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Synthesis of Substituted Imidazo[1,5-*a*]pyrazines via Mono-, Di-, and Directed Remote Metalation Strategies

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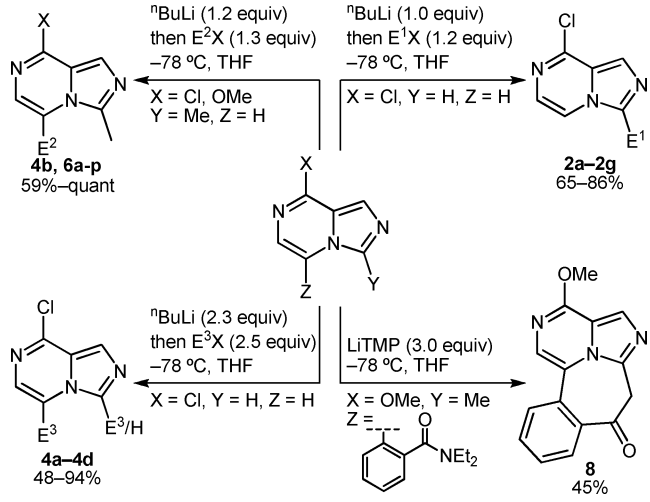
ABSTRACT



Imidazo[1,5-*a*]pyrazines 1 undergo regioselective C3-metalation and C5/C3-dimetalation to afford a range of functionalized derivatives 2a−2g (Table 1), and 4a−4d (Table 2). Under similar conditions, the C3-methyl derivatives 2a and 5 undergo surprising regioselective C5-deprotonation to afford, after electrophile quench, products 4b and 6a−6p (Table 3), results that are rationalized by quantum mechanical calculations. Benzamide 7b, obtained from such metalation chemistry followed by Suzuki cross coupling, undergoes directed remote metalation-cyclization to afford 8, representing the hitherto unknown triazadibenzo[*cd,f*]azulen-7(6*H*)-one tricyclic ring system.

We have recently reported[1] the first palladium catalyzed Heck-type direct substitution reaction on the π-deficient pyrazine ring of the imidazo[1,5-*a*]pyrazine framework (Figure 1A). The dearth of knowledge concerning metalation reactivity of this and related ring systems stimulated our interest to undertake a systematic study to contribute to the signficant area of carbanionic heteroaromatic chemistry.[2] Herein we report results which demonstrate (a) regioselective mono- as well as dimetalation of derivative **1** (Figure 1C) and (b) C5 metalation of the C3-methyl derivative (Figure 1B), both leading to new imidazo[1,5-*a*]pyrazine derivatives

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(1) Wang, J.-X.; McCubbin, J. A.; Jin, M.; Laufer, R. S.; Mao, Y.; Crew, A. P.; Mulvihill, M. J.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2923.

(2) Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187. Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489.

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which provide considerable potential for further manipulation of this heterocyclic ring system. In addition, we establish a new illustration of the directed remote metalation (DreM) concept[3] on the Suzuki-derived heterobiaryl **7** leading to the new heterocyclic 2,5,11c-triazadibenzo[*cd*,*f*]azulen-7(6*H*)-one framework **8**. These results constitute the first investigation of carbanionic chemistry on the imidazo[1,5-*a*]pyrazine ring system which is of current interest in the development of new antimicrobial, cardiovascular, and antitumor drugs[4] and which also portends broader significance for synthetic studies for this and related heterocyclic systems.

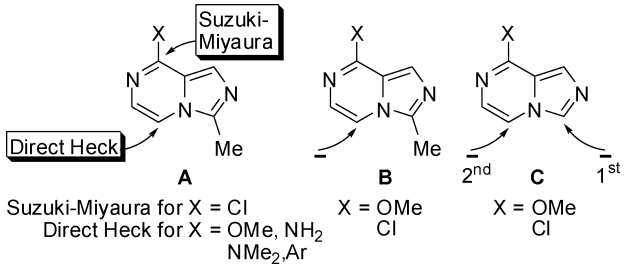


Figure 1. The direct Heck and Suzuki−Miyaura reaction sites (A) and observed metalation sites (B, C) for imidazo[1,5-*a*]pyrazines.

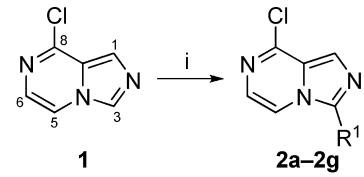
To initiate this study, the readily accessible[5] 8-chloroimidazo[1,5-*a*]pyrazine **1** was subjected to reaction with ^{n}BuLi (1 equiv) and quenched with various electrophiles to afford exclusively C3-substitution products **2a**−**2g** (Table 1). Reactions with carbon electrophiles at three oxidation states (entries 1−6) and iodine (entry 8) proceeded uneventfully whereas that with TMSCl failed, an observation which may be due to product instability, related to the known lability of the imidazole C2−Si bond.[6]

Efforts then turned to investigating the potential for dimetalation of this heterocyclic core and for the sequential introduction of various electrophiles. Compound **1** was treated with 2.3 equiv of ^{n}BuLi (optimal conditions) followed by quench with 2.5 equiv of several electrophiles to give C3/C5-disubstituted imidazopyrazines **4a**−**4d** in moderate to excellent yields (Table 2). The formation of product with high deuterium incorporation (entry 1) constitutes evidence for the intermediacy of the dilithiated species **3**.[7] Consistent with the observation of Table 1, entry 7, quench with 2.5 equiv of TMSCl gave only the C5-silylated product **4d** in moderate yield, presumably owing to the derived C3-TMS derivative instability. Nevertheless, this result remains of value since it potentially offers access to other C5 analogues, either directly through *ipso*-desilylation[8] or through Hiyama type cross-coupling chemistries via C5 siloxanes or fluorosilanes.[9]

In view of the selective C3 over C5 kinetic anion reactivity established by the results of Table 1, we tested the thereby expected greater nucleophilic reactivity at the C5 site of the dianion **3**.[10] Thus, treatment of **1** with 2 equiv of ^{n}BuLi[11] followed by 1 equiv of iodine or CD_3OD initially provided evidence of selectivity; however, subsequent results were inexplicably inconsistent giving ratios between 4:1 and 1:8 of C5:C3 products within the same batch of reactions, and despite close control of the various reaction variables.[12]

With the results of studies on compound **1** in hand, we turned our attention to the metalation of the equally accessible[5] 8-chloro-3-methylimidazo[1,5-*a*]pyrazine **2a**. In contrast to expectation,[13] treatment of **2a** with 1.1 equiv

Table 1. Synthesis of 3-Substituted 8-Chloroimidazo[1,5-*a*]pyrazines **2a**−**2g**



i. ^{n}BuLi (1.0 equiv), THF, −78 °C 15 min then EX (1.2 equiv), −78 °C to rt over 15 min

	EX	R^1	product (%)[a]
1	MeI	Me	**2a** (70)[b]
2	DMF	CHO	**2b** (72)
3	4-$MeOC_6H_4C(O)H$	4-$MeOC_6H_4CHOH$	**2c** (74)
4	Mesitaldehyde	MesCHOH	**2d** (83)
5	CO_2	CO_2Me	**2e** (86)[c]
6	$ClCONEt_2$	Et_2NCO	**2f** (65)
7	$ClSiMe_3$	H	n.r.[d]
8	I_2	I	**2g** (78%)

[a] Yield of isolated material. [b] Purified by supercritical fluid chromatography to remove bis-Me byproduct. [c] Isolated as the methyl ester due to purification difficulties. [d] No reaction as confirmed by ^{1}H NMR of the recovered material.

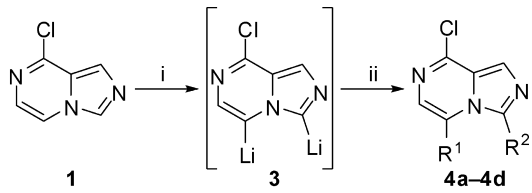
(3) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.

(4) Examples of such biological applications are: IGF-IR inhibitors, for example: (a) Mulvihill, M. J.; Ji, Q.-S.; Coate, H. R.; Cooke, A.; Dong, H.; Feng, L.; Foreman, K.; Rosenfeld-Franklin, M.; Honda, A.; Mak, G.; Mulvihill, K. M.; Nigro, A. I.; O'Connor, M.; Pirrit, C.; Steinig, A. G.; Siu, K.; Stolz, K. M.; Sun, Y.; Tavares, P. A. R.; Yao, Y.; Gibson, N. W. *Bioorg. Med. Chem.* **2008**, *16*, 1359. c-SRC inhibition and treatment of acute ischemic stroke: (b) Mukaiyama, H.; Nishimura, T.; Kobayashi, S.; Ozawa, T.; Kamada, N.; Komatsu, Y.; Kikuchi, S.; Oonota, H.; Kusama, H. *Bioorg. Med. Chem.* **2007**, *15*, 868. Corticotropin releasing hormone receptor ligands: (c) Hartz, R. A.; Gilligan, P. J.; Nanda, K. K.; Tebben, A. J.; Fitzgerald, L. W.; Miller, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 291.

(5) Initial syntheses of imidazo[1,5-*a*]pyrazines: (a) Abushanab, E.; Bindra, A. P.; Goodman, L.; Peterson, H., Jr. *J. Org. Chem.* **1973**, *38*, 2049. (b) Abushanab, E.; Bindra, A. P.; Lee, D. Y.; Goodman, L. *J. Heterocycl. Chem.* **1975**, *12*, 211. (c) Abushanab, E.; Bindra, A. P.; Goodman, L. *J. Heterocycl. Chem.* **1975**, *12*, 207. (d) Abushanab, E.; Bindra, A. P.; Lee, D. Y.; Goodman, L. *J. Org. Chem.* **1975**, *40*, 3373. (e) Abushanab, E.; Lee, D. Y.; Goodman, L. *J. Org. Chem.* **1975**, *40*, 3376. (f) Abushanab, E.; Lee, D. Y.; Goodman, L. *J. Org. Chem.* **1975**, *40*, 33792. Syntheses of more highly substituted imidazo[1,5-*a*]pyrazines: (g) Albert, A.; Ohta, K. *J. Chem. Soc. (C)* **1970**, *11*, 1540. (h) Davey, D. D. *J. Org. Chem.* **1987**, *52*, 4379. (I) Chattopadhyay, G.; Ray, S. *J. Chem. Res. Synop.* **1992**, *5*, 170. (j) Marchand, E.; Morel, G. *Tetrahedron Lett.* **1993**, *34*, 2319. (k) Trček, T.; Meden, A.; Verček, B. *Synlett* **2000**, *10*, 1458. (l) Eltsov, O. S.; Mokrushin, V. S.; Tkachev, A. V. *Russ. Chem. Bull., Int. Ed.* **2004**, *53*, 2293. (m) Trček, T.; Verček, B. *Synthesis* **2006**, *20*, 3437. (n) Mulvihill, K. M.; Castelhano, A. L. US Patent 2007/0129547 A1.

(6) The *N*-protected imidazole C2-TMS system is moderately unstable towards nucleophilic attack at silicon even when generated *in situ*, and its isolation can be highly problematic due to hydrolysis: Carpenter, A. J.; Chadwick, D. J. *Tetrahedron* **1986**, *42*, 2351.

Table 2. Synthesis of C3/C5 Disubstituted 8-Chloroimidazo[1,5-*a*]pyrazines **4a**−**4d**



1 **3** **4a–4d**

i. *n*-BuLi (2.3 equiv), THF, –78 °C, 15 min; ii. EX (2.5 equiv), THF, –78 °C to rt, 15 min.

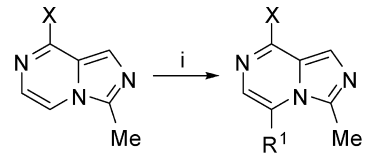
	EX	R^1	R^2	product (%)[a]
1	CD_3OD	D	D	**4a** (94)[b]
2	MeI	Me	Me	**4b** (82)
3	Cl_2	Cl	Cl	**4c** (62)
				4d (48)[c]
4	$ClSiMe_3$	$SiMe_3$	H	

[a] Yield of isolated material. [b] 86% deuterium incorporation as determined by integration of the appropriate signals in the ^{1}H NMR spectrum. [c] Average of two independent reactions.

of ^{n}BuLi and subsequent reaction with methyl iodide afforded the C5-methylated product **4b** in excellent yield (entry 1, Table 3). Similarly, and usually with greater efficacy than the reactions of compound **1** (Table 1), compound **2a** underwent reaction with other carbon (entries 2−7), silicon (entry 8), and halogen (entries 9−12) electrophiles to afford C5-substituted products **6a**−**6i** in good to excellent yields. To extend the scope of the reaction, the C8-methoxy derivative **5** was subjected to the same metalation/quenching conditions to provide similarly synthetically useful yields of products **6j**−**6p** (entries 13−20).

Quantum calculations on compound **2a** suggest that the approximate difference in pK_a values are in accord with the observation of C5 over C3-methyl deprotonation. Figure 2a shows the calculated partial charges on the carbons bound to the most acidic protons, with more electron richness on the carbons correlating with a lower absolute calculated pK_a. Use of perturbative methods has previously successfully predicted unexpected lithiation sites[14] and its application here confirms the predictions from the more approximate pK_a calculation. Figure 2b shows the calculated Fukui indices, with values closer to 1 indicating, in this case, a greater proclivity to undergo

Table 3. Synthesis of 5-Substituted 8-Chloro-3-methylimidazo[1,5-*a*]pyrazines **4b** and **6a**−**6p**



2a: X = Cl
5: X = OMe

4b, 6a–6p

i. *n*-BuLi (1.0 – 1.2 equiv), 15 min then EX (1.2 – 1.3 equiv), 15 min, THF –78 °C

	EX	X	R^1	product (%)[a]
1	MeI[b]	Cl	CH_3	**4b** (91)
2	DMF	Cl	CHO; Cl→NMe_2	**6a** (79)[c]
3	4-$O_2NC_6H_4CHO$	Cl	4-$O_2NOC_6H_4CHOH$	**6b** (83)
4	4-$MeOC_6H_4CHO$	Cl	4-$MeOC_6H_4CHOH$	**6c** (84)[d]
5	Mesitaldehyde	Cl	MesCHOH	**6d** (87)
6	CO_2	Cl	CO_2H	**6e** (quan)
7	$ClCONEt_2$	Cl	Et_2NCO	n.r.[e]
8	$ClSiMe_3$	Cl	$SiMe_3$	**6f** (81)
9	Cl_3CCCl_3	Cl	Cl	**6g** (98)
10	CBr_4	Cl	Br	**6h** (59)
11	Br_2	Cl	Br	**6h** (74)
12	I_2	Cl	I	**6i** (quan)
13	MeI	OMe	Me	**6j** (65)
14	DMF	OMe	CHO	**6k** (77)
15	4-$MeOC_6H_4CHO$	OMe	4-$MeOC_6H_4CHOH$	**6l** (76)[d]
16	Mesitaldehyde	OMe	MesCHOH	**6m** (62)
17	CO_2	OMe	CO_2Me[f]	**6n** (64)[f]
18	$ClCONEt_2$	OMe	Et_2NCO	n.r.[e]
19	$ClSiMe_3$	OMe	$SiMe_3$	**6o** (70)[d]
20	I_2	OMe	I	**6p** (79)

[a] Yield of isolated material. [b] Sequential addition of 2 portions of 1.2 equiv of MeI. [c] Isolated as the C-8 dimethylamino analogue due to unavoidable nucleophilic displacement of Cl by NMe_2. [d] Average of two independent reactions. [e] No reaction as confirmed by ^{1}H NMR of the recovered starting material. [f] Isolated as the methyl ester due to purification difficulties.

lithiation. Both calculations are in accord with the experimentally observed C5 lithiation of **2a**.[15]

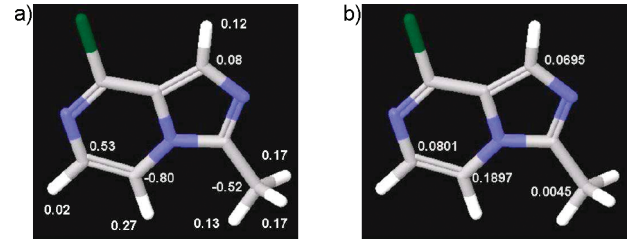
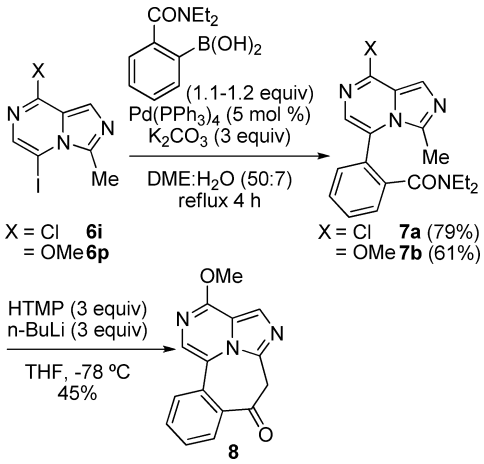


Figure 2. Key calculated properties for 8-chloro-3-methylimidazo[1,5-*a*]pyrazine **2a** at potential reactive sites. (a) Partial charges on the molecule. (b) Fukui indices for the LUMO of the molecule.

The knowledge that remote lateral metalation of vinylogously acidic 2′-methylbiaryl-2-amides to give phenanthrols may be achieved[3,16] suggested that compound **7** (Scheme

(7) For previous work on benzamide dianions, see: Mills, R. J.; Horvath, R. F.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 1145.
(8) Zhao, Z.; Jaworski, A.; Piel, I.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2617.
(9) Denmark, S. E.; Sweis, R. F. *Metal-Catalysed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, Chapter 4, p 163.
(10) For successful results of such an expectation in furan and thiophene amide directed *ortho* metalation derived dianions, see: Doadt, E. G.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 1149.
(11) An investigation of bases, ^{n}BuLi, KO^{t}Bu, MeMgBr, EtMgBr, and ^{i}PrMgBr:LiCl, showed that only the use of ^{n}BuLi led to the formation of the dianion. Interestingly, although normal Grignard reagents were insufficiently basic to form the dianion, application of ^{i}PrMgBr:LiCl led exclusively to the formation of the C3 monoanion, as established by I_2 quench experiment, even when excess base was used.

Scheme 1. Directed Remote Metalation-Cyclization Route to the Triazadibenzo[*cd*,*f*]azulen-7(6*H*)-one **8**



1) may provide similar reactivity at the enhanced acidic C3-methyl site to afford cyclized products. To this end, compound **7b**, readily prepared from compound **6p** via a Suzuki coupling with 2-(diethylcarbamoyl)phenylboronic acid,[17] was treated at −78 °C with preformed LiTMP (3 equiv) and was observed to undergo cyclization to give the triazadibenzo[*cd*,*f*]azulen-7(6*H*)-one **8** in modest yield.[18,19] The methylene ^{1}H NMR signal at δ = 4.48 ppm for compound **8** is clear evidence for the ketonic structure shown.

In conclusion, we have demonstrated useful and convenient metalation routes for the synthesis of C3- and C3/C5-derived 8-substituted imidazo[1,5-*a*]pyrazines **2a**−**2g**, **4a**−**4d**, and **6a**−**6p**. Such substitutions serve as functional handles for further derivatization of this privileged and biologically significant heterocyclic scaffold. Furthermore, adaption of the directed remote metalation (DreM) concept, as yet sparsely investigated within heterocyclic frameworks,[3] on the imidazo[1,5-*a*]pyrazine **7** has afforded the hitherto unknown triazadibenzo[*cd*,*f*]azulen-7(6*H*)-one **8**. The considerably extended scope of this imidazo[1,5-*a*]pyrazine metalation chemistry over that of the imidazo[1,2-*a*]pyrazine system,[20] together with the DFT calculations, provides new insight into the carbanionic reactivity of this less common heterocycle and may be of value for synthesizing heterocycles of greater complexity. Further investigations on the DreM chemistry leading to the new heterocyclic scaffold **8** are in progress.

Acknowledgment. We gratefully acknowledge OSI Pharmaceuticals, Inc. for a grant to V.S. in support of this work. Dr. Ruiyao Wang of Queen's University is warmly thanked for prompt solution of the X-ray crystal structure of compound **8** and for his enthusiastic interest.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See Supporting Information.

(13) Strong base deprotonation of *N*-protected-2-methylimidazole (Iddon, B.; Ngochindo, R. I. *Heterocycles* **1994**, *11,* 2487.) most 2-methyl-heteroaromatics, (e.g. 2-picoline with $NaNH_2$, see Kantlehner, W.; Kapassakalidis, J. J. *Synthesis* **1981**, *6*, 480. with LDA, see Bhasin, K. K.; Singh, J.; Singh, K. N. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 597. with ^{n}BuLi, see Andrews, I. P; Lewis, N. J.; McKillop, A.; Wells, A. S. *Heterocycles* **1996**, *43,* 1151.) usually occurs at the alkyl group.

(14) Ayers, P. W.; Anderson, J. S. M.; Bartolotti, L. J. *Int. J. Quantum Chem.* **2004**, *101*, 520.

(15) The general applicability of this approach to predict metalation sites is being actively explored.

(16) Fu, J.-M.; Snieckus, V. *Can. J. Chem.* **2000**, *78*, 905.

(17) Zhao, Z.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2523.

(18) The structure was confirmed by single crystal X-ray analysis, see Supporting Information.

(19) Under the same reaction conditions, the C8-Cl analogue **7a** gave only a chromatographically inseparable mixture (silica gel flash chromatography) of at least three compounds, presumably due to complications, in part, resulting from the greater reactivity of the C8-Cl over C8-OMe group.

(20) Generation of an imidazo[1,2-*a*]pyrazine dilithiated species, as evidenced by the formation of dideuterated product upon DCl quench, has been previously reported, see: Vitse, O.; Bompart, J.; Subra, G.; Viols, H.; Escale, R.; Chapat, J. P.; Bonnet, P. A. *Tetrahedron* **1998**, *54*, 6485.