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Addition of lithioimidazoles to isocyanates followed by Pd-coupling: access to 4-substituted imidazole-2,5-dicarboxamides

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Abstract—Facile access to 4-substituted *N*-butyl 2,5-dicarboxamides is achieved via direct lithiation of *N*-butyl imidazole and subsequent quenching with isocyanates followed by Pd-catalyzed coupling reactions.

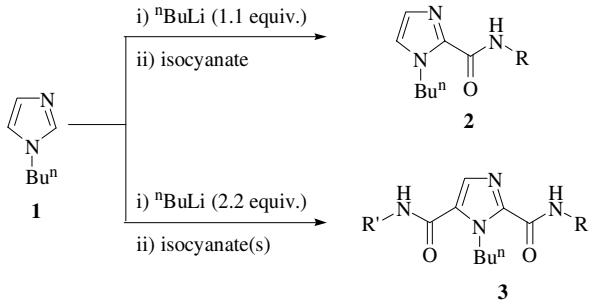
Substituted imidazoles are important structural components of a variety of biologically active compounds. They possess anti-hypertensive, anti-inflammatory, anti-microbial, anti-oxidant, anti-tumor, cardiotonic, fungicidal, immunosuppressive, insecticidal, and other activities.[1] In light of this broad spectrum of biological properties, substituted imidazoles continue to draw the attention of synthetic organic and medicinal chemists. Among the various functionalized imidazoles, carboxamide derivatives comprise a class of quite useful compounds and form the structural components of HIV-1 protease inhibitors and antibiotics.[2] Incredibly, however, there are few reports in the literature for the synthesis of imidazole carboxamides. The known methods include conversion of imidazole carboxylic acids to the corresponding carboxamides[3] and direct addition of isocyanates to imidazoles at elevated temperatures or in the presence of iridium catalyst.[4]

Both methods suffer from harsh reaction conditions and low yields of the products. As part of our ongoing infectious disease program, we have developed a new one-pot method for the preparation of imidazole 2-carboxamides or 2,5-dicarboxamides.

A brief literature survey revealed limited success in the direct lithiation of *N*-alkyl imidazoles.[5] The primary method for adding electrophiles to imidazoles involves metal–halogen exchange on the corresponding haloimidazoles, facilitated by coordination of the metal counter ion with a suitable nitrogen protecting group.[6]

In this paper we describe the synthesis of imidazole 2-carboxamides and 2,5-dicarboxamides through the direct lithiation of readily available *N*-butyl imidazole and subsequent quenching with various isocyanates (Scheme 1).

The various imidazole carboxamides that were prepared are listed in Table 1. In the first instance, *N*-butyl imidazole **1** was treated with 1.1 equiv of *n*-BuLi, which led to the formation of 2-lithioimidazole. Upon treatment with phenyl (**A**), benzyl (**B**), or *tert*-butyl (**C**) isocyanates, the corresponding 2-carboxamides **2a**, **2b**, and **2c** were obtained in 72%, 64%, and 74% yields, respectively. Furthermore, treatment of *N*-butyl imidazole with 2.2 equiv of *n*-BuLi followed by the addition of 2.2 equiv of isocyanates (**A**, **B**, or **C**) yielded the



Scheme 1. Isocyanate(s): R = R′ = Ph, Bn, ^{t}Bu, (**A**) PhNCO; (**B**) BnNCO; (**C**) ^{t}BuNCO.

Keywords: Isocyanates; Lithiation; Imidazoles; Palladium coupling.
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Table 1. Reaction of isocyanates with lithioimidazoles

Entry	Isocyanate (ratio)[a]	R	R′	Product	Yield (%)[b]
1	**A** (1.1)	Ph	—	**2a**	72
2	**B** (1.1)	Bn	—	**2b**	64
3	**C** (1.1)	^{t}Bu	—	**2c**	74
4	**A** (2.2)	Ph	Ph	**3a**	62
5	**B** (2.2)	Bn	Bn	**3b**	56
6	**C** (2.2)	^{t}Bu	^{t}Bu	**3c**	63
7	**A** (1.1) + **B** (1.1)	Ph	Bn	**3d** (**2a**)	53 (14)
8	**B** (1.1) + **A** (1.1)	Bn	Ph	**3e** (**2b**)	43 (12)
9	**A** (1.1) + **C** (1.1)	Ph	^{t}Bu	**3f** (**2a**)	64 (8)
10	**C** (1.1) + **A** (1.1)	^{t}Bu	Ph	**3g** (**2c**)	61 (10)
11	**B** (1.1) + **C** (1.1)	Bn	^{t}Bu	**3h** (**2b**)	45 (15)
12	**C** (1.1) + **B** (1.1)	^{t}Bu	Bn	**3i** (**2c**)	51 (10)

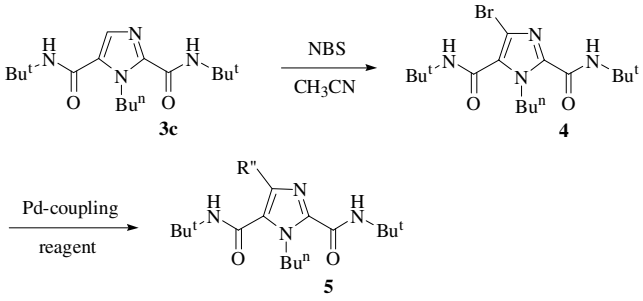
[a] Isocyanate: substrate.
[b] Isolated yields.

corresponding symmetrical 2,5-dicarboxamides **3a**, **3b**, **3c**, respectively.

Having successfully completed the synthesis of the 2-carboxamides and symmetrical 2,5-dicarboxamides, we turned our attention to developing a one-pot method for the preparation of unsymmetrical 2,5-dicarboxamides. Our initial attempts involved treating *N*-butyl imidazole with 2.2 equiv of *n*-BuLi to form the corresponding 2,5-dilithioimidazole, followed by the addition of 1.1 equiv of an isocyanate and then 1.1 equiv of a second isocyanate after stirring for 1 h. Unfortunately, this method led to the formation of a complex mixture of products. Thus, we conceived the following procedure for the preparation of unsymmetrical 2,5-dicarboxamides. Initially, *N*-butyl imidazole was treated with 1.1 equiv of BuLi, to lithiate at the C-2 position, followed by addition of an appropriate isocyanate (1 equiv). After stirring at −30 °C for 45 min, an additional 1.1 equiv of *n*-BuLi was added to lithiate at the C-5 position. Addition of a second isocyanate (1 equiv) gave the corresponding 2,5-dicarboxamide in good to moderate yields along with 8–15% of the 2-carboxamide. Using this method, a variety of unsymmetrical 2,5-dicarboxamides were prepared with three isocyanates (**A**, **B**, and **C**) in various combinations to give products **3d**–**i** (Table 1, entries 7–12).[13]

Our efforts to further lithiate at the fourth position proved unsuccessful, however. Hence a different method was adopted to functionalize at the fourth position of imidazole using Pd-catalyzed cross-couplings,[7] which has proven to be a powerful reaction for mild and highly efficient carbon–carbon bond formation in organic synthesis.[8]

In order to demonstrate the feasibility of Pd-catalyzed coupling we have chosen compound **3c** as a model dicarboxamide. Compound **3c** was treated with *N*-bromosuccinimide (NBS) to give bromoimidazole **4**, which was subjected to Heck, Stille, Suzuki, and Sonagashira coupling conditions to give the corresponding 4-substituted imidazole dicarboxamides[13] (Scheme 2). The results are summarized in Table 2. In the first case, bromoimidazole **4** was treated with methyl acrylate under Heck coupling reaction conditions ($Pd(OAc)_2$, Ph_3P, Et_3N, DMF, 60 °C),[9] to give the coupled product **5a** in 85% yield (Table 2, entry1). Similarly, 4-methoxy styrene gave the corresponding coupled product **5b** in 43% yield. Interestingly, the reaction of **4** with allyl and 2-furoyl tributyl tin compounds under Stille coupling conditions[10] gave the 4-allyl and 4-(2-furoyl)-imidazole 2,5-dicarboxamides **5c** and **5d** in 65% and 76% yields, respectively (Table 2, entry 3 and 4). Suzuki coupling[11] of **4** with 4-formyl and 3-formyl boronic acids gave the corresponding coupled products **5e** and **5f** (Table 2, entries 5 and 6,). Sonagashira coupling[12] of **4** with 5-(*N*,*N*-dimethyl)-1-pentyne and 1-hexyne was also successful, although the yields were somewhat lower (Table 2, entries 7 and 8).

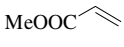
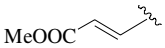
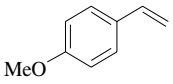
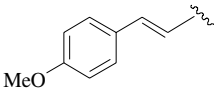
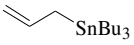
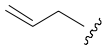
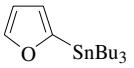
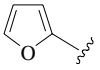
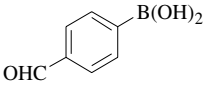
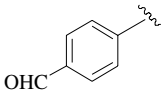
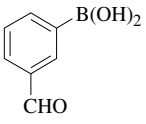
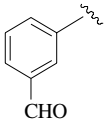
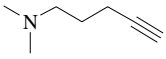
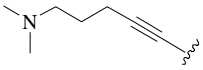
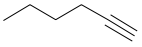
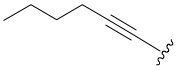


Scheme 2.

In summary, we have successfully developed a new strategy for the synthesis of both symmetrical as well as unsymmetrical 2,5-dicarboxamides and their subsequent conversion to 4-substituted derivatives using Pd-catalyzed coupling reactions.

Typical experimental procedure for the preparation of unsymmetrical 2,5-dicarboxamides: To a stirred solution of *N*-butyl imidazole **1** (0.5 g, 4.03 mmol) in dry THF (35 mL) at −30 °C was added *N*-butyl lithium (1.77 mL of 2.5 M solution in hexanes, 4.43 mmol). After stirring for 30 min phenyl isocyanate (0.44 mL, 4.03 mmol) in THF (2 mL) was added, and the resulting mixture was stirred at the same temperature. After 45 min, an additional equivalent of *N*-butyl lithium (1.77 mL of 2.5 M solution in hexanes, 4.43 mmol) was added. After stirring for 30 min, *tert*-butyl isocyanate (0.46 mL, 4.03 mmol) in

Table 2. Pd-couplings of 4-bromo *N*-butyl-2,5-di-*tert*-butylcarboxamide (**4**)

Entry	Reagent	Conditions	R″	Product	Yield (%)
1		**A**		**5a**	85
2		**A**		**5b**	43
3		**B**		**5c**	65
4		**B**		**5d**	76
5		**C**		**5e**	63
6		**C**		**5f**	73
7		**D**		**5g**	46
8		**D**		**5h**	37

A = $Pd(OAc)_2$, Ph_3P, Et_3N, DMF, 60 °C, 1.5 h; **B** = $Pd(PPh_3)_4$, Et_3N, DMF, 60 °C, 6 h; **C** = $Pd(PPh_3)_4$, aq Na_2CO_3, toluene, EtOH, 80 °C, 6 h; **D** = $Pd(PPh_3)_4$, Et_3N, 60 °C, 6 h.

THF (2 mL) was added at −30 °C, and the mixture was stirred for an additional 2 h. After completion of the reaction, the reaction mixture was quenched with saturated aq NH_4Cl (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography, eluting with 4:1 hexanes/EtOAc to give the imidazole 2,5-dicarboxamide **3f** (0.88 g, 64% yield).

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References and notes

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13. Spectral data for selected compounds: (**3f**): ^{1}H NMR ($CDCl_3$, 400 MHz): 9.40 (br s, 1H), 7.68 (d, 2H, $J = 7.8$ Hz) 7.38 (t, 2H, $J = 7.8$ Hz); 7.3 (s, 1H); 7.16 (t, 1H, $J = 7.8$ Hz), 5.85 (br s, 1H); 4.93 (t, 2H, $J = 7.5$ Hz); 1.81 (m, 2H); 1.49 (s, 9H); 1.4 (m, 2H); 0.96 (t, 3H, $J = 7.3$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 159.5, 156.4, 140.6, 137.4, 131.0, 129.0 (3C), 124.4, 119.8 (2C), 52.0, 46.3, 38.8, 28.8, 19.8, 13.8. HRMS (ESI): calcd for $C_{19}H_{26}N_4O_2$: 343.2134 $[M+H]^+$, found: 343.2147. (**4**): ^{1}H NMR ($CDCl_3$, 300 MHz): 7.13 (br s, 1H); 6.13 (br s, 1H); 4.72 (t, 2H, $J = 7.32$ Hz); 1.60 (m, 2H); 1.34 (s, 9H); 1.32 (s, 9H); 1.20 (m, 2H); 0.80 (t, 3H, $J = 7.29$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): 158.4, 157.3, 140.7, 127.8, 115.0, 52.6, 51.9, 47.0, 33.9, 29.0 (6C), 20.0, 14.0. HRMS (ESI): calcd for $C_{17}H_{29}BrN_4O_2$: 401.1474 $[M+H]^+$, found: 401.1468. (**5a**): ^{1}H NMR ($CDCl_3$, 300 MHz): 7.50 (d, 1H, $J = 15.4$ Hz); 7.28 (br s, 1H); 6.55 (d, 1H, $J = 15.4$ Hz); 6.20 (br s, 1H); 4.53 (t, 2H, $J = 7.25$ Hz); 3.60 (s, 3H); 1.63 (m, 2H); 1.41 (s, 9H); 1.37 (s, 9H); 1.26 (m, 2H); 0.83 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): 167.1, 159.1, 157.5, 140.4, 134.1, 133.7, 131.9, 118.5, 52.4, 51.3, 51.3, 46.0, 33.4, 28.5, 19.6, 13.5. HRMS (ESI): calcd for $C_{21}H_{34}N_4O_4$: 407.2652 $[M+H]^+$, found: 407.2654. (**5g**): ^{1}H NMR ($CDCl_3$, 300 MHz): 7.23 (br s, 1H); 6.8 (br s, 1H); 4.91 (t, 2H, $J = 7.35$ Hz); 2.51 (t, 2H, $J = 7.32$ Hz); 2.37 (t, 2H, $J = 7.12$ Hz); 2.21 (s, 6H); 1.78 (m, 2H); 1.69 (m, 2H); 1.43 (s, 9H); 1.40 (s, 9H); 1.32 (m, 2H); 0.89 (t, 3H, $J = 7.33$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): 158.9, 157.9, 141.2, 131.2, 123.6, 96.2, 68.7, 59.0, 52.1, 52.0, 47.0, 45.8, 34.1, 29.2 (3C), 29.1 (3C), 27.0, 20.0, 17.8, 14.1. HRMS (ESI): calcd for $C_{24}H_{41}N_5O_2$: 432.3260 $[M+H]^+$, found: 432.3264.