Synthesis of 4-Substituted Imidazo[1,2-*a*]quinoxalines

Clemens Lamberth

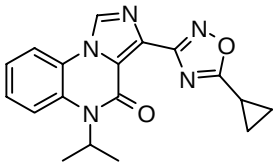
Basel (Switzerland) Novartis Crop Protection AG, Research Department

Received March 8th, 1999, respectively April 15th, 1999

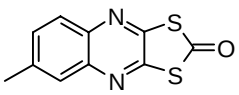
Keywords: Acylations, Cyclizations, Heterocycles, Imidazo[1,2-*a*]quinoxaline, Quinoxaline

Abstract. A concise approach to 4-substituted imidazo[1,2-*a*]quinoxalines **7** is described, starting from 1-fluoro-2-nitrobenzene (**3**). The high variability in the functionalization of the imidazo [1,2-*a*]quinoxaline-4-position is due to the easy introduction of these substituents by *N*-acylation in the second last step.

Quinoxalines, which are hetero-annelated in their pyrazine moiety often display astonishing biological activities. Examples for this are the anxiolytic benzodiazepine antagonist pandiplon **1** [1] and the acaricidal and fungicidal agent oxythioquinox (quinomethionate) **2** [2]. Just recently, imidazo[1,2-*a*]quinoxalin-4-amines have been identified as novel class of nonxanthine A_1-adenosine receptor antagonists [3].



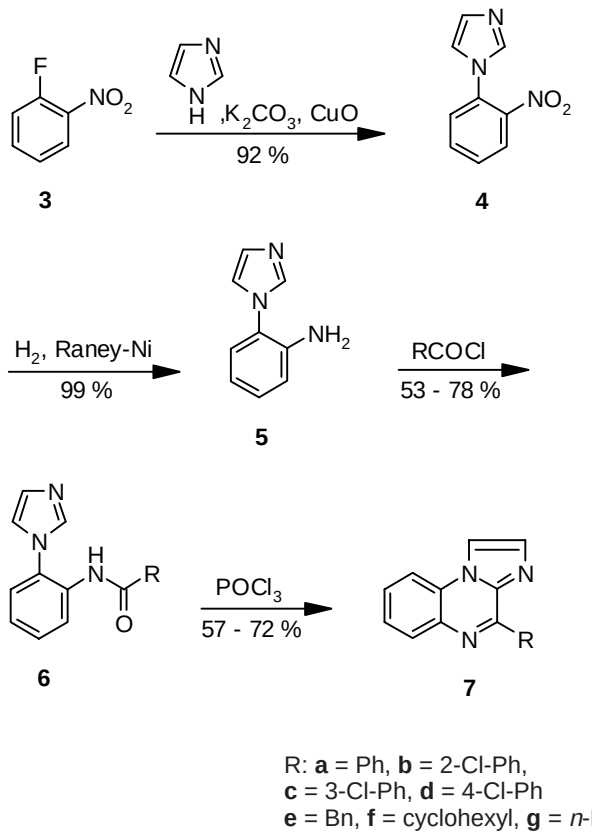
1



2

During a synthesis program we needed a reliable approach to similar imidazo[1,2-*a*]quinoxalines with carbon substituents in the 4-position. Although several syntheses to pyrrolo[1,2-*a*]quinoxalines [4, 5], pyrazolo[1,5-*a*]quinoxalines [6, 7] and triazolo[4,3-*a*]quinoxalines [8, 9] have been described, which enable the selective and diverse substitution of the 4-position, this is not the fact for imidazo[1,2-*a*]quinoxalines. Known procedures for the preparation of imidazo[1,2-*a*]quinoxalines either start from 2-chloroquinoxalines [10, 11], in which a future 4-substituent would have to be installed already in the starting material, or use the intramolecular condensation of 2-methyl or 2-formyl substituted 1-(2-aminophenyl)imidazoles [12, 13] with no possibility for the introduction of a 4-function. Only one example in the patent literature describes an appropriate approach to 4-substituted imidazo[1,2-*a*]quinoxalines, based on the intramolecular ring closure between an acylamino function and the 2-position of an 1-arylsubstituted imidazole [14]. Unfortunately, the application of this method was limited so far, because many products are formed in extraordinary low yields. Herein we present an improved procedure, by which the amount of phosphorus oxychloride in the key step could be reduced dramatically, resulting in increased yields of the products.

The synthesis starts with the known copper oxide catalyzed arylation of imidazole with 1-fluoro-2-nitrobenzene (**3**). The nitro-function of the obtained 1-arylimidazole **4** [15, 16] is easily reduced to an aminogroup by standard Raney nickel catalyzed hydrogenation, leading to the central intermediate **5** [15]. The introduction of the future sidechain of the target molecule is achieved by simple *N*-acylation with different acyl chlorides. Finally, cyclization of the carboxy function with the imidazole-2-position affords the desired tricyclic heteroaromatic ring system **7**.



Scheme 1 Synthesis of 4-Substituted Imidazo[1,2-*a*]quinoxalines

  1436-9966/99/3410X-492 $ 17.50 + .50/0

A similar approach to imidazo[1,2-*a*]quinoxalinones (**7**, R = OH) has been described recently by reaction of **5** with 1,1'-carbonyldiimidazole [17]. In conclusion, we presented a straightforward four-step sequence to imidazo[1,2-*a*]quinoxalines which allows the easy introduction and variation of substituents in the 4-position.

The author is very grateful to S. Guelfi for excellent technical assistance.

Experimental

All compounds were characterized by standard spectroscopical and microanalytical methods. ^{1}H NMR spectra were recorded on a Varian Gemini 300 spectrometer at 300 MHz, using $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts are reported in ppm downfield from the standard (δ = 0.00). Mass spectra were obtained on a Micromass Platform II by electrospray ionization, using acetonitrile/water (8 : 2) as solvent. Melting points were determined on a Buechi 535 melting point apparatus and are uncorrected, column chromatography was performed on E. Merck silica gel 60 (40–63 mm).

N-[2-(Imidazol-1-yl)phenyl]benzamide (**6a**)

To a solution of 5.0 g (31 mmol) 1-(2-aminophenyl)imidazole (**5**) [15] in 50 ml dioxane are added slowly 4.3 g (31 mmol) of benzoyl chloride. This mixture is stirred for 4 h at room temperature and subsequently poured on water. After extraction with ethyl acetate, the combined organic phases are washed with water, dried over magnesium sulfate and evaporated *in vacuo*. The remainder is crystallized from ethyl acetate/hexane. Yield 4.8 g (18 mmol, 58%) **6a**. *m.p*. 147 °C. – ^{1}H NMR: δ/ppm = 8.53 (d, 1H), 7.78–7.17 (m, 11H). – MS: 264 (M + 1), 265 (M + 2).

$C_{16}H_{13}N_3O$	Calcd.:	C 72.99	H 4.97	N 15.96
(263.27)	Found:	C 73.14	H 4.91	N 16.23.

The compounds **6b**–**g** are obtained analogously.

2-Chloro-N-{2-(imidazol-1-yl)phenyl]benzamide (**6b**)

Yield 57%. *m.p*. 200–202 °C. – ^{1}H NMR: δ/ppm = 8.60 (d, 1H), 7.92–7.26 (m, 10H). – MS: 298 (M^+), 299 (M + 1), 300 (M + 2).

3-Chloro-N-{2-(imidazol-1-yl)phenyl]benzamide (**6c**)

Yield 69%. *m.p*. 143–145 °C. – ^{1}H NMR: δ/ppm = 8.48 (d, 1H), 7.79–7.18 (m, 10H). – MS: 298 (M^+), 300 (M + 2).

4-Chloro-N-{2-(imidazol-1-yl)phenyl]benzamide (**6d**)

Yield 78%. *m.p*. 166 °C. – ^{1}H NMR: δ/ppm = 8.51 (d, 1H), 7.72–7.17 (m, 10H). – MS: 298 (M^+), 299 (M + 1), 300 (M + 2).

N-[2-(imidazol-1-yl)phenyl]benzeneacetamide (**6e**)

Yield 53%. *m.p*. 148 °C. – ^{1}H NMR: δ/ppm = 8.28 (d, 1H), 7.67–7.08 (m, 10H), 6.78 (s, 1H), 3.65 (s, 2H). – MS: 278 (M + 1), 279 (M + 2).

N-[2-(imidazol-1-yl)phenyl]cyclohexanecarboxamide (**6f**)

Yield 64%. *m.p*. 140–142 °C. – ^{1}H NMR: δ/ppm = 8.26 (d, 1H), 7.70–7.18 (m, 6H), 2.04–1.11 (m, 11H). – MS: 269 (M^+), 270 (M + 1), 271 (M + 2).

N-[2-(imidazol-1-yl)phenyl]butanamide (**6g**)

Yield 65%. *m.p*. 109–111 °C. – ^{1}H NMR: δ/ppm = 8.25 (d, 1H), 7.82–7.26 (m, 6H), 2.24 (t, 2H), 1.68–163 (m, 2H), 0.93 (t, 3H). – MS: 230 (M + 1), 231 (M + 2).

4-Phenylimidazo[1,2-a]quinoxaline (**7a**)

A mixture of 3.0 g (11 mmol) *N*-[2-(imidazol-1-yl)phenyl] benzamide (**6a**), 2.3 g (15 mmol) phosphorus oxychloride and 15 ml pyridine was heated to reflux for 3 hours. Afterwards the reaction mixture is poured on water and evaporated *in vacuo*. The residue is dissolved in ethyl acetate, washed with water, dried over magnesium sulfate and evaporated. The remainder is chromatographed on silica gel. Yield 1.7 g (7.0 mmol, 61%) **7a**. *m.p*. 147–149. – ^{1}H NMR: δ/ppm = 8.70–8.63 (m, 2H), 8.24–8.19 (m, 2H), 7.93–7.57 (m, 7H). – MS: 246 (M + 1), 247 (M + 2).

$C_{16}H_{11}N_3$	Calcd.:	C 78.35	H 4.52	N 17.13
(245.27)	Found:	C 78.57	H 4.61	N 16.98.

The compounds **7b**–**g** are obtained in an analogous manner.

4-(2-Chlorophenyl)imidazo[1,2-a]quinoxaline (**7b**)

Yield 59%. *m.p*. 165 °C. – ^{1}H NMR: δ/ppm = 8.25–8.20 (m, 2H), 7.98 (d, 1H), 7.83 (s, 1H), 7.77–7.43 (m, 6H). – MS: 280 (M^+), 281 (M + 1), 282 (M + 2).

4-(3-Chlorophenyl)imidazo[1,2-a]quinoxaline (**7c**)

Yield 66%. *m.p*. 131–133 °C. – ^{1}H NMR: δ/ppm = 8.82 (d, 1H), 8.76–8.69 (m, 2H), 8.24–8.20 (m, 2H), 8.00–7.51 (m, 5H). – MS: 280 (M^+), 282 (M + 2).

4-(4-Chlorophenyl)imidazo[1,2-a]quinoxaline (**7d**)

Yield 67%. *m.p*. 171–173 °C. – ^{1}H NMR: δ/ppm = 8.75–8.71 (m, 2H), 8.31–8.23 (m, 2H), 7.96–7.55 (m, 6H). – MS: 280 (M^+), 282 (M + 2).

4-Benzylimidazo[1,2-a]quinoxaline (**7e**)

Yield 60%. *m.p*. 141 °C. – ^{1}H NMR: δ/ppm = 8.12–8.08 (m, 2H), 7.83–7.18 (m, 9H), 4.65 (s, 2H). – MS: 260 (M + 1), 261 (M + 2).

4-Cyclohexylimidazo[1,2-a]quinoxaline (**7f**)

Yield 72%. *m.p*. 108–110 °C. – ^{1}H NMR: δ/ppm = 8.09–8.02 (m, 2H), 7.87–7.35 (m, 4H), 1.91–1.39 (m, 11H). – MS: 252 (M + 1), 253 (M + 2).

4-Propylimidazo[1,2-a]quinoxaline (**7g**)

Yield 57%. *m.p*. 110–112 °C. – ^{1}H NMR: δ/ppm = 8.15–8.09 (m, 2H), 7.90–7.25 (m, 4H), 2.18 (t, 2H), 1.59–1.54 (m, 2H), 0.96 (t, 3H). – MS: 211 (M^+), 212 (M + 1).

References

[1] J. W. Mickelson, E. J. Jacobsen, D. B. Carter, H. K. Im, W. B. Im, P. J. K. D. Schreur, V. H. Sethy, A. H. Tang, J. E. McGee, J. D. Petke, J. Med. Chem. **1996**, *39*, 4654

[2] K. Sasse, R. Wegler, G. Unterstenhoefer, F. Grewe, Angew. Chem. **1960**, *72*, 973

[3] S. Ceccarelli, A. D'Alessandro, M. Prinzivalli, S. Zanarella, Eur. J. Med. Chem. **1998**, *33*, 943

[4] J. Guillon, P. Dallemagne, B. Pfeiffer, P. Renard, D. Manechez, A. Kervran, S. Rault, Eur. J. Med. Chem. **1998**, *33*, 293
[5] D. Hou, H. Balli, Helv. Chim. Acta. **1992**, *75*, 2608
[6] A. Albini, G. Bettinetti, G. Minoli, J. Chem. Soc., Perkin Trans. I **1983**, 2491
[7] J. M. Lindley, I. M. McRobbie, O. Meth-Cohn, H. Suschitzky, J. Chem. Soc., Perkin Trans. I **1980**, 982
[8] B. Matuszczak, E. Pekala, C. E. Mueller, Arch. Pharm. Pharm. Med. Chem. **1998**, *331*, 163
[9] K. T. Potts, S. W. Schneller, J. Heterocycl. Chem. **1968**, *5*, 485
[10] M. Vogel, E. Lippmann, J. Prakt. Chem. **1989**, *331*, 69
[11] R. F. Cookson, R. E. Rodway, J. Chem. Soc., Perkin Trans. I **1975**, 1854
[12] R. G. R. Bacon, S. D. Hamilton, J. Chem. Soc., Perkin Trans. I **1974**, 1970
[13] I. Antonini, F. Claudi, G. Cristalli, P. Franchetti, M. Grifantini, S. Martelli, Eur. J. Med. Chem. – Chim. Ther. **1979**, *14*, 89
[14] P. L. Warner, E. J. Luber, U.S. Pat. Appl. 4, 191, 767 (Chem. Abstr. **1980**, *93*, 114568), 4,200, 750 (Chem. Abstr. **1980**, *93*, 114572), 4,229, 452 (Chem. Abstr. **1981**, *94*, 103429)
[15] A. J. Blake, B. A. J. Clark, H. McNab, C. C. Sommerville, J. Chem. Soc., Perkin Trans. I **1997**, 1605
[16] M. F. Mackay, G. J. Trantino, J. F. K. Wilshire, Aust. J. Chem. **1993**, *46*, 417
[17] D. D. Davey, P. W. Erhardt, E. H. Cantor, S. S. Greenberg, W. R. Ingebretsen, J. Wiggins, J. Med. Chem. **1991**, *34*, 2671

Address for correspondence:
Dr. Clemens Lamberth
Novartis Crop Protection AG
Research Department
Schwarzwaldallee 211
CH-4002 Basel
Switzerland
Fax: Internat. code (0)61-6978529
E-mail: clemens.lamberth@cp.novartis.com