Synthesis and Chemistry of 4,5-Dimagnesioimidazole Dianions

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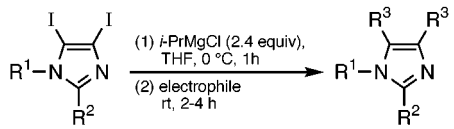
Abstract: An experimentally convenient procedure for the generation of 4,5-dimagnesioimidazoles is described. N-Protected 2-substituted 4,5-diiodoimidazoles were treated with *i*-PrMgCl (2.4 equiv) in THF at 0−5 °C. The resulting vicinal dianions reacted with electrophiles to give 4,5-disubstituted imidazoles in 27−71% yields.

The generation of imidazolyl carbanions, either by metal−halogen exchange or by direct metalation, followed by their reaction with electrophiles provides a powerful method for the synthesis of functionalized imidazoles.[1] For example, fungicidally active cyanoimidazoles,[2] the antitumor agent carmethizole,[3] the α_2-adrenergic agonist medetomidine,[4] and the histamine H_3 antagonist thioperamide[5] have all been efficiently prepared using imidazolyl anion chemistry. Most synthetic examples have utilized imidazolyl monoanions, but dianions are also known. Thus, the synthesis and reactions of 1,2-,[6] 1,4-,[5,7] 2,4-,[8] and 2,5-dilithioimidazoles[8−10] have been reported. The preparation of a 2,4,5-trilithioimidazole has also been described.[10] In this paper, as part of our continuing interest in imidazolyl anion chemistry,[11] we describe a facile procedure for the synthesis of 4,5-dimagnesioimdiazoles by treatment of 4,5-diiodoimidazoles with *i*-PrMgCl (2.4 equiv) in THF at 0−5 °C. To the best of our knowledge, such vicinal 4,5-dianions of imidazole have not been previously described.

The starting materials **1**−**6** for the current work were synthesized by adapting standard methodology as follows. Commercially available 2-phenyl- and 2-methylimidazole were diiodinated with I_2/KI/NaOH,[11] and the resulting 4,5-diiodides were deprotonated with NaH in DMF[11] and treated with MeI or $EtOCH_2Cl$ to give compounds **1**, **4**, and **6**. Triiodoimidazole[12] was similarly N-protected to give 1-methyl- and 1-ethoxymethyl-2,4,5-triiodoimidazole. A regioselective palladium-catalyzed coupling of 1-methyltriiodoimidazole with 4-chlorophenylboronic acid[13] then yielded the 2-aryl-4,5-diiodide **2**. Finally, treatment of the two N-protected triiodoimidazoles with *n*-Buli to effect metal halogen exchange at the 2-position,[3] followed by addition of either dimethyl disulfide or hexachloroethane, afforded diiodides **3** and **5**.



7-14

1, R^1 = Me, R^2 = Ph
2, R^1 = Me, R^2 = 4-ClC_6H_4
3, R^1 = Me, R^2 = SMe
4, R^1 = CH_2OEt, R^2 = Ph
5, R^1 = CH_2OEt, R^2 = Cl
6, R^1 = CH_2OEt, R^2 = Me

Treatment of the 4,5-diiodoimidazoles **1**−**6** with *i*-PrMgCl (2.4 equiv) in dry THF at 0−5 °C led to formation of the 4,5-dimagnesio species, which reacted with electrophiles to give products **7**−**14** in 27−71% yield as summarized in Table 1.[14] The yield of dianion-derived product isolated at the end of the reaction was dependent upon the nature of the imidazole 2-substituent and on the quenching electrophile. The best results were obtained when the imidazole 2-position was blocked by a stable nonreactive moiety and when reactive electrophiles were employed. Accordingly, when the dianions generated from the 2-arylimidazoles **1**, **2**, and **4** were quenched with benzaldehyde or water, products **7**, **9**, **10**, and **12** were isolated in good yields (59−71%; Table 1, entries 1, 3, 4, and 6). In contrast, the imidazoles **5** and **6**, which contain the more reactive 2-chloro and 2-methyl substituents, gave lower yields of the bis-carbinols **13** and **14** with benzaldehyde (43 and 27%, respectively; Table 1, entries 7 and 8). In the latter case, the 5-monoanion-derived product **15** was also isolated in 22% yield. Under similar conditions, the analogous 2-unsubstituted imidazole, 1-ethoxymethyl-4,5-diiodoimidazole, also yielded a monoanion derived product **16** (40% yield) but in this case no dianion derived product was isolated.

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(14) The reaction also proceeds but in much lower yield with EtMgBr. For example, treatment of the diodide **2** with EtMgBr (2.4 equiv) followed by addition of benzaldehyde gave the 4,5-disubstituted product **9** (12% yield) together with the monocarbinol **20** (47% yield). The carbinol **20** was the only product isolated when PhMgBr (2.4 equiv) or *t*-BuMgCl (2.4 equiv) was employed (>85% yield). Similarly, treatment of 4,5-dibromoimidazoles with *i*-PrMgCl (2.4 equiv) gave only 5-monoanion-derived products (>80% yield). Treatment of 4,5-diiodoimidazoles with a single equivalent of *i*-PrMgCl or EtMgBr gives exclusively 5-monoanion-derived products (38−90%).[11]

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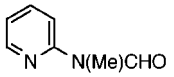
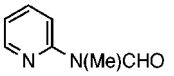
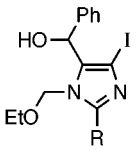
Table 1. Reaction of 4,5-Dimagnesioimidazoles with Electrophiles

entry no.	starting material	product	R^1	R^2	R^3	electrophile	isolated yield (%)
1	**1**	**7**	Me	Ph	CH(OH)Ph	PhCHO	71[a]
2	**1**	**8**	Me	Ph	CHO		30
3	**2**	**9**	Me	4-ClC_6H_4	CH(OH)Ph	PhCHO	64[a]
4	**2**	**10**	Me	4-ClC_6H_4	H	H_2O	61
5	**3**	**11**	Me	SMe	CHO		37
6	**4**	**12**	CH_2OEt	Ph	CH(OH)Ph	PhCHO	59[a]
7	**5**	**13**	CH_2OEt	Cl	CH(OH)Ph	PhCHO	43[a]
8	**6**	**14**	CH_2OEt	Me	CH(OH)Ph	PhCHO	27[a,b]

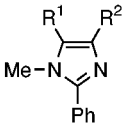
[a] Ca. 10:9 mixture of diastereoisomers. [b] Product **15** was also isolated (22%).

When *N*-methyl-*N*-(2-pyridyl)formamide was utilized as the quenching electrophile, the 4,5-dicarboxaldehyde products **8** and **11** were isolated in 30 and 37% yield, respectively (Table 1, entries 2 and 5). Although these yields are quite modest, the current methodology offers a very direct route for synthesizing these useful intermediates, which have been used to synthesize a variety of fused ring systems.[15] In addition, the 2-methylmercapto compound **11** is a precursor used in the synthesis of the antitumor agent carmethizole.[3]

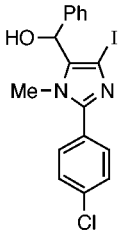
The bis-carbinols **7**, **9**, **12**, **13**, and **14** were all formed as ca. 10:9 mixtures of diastereoisomers (Table 1) indicating that the reaction between the dimagnesioanions and benzaldehyde was not diastereoselective. The question remained, however, as to whether the 4- and 5-anions might react with electrophiles at different rates in a regioselective manner. To answer this question, benzaldehyde (1.0 equiv) was added to a solution of the dianion derived from diiodide **1** at −78 °C. The reaction was then allowed to warm to ambient temperature and fully quenched with water to give products **7** (34%; 10:9 ratio of diastereoisomers), **17** (24%), **18** (10%), and **19** (17%). The regiochemistry of products **17** and **18** was established by measuring ^{1}H NMR NOE effects. Irradiation of the *N*-Me signal in the ^{1}H NMR spectra of **17** and **18** resulted in a positive NOE signal for the benzylic methine of **17** and for the imidazole C(5)H of **18**. Overall, the results do not indicate any synthetically useful differences in reactivity between the two carbanions.



15, R = Me
16, R = H



17, R^1 = CH(OH)Ph, R^2 = H
18, R^1 = H; R^2 = CH(OH)Ph
19, R^1 = R^2 = H



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Vicinal dilithiated derivatives of other heterocyclic systems have been prepared by treating the corresponding diiodo or dibromo heterocycles with *n*-Buli (2.0−2.5 equiv) at −95 to −50 °C.[16] In several cases, however, larger excesses of *t*-Buli (5−10 equiv) have been necessary to achieve dianion formation.[17] In our case, treatment of the diiodomidazole **2** with *n*-Buli (2 equiv) at −78 °C followed by addition of benzaldehyde did not yield any dianion-derived products. Instead, the iodo compound **20**, arising from 5-monoanion formation, was isolated in 76% yield. A reaction performed with *t*-Buli (4.4 equiv) at −78 °C, followed by addition of benzaldehyde at ambient temperature, did yield the desired 4,5-disubstituted product **9** but only in 15% yield (5:3 ratio of diastereoisomers). These conditions were experimentally less convenient than those using *i*-PrMgCl, so this result was not pursued further. However, it is interesting to note that 4,5-dimagnesioimidazoles appear to be more readily formed than the corresponding dilithio compounds. A possible explanation is that destabilizing electrostatic interactions in the transition state leading from the presumed 5-monomagnesio intermediate to the vicinal diamagnesio compound are reduced (in comparison to the dilithio species) due to the greater covalency of the C−Mg bond.

In summary, a general method has been developed for preparing 4,5-dimagnesioimidazoles by treating *N*-protected-2-substituted-4,5-diiodoimidazoles with *i*-PrMgCl (2.4 equiv) in THF for 1 h at 0−5 °C. These previously unknown vicinal dianions reacted with different electrophiles to yield 4,5-disubstituted imidazoles in 27−71% yield.

Experimental Section

Melting points are uncorrected. IR spectra were recorded on the pure substances using a Golden Gate detector. ^{1}H NMR spectra were recorded in solution at 300 MHz using TMS as internal reference. Dry column chromatography[18] was perfomed on prepacked "Isolute" silica gel cartridges purchased from IST. HPLC separations were performed on a LiChrosphor Si 60 column (50 × 250 mm). Experiments involving organometallic reagents were conducted in oven dried glassware using solvents dried over 0.4 nm molecular sieves prior to use. Other solvents and reagents were used as purchased.

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4,5-Bis(α-hydroxybenzyl)-1-methyl-2-phenylimidazole (7). A 2 M solution of *i*-PrMgCl in THF (1.46 mL, 2.92 mmol) was instilled into a cooled (0−5 °C; ice/water) solution of the diiodide **1** (500 mg, 1.22 mmol) in dry THF (20 mL) under an argon atmosphere over a period of ca. 10 min. The resulting solution was allowed to warm to rt and stirred for 1 h, and then neat benzaldehyde (0.30 mL, 2.95 mmol) was slowly added at such a rate that the internal temperature did not exceed 30 °C. After being stirred for a further 2 h, saturated aqueous NH_4Cl solution (0.3 mL) was added, and the mixture was diluted with CH_2Cl_2 (100 mL), dried over $MgSO_4$, and evaporated in vacuo at 40 °C. HPLC chromatography (4:1 EtOAc/heptane) yielded the two diastereoisomers of the title compound **7**:

Diastereoisomer A (154 mg, 0.42 mmol, 34%); mp 142−145 °C dec; IR ν_{max} 3400 (w), 3026 (w), 1602 (w), 1473 (m), 1449 (m), 1394 (m), 1024 (m), 696 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.3−3.4 (bs, 2H, exch. with D_2O), 3.32 (s, 3H), 5.85 (s, 1H), 6.07 (s, 1H), 7.13−7.53 (m, 15H); MS (EI) *m*/*z* 370 (M^+, 4), 352 (76), 275 (50), 247 (22), 77 (100). Anal. Calcd for $C_{24}H_{22}N_2O_2 \cdot 1.0H_2O$: C, 74.21; H, 6.23; N, 7.21. Found: C, 74.10; H, 6.33; N, 7.18.

Diastereoisomer B (168 mg, 0.45 mmol, 37%): mp 142−145 °C dec; IR ν_{max} 3600 (w), 3030 (w), 1601 (w), 1471 (m), 1450 (m), 1396 (m), 1023 (m), 696 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.28 (s, 3H), 5.99 (s, 1H), 6.06 (s, 1H), 7.13−7.51 (m, 15H); MS (EI) *m*/*z* 370 (M^+, 4), 352 (37), 275 (27), 247 (19), 77 (100). Anal. Calcd for $C_{24}H_{22}N_2O_2 \cdot 1.5H_2O$: C, 72.52; H, 6.34; N, 7.05. Found: C, 72.31; H, 6.05; N, 6.95.

All other dianion reactions were performed using essentially identical conditions (2.4 equiv of both *i*-PrMgCl and quenching agent, etc.) with the following exceptions. After addition of the electrophile *N*-methyl-*N*-(2-pyridyl)formamide, the reaction mixtures were stirred for 3.5 h before addition of aqueous NH_4Cl. Dry column chromatography[18] was used to purify the dicarboxaldehydes **8** and **11** (1:4 EtOAc/heptane) and product **10** (4:1 EtOAc/heptane).

1-Methyl-2-phenylimidazole-4,5-dicarboxaldehyde (8) (157 mg from 1.0 g of diiodide **1**, 0.73 mmol, 30%): IR υ_{max} 3056 (w), 2960 (w), 1695 (m), 1668 (m), 1470 (m), 1299 (m), 749 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.02 (s, 3H), 7.53−7.70 (m, 4H), 10.15 (s, 1H), 10.48 (s, 1H); MS (EI) *m*/*z* 214 (M^+, 12), 186 (58), 116 (33), 83 (100). Anal. Calcd for $C_{12}H_{10}N_2O_2 \cdot 0.1H_2O$: C, 66.72; H, 4.76; N, 12.97. Found: C, 66.78; H, 4.79; N, 12.76.

2-(4′-Chlorophenyl)-4,5-bis(α-hydroxybenzyl)-1-methylimidazole (9). Diastereoisomer A (132 mg from 500 mg of diiodide **2**, 0.33 mmol, 29%): mp 147−149 °C dec; IR ν_{max} 3460 (w), 3030 (w), 1603 (w), 1466 (m), 1092 (m), 722 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.31 (s, 3H), 3.35−4.0 (bs, 2H, exch. with D_2O), 5.83 (s, 1H), 6.07 (s, 1H), 7.11−7.47 (m, 14H); MS (EI) *m*/*z* 404 (M^+, 7), 386 (92), 309 (61), 105 (45), 77 (100). Anal. Calcd for $C_{24}H_{21}N_2O_2Cl \cdot 1.8H_2O$: C, 65.92; H, 5.67; N, 6.41. Found: C, 66.00; H, 5.36; N, 6.18.

Diastereoisomer B (158 mg from 500 mg of diiodide **2**, 0.395 mmol, 35%): mp 110−115 °C dec; IR ν_{max} 3350 (w), 3060 (w), 1601 (w), 1466 (m), 1092 (m), 697 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.80−3.40 (bs, 2H, exch. with D_2O), 3.27 (s, 3H), 5.97 (s, 1H), 6.08 (s, 1H), 7.07−7.49 (m, 14H); MS (EI) *m*/*z* 404 (M^+, 7), 386 (75), 309 (47), 105 (57), 77 (100). Anal. Calcd for $C_{24}H_{21}N_2O_2Cl \cdot 0.5H_2O$: C, 69.65; H, 5.36; N, 6.77. Found: C, 69,65; H, 5.48; N, 6.92.

(4′-Chlorophenyl)-1-methylimidazole (10) (132 mg from 500 mg of diiodide **2**, 0.69 mmol, 61%): IR ν_{max} 3106 (w), 2953 (w), 1602 (w), 1469 (s), 1092 (s), 1010 (s), 725 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (s, 3H),6,96 (s, 1H), 7.11 (s, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H); MS (EI) *m*/*z* 192 (M^+, 87), 191 (100), 157 (11), 156 (32). Anal. Calcd for $C_{10}H_9N_2Cl \cdot 0.4H_2O$: C, 60.10; H, 4.94; N, 14.02. Found: C, 60.58; H, 5.35; N, 13.52.

1-Methyl-2-methylmercaptoimidazole-4,5-dicarboxaldehyde (11) (260 mg from 1.47 g of diiodide **3**, 1.4 mmol, 37%): mp 100−103 °C; IR ν_{max} 3054 (w), 2987 (w), 1698 (m), 1672 (m), 1422 (w), 1262 (s), 749 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.77 (s. 3H), 3.87 (s, 3H), 10.06 (s, 1H), 10.28 (s, 1H); MS (EI) *m*/*z* 184 (M^+, 35), 156 (74), 141 (29), 109 (100), 83 (87). Anal. Calcd for $C_7H_8N_2SO_2$: C, 45.64; H, 4.38; N, 15.21. Found: C, 46.00; H, 4.48; N, 15.05.

1-Ethoxymethyl-4,5-bis(α-hydroxybenzyl)-2-phenylimidazole (12). Diastereoisomer A (144 mg from 500 mg of diiodide **4**, 0.35 mmol, 31%): mp 80−83 °C; IR ν_{max} 3650 (w), 3061 (w), 2976 (w), 1602 (w), 1492 (m), 1449 (m), 1378 (m), 1023 (m), 696 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (t, J = 8 Hz, 3H), 3.16−3.33 (m, 2H), 4.79 (d, J = 8 Hz, 1H), 5.05 (d, J = 8 Hz, 1H), 5.85 (s, 1H), 6.08 (s, 1H), 7.16−7.63 (m, 15H); MS (EI) *m*/*z* 414 (M^+, 4), 396 (17), 337 (55), 105 (72), 77 (100). Anal. Calcd for $C_{26}H_{26}N_2O_3 \cdot 0.5H_2O$: C, 73.74; H, 6.43; N, 6.61. Found: C, 73.91; H, 6.57; N, 6.47.

Diastereoisomer B (130 mg from 500 mg of diiodide **4**, 0.31 mmol, 28%): mp 70−73 °C; IR ν_{max} 3650 (w), 3061 (w), 2976 (w), 1602 (w), 1492 (m), 1449 (m), 1378 (m), 1023 (m), 696 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (t, J = 8 Hz, 3H), 3.16−3.27 (m, 2H), 4.75 (d, J = 8 Hz, 1H), 5.00 (d, J = 8 Hz, 1H), 5.99 (s, 1H), 6.15 (s, 1H), 7.20−7.59 (m, 15H); MS (EI) *m*/*z* 414 (M^+, 2), 396 (13), 337 (28), 105 (63), 77 (100). Anal. Calcd for $C_{26}H_{26}N_2O_3 \cdot 0.2H_2O$: C, 74.69; H, 6.36; N, 6.70. Found: C, 74.72; H, 6.49; N, 6.69.

2-Chloro-1-ethoxymethyl-4,5-bis(α-hydroxybenzyl)imidazole (13). Diastereoisomer A (79 mg from 400 mg of diiodide **5**, 0.27 mmol, 22%): IR ν_{max} 3350 (w), 3031 (w), 2980 (w), 1602 (w), 1491 (m), 1472 (m), 1174 (m), 1105 (s), 696 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (t, J = 8 Hz, 3H), 3.43 (m, 3H, 1H exch. with D_2O), 4.00 (bs, 1H, exch. with D_2O), 4.83 (d, J = 12 Hz, 1H), 5.08 (d, J = 12 Hz, 1H), 5.79 (s, 1H), 6.08 (s, 1H), 7.16−7.44 (m, 10H); MS (CI) *m*/*z* 373 ($M^+ + H$, 100), 355 (23). Anal. Calcd for $C_{20}H_{21}N_2O_3Cl \cdot 2.0H_2O$: C, 58.75; H, 6.16; N, 6.85. Found: C, 58.64; H, 5.86; N, 6.64.

Diastereoisomer B (73 mg from 400 mg of diiodide **5**, 0.24 mmol, 21%): IR ν_{max} 3350 (w), 3040 (w), 2980 (w), 1602 (w), 1493 (m), 1473 (m), 1174 (m), 1105 (s), 696 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 8 Hz, 3H), 3.28 (bs, 1H), 3.41 (m, 2H), 4.03 (bs, 1H), 4.80 (d, J = 12 Hz, 1H), 5.05 (d, J = 12 Hz, 1H), 5.88 (s, 1H), 6.13 (s, 1H), 7.27−7.47 (m, 10H); MS (CI) *m*/*z* 373 ($M^+ + H$, 100), 355 (25); HRMS (EI) calcd for $C_{20}H_{21}N_2O_3Cl$ 372.1241, found 372.1229.

1-Ethoxymethyl-4,5-bis(α-hydroxybenzyl)-2-methylimidazole (14). Diastereoisomer A (64 mg from 500 mg of diiodide **6**, 0.18 mmol, 14%): IR ν_{max} 3350 (w), 3060 (w), 2977 (w), 1586 (w), 1493 (m), 1449 (m), 1185 (m), 1097 (m), 697 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, J = 8 Hz, 3H), 2.27 (s, 3H), 3.15 (q, J = 8 Hz, 2H), 4.81 (bs, 2H), 4.97 (q, J = 12 Hz, 2H), 5.99 (s, 1H), 6.20 (s, 1H), 7.17−7.47 (m, 10H); MS (EI) *m*/*z* 352 (M^+, 2), 334 (10), 288 (20), 275 (13), 77 (77), 59 (100); HRMS (Auto CI) calcd for $C_{21}H_{24}N_2O_3$ 353.1865, found 353.1885.

Diastereoisomer B (59 mg from 500 mg of diiodide **6**, 0.17 mmol, 13%): IR ν_{max} 3350 (w), 3070 (w), 2970 (w), 1601 (w), 1493 (m), 1449 (m), 1185 (m), 1095 (m), 696 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (t, J = 8 Hz, 3H), 2.25 (s, 3H), 3.19 (m, 2H), 3.96 (bs, 2H), 4.88 (q, J = 8 Hz, 2H), 5.88 (s, 1H), 6.09 (s, 1H), 7.16−7.43 (m, 10H); MS (EI) *m*/*z* 352 (M^+, 11), 334 (13), 288 (75), 275 (100), 77 (83), 59 (73). Anal. Calcd for $C_{21}H_{24}N_2O_3 \cdot 2.5\ H_2O$: C, 63.46; H, 7.35; N, 7.05. Found: C, 63.59; H, 6.92; N, 7.18.

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Supporting Information Available: Copies of 300 MHz ^1H NMR spectra for compounds **7**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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