Metalation and Halogen-metal Exchange in the Imidazo[1,2-*a*]quinoxaline Series

Stéphanie Parra, Olivier Vitse, Véronique Bénézech, Carine Deleuze-Masquéfa, Guy Subra, Jacques Bompart, Roger Escale, Jean P. Chapat and Pierre A. Bonnet*

EA 2414 Pharmacochimie & Biomolécules, Faculté de Pharmacie, 15, av. Charles Flahault, 34060 Montpellier Cedex, France

Received January 31, 2000

The *n*-butyllithium and lithium 2,2,6,6-tetramethylpiperidide metalation and the halogen-metal exchange of imidazo[1,2-*a*]quinoxaline derivatives followed by quenching with various electrophiles were studied. The reaction conditions have been optimized and various C_1 substituted imidazo[1,2-*a*]quinoxalines were obtained in high yields.

J. Heterocyclic Chem., **38**, 41 (2001).

The aromatic lithiation reaction is an efficient synthetic method for heterocycle substitution [1]. Recently, we reported on the lithiation and halogen-lithium exchange in the imidazo[1,2-*a*]pyrazine series, a bridgehead nitrogen aza-indolizine [2]. In continuation of this work, we investigate in the present paper the reactivity of diverse lithiating reagents, *n*-butyllithium (*n*-BuLi) and lithium 2,2,6,6-tetramethylpiperidide (LTMP), toward the imidazo[1,2-*a*]-quinoxaline heterocycle.

Imidazo[1,2-*a*]quinoxalines have attracted attention as analogues of the immunomodulating agent imiquimod [3]. Furthermore, imidazo[1,2-*a*]quinoxaline and imidazo-[1,2-*a*]pyrazine derivatives have been found to exhibit phosphodiesterase inhibitory properties and as such, smooth muscle relaxant activities [4].

In this work, we report on examples of lithiation and halogen-exchange reactions followed by quenching with various electrophiles in order to open new synthetic routes to new imidazo[1,2-*a*]quinoxalines.

Lithiation.

To our knowledge, there is no report on lithiation in the imidazo[1,2-*a*]quinoxaline series. It appeared interesting to determine the best conditions of reaction (lithiating reagent, temperature, electrophiles) to obtain in high yields derivatives in this series.

From results in the imidazo[1,2-*a*]pyrazine series [2], we can consider position 1 as the most prone to undergo the formation of lithio intermediates in the imidazo[1,2-*a*]-quinoxaline series.

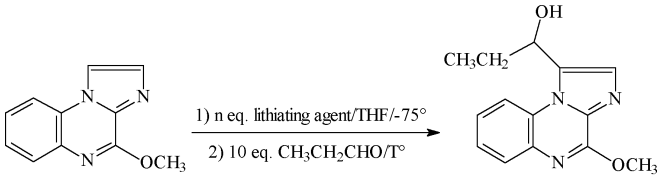
Alkyllithium species, which are strong bases, are also good nucleophiles. On imidazo[1,2-*a*]pyrimidine and imidazo[1,2-*a*]pyrazine, it was shown that phenyl lithium [5] and methyl lithium [6] led only to nucleophilic substitution rather than lithiation. However, the lithiation of imidazo[1,2-*a*]pyrazine substituted at position 8 by a directing group was performed in good conditions with the *n*-butyllithium as the lithiating reagent [2].

In our case, in order to avoid nucleophilic substitution on position 4 and to activate the aromatic ring, a methoxy group was introduced on position 4 of the heterocycle to get our starting product. Indeed no lithiation occured on the unsubsituted heterocycle and the methoxy group was necessary for reaction.

Lithium 2,2,6,6-tetramethylpiperidide is a less powerful base and less prone to undergo nucleophilic addition rather than alkyllithium. Moreover, opposite to *n*-butyllithium, lithium 2,2,6,6-tetramethylpiperidide afforded the lithio derivatives when applied to the unsubstituted imidazo-[1,2-*a*]pyrazine [2].

A first series of studies were performed on 4-methoxy-imidazo[1,2-*a*]quinoxaline **1** using *n*-butyllithium or lithium 2,2,6,6-tetramethylpiperidide as the metalating agents and with propionaldehyde as the electrophile (Scheme 1, Table 1).

Scheme 1



1 **2**

Table 1

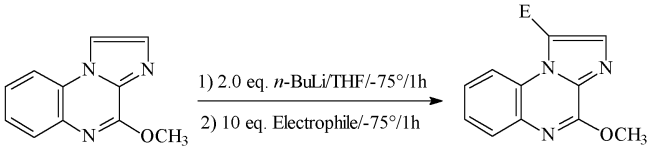
Lithiation of 4-Methoxyimidazo[1,2-*a*]quinoxaline **1** by two Metalating Agents

Lithiating Agent	Equivalents (n)	Reaction Temperature (T°)	Procedure	Yield (%)
n-BuLi	2.0	-75	A	93
n-BuLi	1.0	-75	B	29
n-BuLi	2.0	-35	C	83
LTMP	1.2	-75	D	19
LTMP	2.0	-75	E	27
LTMP	2.0	-35	F	no reaction
LTMP	4.0	-75	G	31 %

The reaction occurred at the C1 position exclusively regardless of the experimental conditions. It is clear that a strong metalating base (*n*-butyllithium) was needed to lithiate the imidazo[1,2-*a*]quinoxaline **1** in good yields. Lithium 2,2,6,6-tetramethylpiperidide provided poor yields even when used in large excess (Procedure G).

Furthermore, when the electrophile was added at higher temperature (-35°, Procedure F), no substitution occurred with complete recovery of **1**. Such result might be related to the thermodynamic control of the reaction according to the lithiating agent used. The best results were obtained with 2.0 equivalents of *n*-butyllithium at -75° (Procedure A). These experimental conditions were chosen for the further reaction of 4-methoxyimidazo[1,2-*a*]quinoxaline **1** with other electrophiles (Scheme 2, Table 2).

Scheme 2



1 **2-4**

Table 2

Lithiation of 4-Methoxyimidazo[1,2-*a*]quinoxaline **1** with Various Electrophiles

Electrophiles	E	Procedure	Yield
CH_3CH_2CHO	CH_3CH_2CHOH	A	93 % (**2**)
PhCHO	PhCHOH	A	50 % (**3**)
DMF	CHO	A	60 % (**4**)

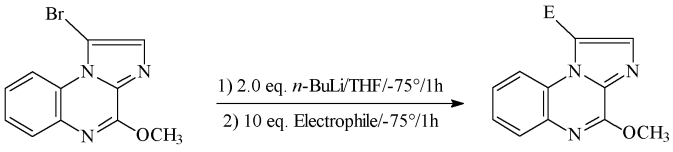
Phenylacetaldehyde, which produced a more sterically hindered electrophile than propionaldehyde, decreased the yield from 93% to 50%. Lower yields with dimethylformamide might be anticipated and related to its lower reactivity.

Halogen-Metal Exchange.

Halogen-metal exchange can be used to overcome the problem of weaker reactions of alkyle halides as electrophiles after lithiation. Moreover, the reaction specifically occurs at the halogenated carbon and might prevent nucleophilic attack [7]. However, this method requires the prior introduction of the halogen atom, *i.e.* bromine or iodine.

1-Bromo-4-methoxyimidazo[1,2-*a*]quinoxaline **5** was obtained in 90% yield *via* bromination of **1** by *N*-bromosuccinimide in dichloromethane according to the procedure described by Bradac *et al*. [8]. Halogen-metal exchange was then performed with **5** uisng *n*-butyllithium as the lithiating agent followed by quenching with two electrophiles (Scheme 3). Two equivalents of the lithiating agent were used for optimal reaction conditions.

Scheme 3



5

6, E = CH_3
2, E = $CH(OH)C_2H_5$

The bromine-lithium exchange reaction followed by trapping with an electrophile occurred in very good yields and gave access to a single derivative substituted at position 1. When methyl iodide was used as the electrophile, **6** was formed in 91% yield. Furthermore, the secondary alcohol **2** was obtained in 92% yield after quenching by propionaldehyde and acidic hydrolysis of the lithio intermediate.

Metalation and halogen-metal exchange allowed us to create new C-C bonds at the 1-position of the heterocycle after treatment of the lithio intermediates with electrophiles such as aldehydic or halogenated compounds. Such reactions might be used for the introduction of various alkyl or hydroxylated groups on the imidazo[1,2-*a*]-quinoxaline nucleus.

EXPERIMENTAL

All melting points, determined with a Büchi capillary apparatus, were uncorrected. Thin Layer Chromatography (TLC) was performed on silica gel SIL G/uv_{254} (Macherey-Nagel) plates and spots were visualised by uv (λ 254 nm). ^1H and ^{13}C nmr spectra were recorded on a Brucker AC 100 or AC 250 spectrometer in chloroform or deuteriodimethyl sulfoxide using tetramethyl silane as an internal standard. Electron impact mass spectrometry was realised on a LKB 2091 spectrometer. The ir spectra were recorded on a Perkin-Elmer 983 spectrophotometer. Column chromatography was performed using Matrex silica gel (200-400 mesh). Elemental analyses were performed by the Microanalytical Centre (Montpellier, France).

Tetrahydrofuran was distilled from benzophenone/sodium and used immediately. Commercial aldehydes were distilled before the reaction. The 1.6 *M* commercial solution of *n*-butyllithium in hexane was titrated according to the procedure of Watson *et al*. [9]. Lithium 2,2,6,6-tetramethylpiperidide (2.4 mmol) was prepared by reaction of 2,2,6,6-tetramethylpiperidide (0.42 ml, 2.48 mmol) in dry tetrahydrofurane (15 ml) and *n*-butyllithium (1.5 ml, 2.42 mmol) at -30° and then at 0° for 30 minutes. The 2,2,6,6-tetramethylpiperidide was distilled from calcium hydride and stored under a dry nitrogen atmosphere.

All reactions involving air-sensitive reagents were performed using syringe-septum cap techniques in oven dried glassware under dry nitrogen atmosphere.

General Procedure A for the Synthesis of **2**, **3**, **6**.

To a solution of 4-methoxyimidazo[1,2-*a*]quinoxaline (**1**) (0.4 g, 2 mmol) or 1-bromo-4-methoxyimidazo[1,2-*a*]quinoxaline (**5**) (0.55 g, 2 mmol) in dry tetrahydrofuran (16 ml), *n*-butyllithium (1.6 *M* in hexane, 2.5 ml, 4 mmol) was added slowly at -75° under a flow of dry nitrogen. The mixture was stirred for 1 hour at -75°. The electrophile was added in excess (10 equivalents) at -75° and the resulting solution was stirred at -75° for 1 hour before hydrolysis (-75°) by 15 ml of hydrochloric acid:ethanol: tetrahydrofuran (1:1:1, v/v/v). The solution was gently warmed to room temperature, basified with a saturated solution of sodium carbonate and extracted with dichloromethane. The organic layer was dried (sodium sulfate) and concentrated to yield a residue that was purified by column chromatography.

1-(1-Hydroxypropyl)-4-methoxyimidazo[1,2-*a*]quinoxaline (**2**).

General procedure A was applied to **1** or **5** and propionaldehyde (1.44 ml, 20 mmol) to obtain **2** in 93% or 92% yield, respectively.

Procedure B, the same method as procedure A but using *n*-butyllithium (1.6 *M* in hexane, 1.25 ml, 2 mmol), was applied to **1** and propionaldehyde (1.44 ml, 20 mmol) to obtain **2** in 29% yield.

Procedure C, the same method as procedure A but propionaldehyde (1.44 ml, 20 mmol) was added at -35°, was applied to **1** to obtain **2** in 83% yield.

Procedure D: A solution of 4-methoxyimidazo[1,2-*a*]quinoxaline (**1**) (0.4 g, 2 mmol) in dry tetrahydrofuran (15 ml) and the propionaldehyde (0.2 ml, 2.78 mmol) were added simultaneously with the cold (-75°) solution of lithium 2,2,6,6-tetramethylpiperidide (2.4 mmol) (*cf.* above). The mixture was stirred for 2 hours at -75° before hydrolysis (-75°) by 9 ml of hydrochloric acid:ethanol:tetrahydrofuran (1:1:1, v/v/v). The solution was gently warmed to room temperature, basified with a saturated solution of sodium carbonate and extracted by dichloromethane. The organic phase was dried (sodium sulfate) and evaporated to give **2** in 19% yield.

Procedure E: A solution of 4-methoxyimidazo[1,2-*a*]quinoxaline (**1**) (0.4 g, 2 mmol) in dry tetrahydrofuran (15 ml) was added slowly to the cold (-75°) solution of lithium 2,2,6,6-tetramethylpiperidide (4 mmol) (*cf.* above). The mixture was stirred for 6 minutes at -75° before addition of the propionaldehyde (1.44 ml, 20 mmol). Stirring was maintained for 30 minutes at -75° before hydrolysis (-75°) by 9 ml of hydrochloric acid:ethanol:tetrahydrofuran (1:1:1, v/v/v). The solution was gently warmed to room temperature, basified with a saturated solution of sodium carbonate and extracted by dichloromethane. The organic phase was dried (sodium sulfate) and evaporated to give **2** in 27% yield.

Procedure F, the same as procedure E but propionaldehyde was added at -35°, was applied to **1.** No reaction occurred with this procedure: after extraction, the starting material was recovered completely.

Procedure G, the same as procedure E but using lithium 2,2,6,6-tetramethylpiperidide (8 mmol), was applied to **1** and propionaldehyde (1.44 ml, 20 mmol) to obtain **2** in 31% yield.

Compound **2**: mp 167° (purified by column chromatography, eluent dichloromethane:methanol 99:1, v/v); R_f 0.24 (eluent dichloromethane:methanol 95:5, v/v); ^{1}H nmr (dimethyl sulfoxide-d_6) δ 8.63 (m, 1H, H_9), 7.88 (m, 1H, H_6), 7.73 (s, 1H, H_2), 7.61 (m, 2H, H_7 + H_8), 5.78 (d, J = 6.8 Hz, 1H, OH), 5.16 (q, 1H, CH), 4.20 (s, 3H, OCH_3), 2.09 (m, 2H, CH_2), 1.10 (t, J = 7, 1 Hz, 3H, CH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): 152.9 (C_4), 134.4, 131.4, 127.5, 126.9, 126.3, 125.6, 117.9, 65.7 (CH), 53.7 (OCH_3), 28.6 (CH_2), 10.8 (CH_3); ms (15eV): m/z 257 ($M^{+\cdot}$, 21%), 228 (-CH_2CH_3, 100%).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$ (257.29): C, 65.35; H, 5.88; N, 16.33. Found: C, 65.06; H, 5.81; N, 16.19.

1-(1-Hydroxy-2-phenylethyl)-4-methoxyimidazo[1,2-*a*]quinoxaline (**3**).

General procedure A was applied to 400 mg of **1** and phenylacetaldehyde (2.6 ml, 20 mmol) to obtain **3** in 50% yield; mp 202°; R_f 0.28 (eluent, dichloromethane:methanol 98:2, v/v); ^{1}H nmr (dimethyl sulfoxide-d_6) δ 8.52 (m, 1H, H_6), 7.74 (s, 1H, H_2), 7.50 (m, 2H, H_7 + H_8), 7.23 (m, 5H, H_{Ar}), 5.88 (d, J = 7.64 Hz, 1H, OH), 5.42 (q, J = 13.35 Hz, J = 7.5 Hz, 1H, CH), 4.09 (s, 3H, OCH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): 138.5, 133.9, 129.5, 128.1, 127.5, 126.9, 126.1, 117.9, 65.6 (CH), 53.7 (OCH_3); ms (15eV): m/z 319 ($M^{+\cdot}$, 2%), 228 (100%).

Anal. Calcd. for $C_{18}H_{15}N_3O_2$ (305.33): C, 70.81; H, 4.95; N, 13.76. Found: C, 70.90; H, 5.01; N, 13.89.

1-Formyl-4-methoxyimidazo[1,2-*a*]quinoxaline (**4**).

General procedure A was applied to 400 mg of **1** and freshly distilled dimethylformamide (1.5 ml, 20 mmol) to obtain **4** in 60% yield, mp 210° (purified by column chromatography, eluent dichloromethane:methanol 99:1, v/v); R_f 0.24 (eluent dichloromethane:ethyl acetate 90:10, v/v); ^{1}H nmr (deuteriochloroform) δ 9.98 (s, 1H, CHO), 9.39 (m, 1H, H_9) 8.38 (s, 1H, H_2), 7.87 (m, 1H, H_6), 7.58 (m, 2H, H_8 + H_7), 4.26 (s, 3H, OCH_3); ^{13}C nmr (deuteriochloroform): 176.9 (CHO), 149.9 (C_4), 128.5, 126.3, 119.8, 54.67 (OCH_3); ms (15eV): m/z 227 ($M^{+\cdot}$, 100%), 198 (-CHO, 62%).

Anal. Calcd. for $C_{12}H_9N_3O_2$ (227.22): C, 63.43; H, 3.99; N, 18.49. Found: C, 63.08; H, 4.12; N, 18.25.

1-Bromo-4-methoxyimidazo[1,2-*a*]quinoxaline (**5**).

A solution of **1** (0.5 g, 2.51 mmol) and *N*-bromosuccinimide (0.44 g, 2.47 mmol) in chloroform (25 ml) was refluxed for 2 hours. The solution obtained was cooled, treated with an aqueous solution of sodium carbonate 5%. The organic layer was dried with sodium sulfate, filtered and concentrated. The product obtained was recristallised in chloroform. Yield = 91%; mp 146°; ^{1}H nmr (deuteriochloroform) δ 9.04 (m, 1H, H_9), 7.81 (m, 1H, H_6), 7.75 (s, 1H, H_2), 7.50 (m, 2H, H_7 + H_8), 4.20 (s, 3H, OCH_3); ^{13}C nmr (deuteriochloroform): 152.29 (C_4), 135.31, 133.8, 128.3, 126.8, 124.9, 114.8, 99.0, 54.0 (OCH_3); ms (15eV): m/z 281 ($M^{+\cdot}$ + 4, 100%), 279 ($M^{+\cdot}$ + 2, 100%), 251 (-OMe + H, 58%), 249 (-OMe, 57%), 169 (-Br, -OMe + H, 77%).

Anal. Calcd. for $C_{11}H_8N_3OBr$ (278.11): C, 47.51; H, 2.90; N, 15.11. Found: C, 47.36; H, 3.11; N, 15.27.

1-Methyl-4-methoxyimidazo[1,2-*a*]quinoxaline (**6**).

General procedure A was applied to **5** and methyl iodide (2.8 ml, 20 mmol) to obtain **6** in 91% yield. R_f 0.58 (eluent dichloromethane:methanol 95:5, v/v); ^{1}H nmr (deuteriochloroform) δ 7.92 (m, $1H_{6/9}$), 7.65 (m, $1H_{9/6}$), 7.27 (m, 3H, H_7 + H_8 + H_2), 4.14 (s, 3H, OCH_3), 2.77 (s, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{11}N_3O$ (213.24): C, 67.59; H, 5.20; N, 19.71. Found: C, 67.67; H, 5.31; N, 20.03.

REFERENCES AND NOTES

[1a] G. Queguiner, F. Marsais, V. Snieckus, J. Epsztajn, *Advances in Heterocycic Chem.*, **52**, 187 (1991) and references cited therein; [b] N. Plé, A. Turck, A. Heynderickx, G. Queguiner, *J. Heterocyclic Chem.*, **34**, 551 (1997); [c] N. Plé, A. Turck, A. Heynderickx, G. Queguiner, *Tetrahedron*, **42**, 4899 (1998).

[2] O. Vitse, J. Bompart, G. Subra, H. Viols, R. Escale, J. P. Chapat, P.A. Bonnet, *Tetrahedron*, **54**, 6485 (1998).

[3a] Y. K. Sidky, E. C. Borden, C. E. Weeks, M. J. Reiter, J. F. Hatcher, J. T. Bryan, *Cancer Res.*, **52**, 3528 (1992); [b] K. Megyeri, W. C. Au, I. Rosztoczy, N. Babu, K. Raj, R. L. Miller, M. A. Tomai, P. M. Pitha, *Mol. Cell. Biol.*, **15**, 2207 (1995).

[4a] P. A. Bonnet, O. Vitse, V. Bénézech, G. Subra, J.R. Fabréguettes, L. Zanik, F. Laurent, A. Michel, J. Bompart, J. P. Chapat, *Ann. Pharm. Fr.*, **56**, 155 (1998); [b] P. A. Bonnet, J.

Bompart, O. Vitse, J. R. Fabréguettes, V. Bénézech, G. Subra, H. Viols, F. Laurent, A. Michel, R. Escale, J. P. Chapat, Actualités de Chimie Thérapeutique, Vol **24**, Elsevier ed, 1998, pp 49-60; [c] O. Vitse, F. Laurent, T. M. Pocock, V. Bénézech, Lahcen Zanik, K. R. F. Elliott, G. Subra, K. Portet, J. Bompart, J. P. Chapat, R. C. Small, A. Michel, P. A. Bonnet, *Bioorg. Med. Chem*., **7**, 1059 (1999).

[5] A. Gueiffier, H. Viols, C. Galtier, Y. Blache, O. Chavignon, J. C. Teulade, A. Aumelas, J. P. Chapat, *Heterocycles*, **38**, 551 (1994).

[6] A. Gueiffier, H. Viols, Y. Blache, O. Chavignon, J. C. Teulade, J. C. Debouzi, J. P. Chapat, *Heterocycl. Commun.*, **1**, 83 (1994).

[7] M. Amat, S. Hadidza, S. Sathyanarayana, J. Bosh, *J. Org. Chem.*, **59**, 10 (1994).

[8] J. Bradac, Z. Furek, D. Janezic, S. Molan, I. Smerkolj, M. Tisler, B. Vercek, *J. Org. Chem.*, **42**, 4197 (1977).

[9] S. C. Watson, J. F. Eastham, *J. Organometal. Chem*., **9**, 165 (1967).