +2, 3%), 327 (22), 326 (100), 325 (46), 307 (11), 250 (10), 249 (56), 182 (10), 144 (11), 105 (46), 77 (37). HRMS (DIP):  $M^+$ , found 326.1440,  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}$  requires 326.1419.

***N*-[Phenyl(1-phenyl-1*H*-imidazol-2-yl)methyl]aniline (3g).** White solid; mp 169–171 °C;  $R_f$  0.35 (hexane/EtOAc, 1:1);  $\nu$ (KBr) 3353  $\text{cm}^{-1}$  (NH).  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ): 5.19 (1H, br d,  $J = 7.6$  Hz, CHNH), 5.56 (1H, d,  $J = 7.6$  Hz, CHNH), 6.51, 6.65, 6.99, 7.07, 7.14, 7.43–7.49 (2H, 1H, 1H, 2H, 8H and 3H, 6m, NCHCHN and ArH).  $\delta_C$  (100 MHz,  $\text{CDCl}_3$ ): 54.2 (CHNH), 113.4, 117.7, 121.3, 126.4, 127.3, 127.5, 128.3, 128.5, 128.9, 129.0, 129.5 (17C, ArCH and NCHCHN), 137.2, 140.4, 146.3, 148.3 (ArC and NCN);  $m/z$  (DIP) 326 ( $M^+$ +1, 3%), 325 (11), 234 (18), 233 (100). HRMS (DIP):  $M^+$ , found 325.1585,  $\text{C}_{22}\text{H}_{19}\text{N}_3$  requires 325.1579.

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