Cascade Synthesis of Functionalized 2*H*-Imidazo[5,1-*a*]-isoquinolinium Chlorides from Isoquinoline, Chloroformamidines (= Carbamimidoyl Chlorides), and Isocyanides

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Stable derivatives of 2*H*-imidazo[5,1-*a*]isoquinolinium chloride are obtained in good yields from the cascade reaction between isoquinoline, chloroformamidines (= carbamimidoyl chlorides), and isocyanides in dry MeCN (*Scheme 1*).

Introduction. – Cascade reactions constitute a fascinating branch of organic chemistry, and one which has been the subject of intense research in recent years, as witnessed by the number of reviews that have appeared covering various aspects of these processes [1–3]. The undeniable benefits of cascade reactions are well established, having been recounted on numerous occasions, and include atom economy [4][5], as well as economies of time, labor, resource management, and waste generation.

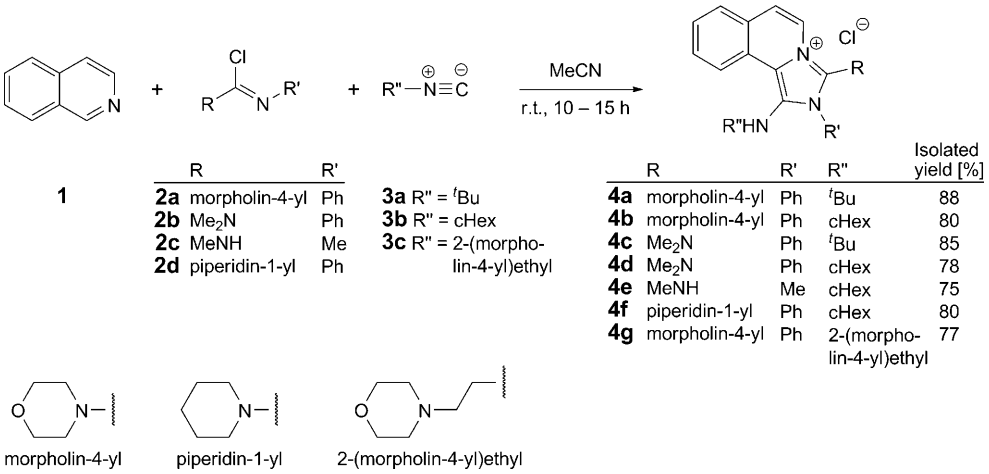
Imidazo[5,1-*a*]isoquinolines have a wide range of unique biological potentialities [6][7]. Several multistep pathways have been reported for the synthesis of these compounds [8–13]. Although the synthesis of 1-aminoimidazo[5,1-*a*]isoquinolinium salts based on multicomponent reactions of isocyanides has been previously reported [14], there is no literature precedence for the reaction of isoquinoline (**1**) with chloroformamidines (= carbamimidoyl chlorides) **2** in the presence of isocyanides. Compounds **2** can be generated from substituted ureas in the presence of Ph_3P/CCl_4 [15].

As part of our current studies on the development of new routes in heterocyclic synthesis [16–20], we report a one-pot synthesis to 2*H*-imidazo[5,1-*a*]isoquinolinium chlorides **4**.

Results and Discussion. – The reaction of isoquinoline (**1**), isocyanides **3**, and chloroformamidines **2** (prepared *in situ* from the reaction of trisubstituted ureas, Ph_3P, and CCl_4) proceeded smoothly in dry MeCN and was complete within 10–15 h (*Scheme 1*). The ^{1}H- and ^{13}C-NMR spectra of the crude products clearly indicated the formation of 2*H*-imidazo[5,1-*a*]isoquinolinium chlorides **4a**–**4g** in 75–88% yield.

The structures of compounds **4** were deduced from their IR and ^{1}H- and ^{13}C-NMR spectra. For example, the ^{1}H-NMR spectrum of **4a** in (D_6)DMSO showed two *singlet*s for NH and the ^{t}Bu group together with two *multiplet*s for CH_2 groups and characteristic *multiplet*s for H-atoms of the Ph and isoquinolinium residue. The ^{1}H-

Scheme 1. *Synthesis of Functionalized* 2H-*Imidazo[5,1-a]isoquinolinium Chlorides from Isoquinoline, Chloroformamidines, and Alkyl Isocyanides*

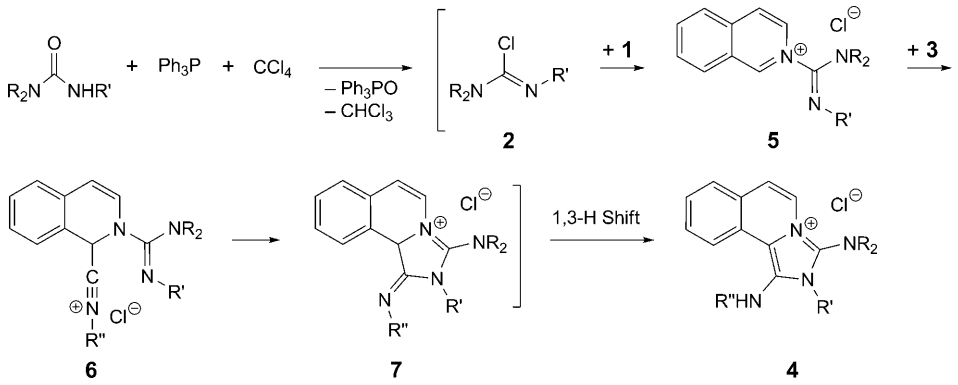


decoupled ^{13}C-NMR spectrum of **4a** showed 19 distinct resonances in agreement with the proposed structure. The IR spectrum of **4a** displayed a characteristic NH (3375 cm^{-1}) band. The ^{1}H- and ^{13}C-NMR spectra of **4b**–**4g** were similar to those of **4a**, except for the signals of the substituents at the N-atoms, which exhibited characteristic resonances in the appropriate regions of the spectrum.

A mechanistic rationalization for the reaction is given in *Scheme 2*. The initial event is the formation of chloroformamidine **2** from the corresponding trisubstituted ureas in the presence of Ph_3P and CCl_4. Nucleophilic attack of isoquinoline on **2** leads to intermediate **5**, which is attacked by alkyl isocyanide **3** to generate **6**. Compound **4** is produced by cyclization of **6** to **7** and subsequent 1,3-H shift.

In summary, we report a synthesis of stable 2*H*-imidazo[5,1-*a*]isoquinolinium chlorides from the cascade reaction between isoquinoline and chloroformamidines in

Scheme 2



the presence of alkyl isocyanides in dry MeCN. The present procedure has the advantage that the reactants can be mixed without any prior activation or modification.

Experimental Part

General. Isoquinoline (**1**) and isocyanides **3** were obtained from *Merck* and used without further purification. Chloroformamidines **2** were prepared *in situ* from the reaction of trisubstituted ureas, Ph_3P, and CCl_4. M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu-IR-460* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-DRX-500-Avance* instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, resp.; δ in ppm, J in Hz. MS: *Finnigan-MAT-8430* mass spectrometer at 70 eV; in m/z (rel. %). Elemental analyses (C, H, N): *Heraeus-CHN-O-Rapid* analyzer.

*2*H-*Imidazo[5,1-*a*]isoquinolinium Chlorides* **4**: *General Procedure.* To a mixture of Ph_3P (0.31 g, 1.2 mmol) and the trisubstituted urea (1 mmol) in dry MeCN was added CCl_4 (0.17 g). The resulting soln. was stirred at r.t. for 5 h. Then, isoquinoline (**1**; 0.13 g, 1 mmol) and isocyanide **3** (1 mmol) were added, and stirring was continued at r.t. After completion of the reaction (5–10 h), as indicated by TLC (AcOEt/hexane 2:1), the solvent was evaporated, and the residue was washed with hot AcOEt (4 ml) to afford pure title compounds.

*1-[(*tert*-Butyl)amino]-3-(morpholin-4-yl)-2-phenyl-2*H*-imidazo[5,1-*a*]isoquinolinium Chloride* (**4a**): Yield 0.38 g (88%). White powder. M.p. 275–277° (dec.). IR (KBr): 3375 (NH), 1647, 1547, 1593, 1550, 1497, 1446, 1362, 1362, 1206, 1103, 980, 774. ^{1}H-NMR (500 MHz, (D_6)DMSO): 0.91 (*s*, ^{t}Bu); 3.03–3.10 (*m*, 2 CH_2N); 3.55–3.60 (*m*, 2 CH_2O); 4.93 (*s*, NH); 7.41 (*d*, ^3J = 7.5, CH); 7.65–7.71 (*m*, 2 CH); 7.72–7.75 (*m*, 5 CH); 7.90 (*d*, ^3J = 7.7, CH); 8.08 (*d*, ^3J = 7.5, CH); 8.90 (*d*, ^3J = 8.0, CH). ^{13}C-NMR (125.7 MHz, (D_6)DMSO): 30.0 (Me_3C); 48.9 (2 CH_2N); 54.9 (Me_3C); 68.8 (2 CH_2O); 117.5 (CH); 119.1 (CH); 119.3 (C); 123.2 (C); 123.5 (CH); 126.4 (C); 127.4 (C); 127.9 (CH); 128.8 (2 CH); 128.9 (CH); 129.0 (CH); 129.4 (2 CH); 130.7 (CH); 132.4 (C); 135.4 (C). EI-MS: 437 (2, M^+), 344 (100), 285 (25), 231 (35), 155 (60), 129 (55), 77 (48), 56 (25), 41 (33). Anal. calc. for $C_{25}H_{29}ClN_4O$ (436.97): C 68.71, H 6.68, N 12.82; found: C 68.64, H 6.58, N 12.54.

*1-(Cyclohexylamino)-3-(morpholin-4-yl)-2-phenyl-2*H*-imidazo[5,1-*a*]isoquinolinium Chloride* (**4b**): Yield 0.37 g (80%). White powder. M.p. 228–230° (dec.). IR (KBr): 3385 (NH), 1650, 1593, 1555, 1497, 1450, 1259, 1104, 789, 694. ^{1}H-NMR (500 MHz, (D_6)DMSO): 0.95–1.80 (*m*, 5 CH_2); 3.02–3.09 (*m*, 2 CH_2N); 3.54–3.59 (*m*, 2 CH_2O); 4.54–4.59 (*m*, CHN); 5.20 (*d*, ^3J = 6.4, NH); 7.34 (*d*, ^3J = 7.5, CH); 7.59 (*t*, ^3J = 7.5, CH); 7.68–7.69 (*m*, CH); 7.70–7.75 (*m*, CH); 7.85 (*d*, ^3J = 7.7, CH); 8.01 (*d*, ^3J = 7.5, CH); 8.58 (*d*, ^3J = 8.0, CH). ^{13}C-NMR (125.7 MHz, (D_6)DMSO): 24.5 (2 CH_2); 25.1 (CH_2); 33.1 (2 CH_2); 40.0 (2 CH_2N); 56.9 (2 CH_2O); 65.7 (CHN); 115.1 (CH); 117.5 (CH); 119.0 (C); 122.9 (C); 123.3 (CH); 126.9 (C); 127.9 (C); 128.3 (CH); 128.4 (2 CH); 128.6 (CH); 129.3 (CH); 129.6 (2 CH); 130.8 (CH); 132.2 (C); 134.7 (C). EI-MS: 463 (2, M^+), 394 (100), 231 (40), 155 (65), 129 (50), 77 (42), 67 (25), 39 (50). Anal. calc. for $C_{27}H_{31}ClN_4O$ (463.00): C 70.03, H 6.74, N 12.10; found: C 70.16, H 6.45, N 12.51.

*1-[(*tert*-Butyl)amino]-3-(dimethylamino)-2-phenyl-2*H*-imidazo[5,1-*a*]isoquinolinium Chloride* (**4c**): Yield 0.33 g (85%). White powder. M.p. 241–244° (dec.). IR (KBr): 3375 (NH), 1602, 1582, 1497, 1457, 1423, 1206, 823, 689. ^{1}H-NMR (500 MHz, (D_6)DMSO): 0.91 (*s*, ^{t}Bu); 2.76 (*s*, 2 Me); 4.97 (*s*, NH); 7.37 (*d*, ^3J = 7.5, CH); 7.63–7.66 (*m*, 2 CH); 7.67–7.74 (*m*, 5 CH); 7.86 (*d*, ^3J = 8.2, CH); 8.05 (*d*, ^3J = 7.5, CH); 8.89 (*d*, ^3J = 8.0, CH). ^{13}C-NMR (125.7 MHz, (D_6)DMSO): 30.0 (Me_3C); 54.6 (Me_3C); 54.9 (2 Me); 117.1 (CH); 119.0 (CH); 119.3 (C); 123.3 (C); 123.6 (CH); 125.8 (C); 127.4 (C); 127.9 (CH); 128.6 (2 CH); 128.7 (CH); 128.8 (CH); 129.4 (2 CH); 130.4 (CH); 132.7 (C); 137.3 (C). EI-MS: 395 (2, M^+), 302 (100), 189 (40), 155 (70), 129 (48), 77 (50), 41 (45). Anal. calc. for $C_{23}H_{27}ClN_4$ (394.98): C 69.94, H 6.89, N 14.18; found: C 70.24, H 6.75, N 14.32.

*1-(Cyclohexylamino)-3-(dimethylamino)-2-phenyl-2*H*-imidazo[5,1-*a*]isoquinolinium Chloride* (**4d**): Yield 0.32 g (78%). Pale yellow powder. M.p. 310–312° (dec.). IR (KBr): 3380 (NH), 1606, 1556, 1473, 1343, 1270, 1137, 791, 651. ^{1}H-NMR (500 MHz, (D_6)DMSO): 1.14–2.21 (*m*, 5 CH_2); 3.33 (*s*, 2 Me); 4.52–4.57 (*m*, CHN); 5.61 (*d*, ^3J = 7.0, NH); 7.39 (*d*, ^3J = 7.4, CH); 7.62 (*t*, ^3J = 7.6, CH); 7.65–7.69 (*m*, CH); 7.69–7.73 (*m*, 5 CH); 7.86 (*d*, ^3J = 7.5, CH); 8.13 (*d*, ^3J = 7.4, CH); 8.44 (*d*, ^3J = 8.0, CH). ^{13}C-NMR (125.7 MHz, (D_6)DMSO): 24.7 (2 CH_2); 25.1 (CH_2); 33.2 (2 CH_2); 54.6 (2 Me); 57.5 (CHN); 117.9 (CH);

118.2 (CH); 119.3 (C); 121.6 (C); 122.7 (CH); 123.0 (C); 124.2 (C); 127.0 (CH); 128.1 (2 CH); 128.5 (CH); 128.7 (CH); 129.5 (2 CH); 130.0 (CH); 132.6 (C); 136.0 (C). EI-MS: 421 (3, M^+), 302 (100), 189 (45), 155 (68), 129 (53), 77 (43), 41 (56), 39 (35). Anal. calc. for $C_{25}H_{29}ClN_4$ (420.97): C 71.32, H 6.94, N 13.31; found: C 71.12, H 6.57, N 13.68.

*1-(Cyclohexylamino)-2-methyl-3-(methylamino)-2*H-*imidazo[5,1-*a*]isoquinolinium Chloride* (**4e**): Yield 0.25 g (75%). White powder. M.p. 312–315° (dec.). IR (KBr): 3378 (NH), 1647, 1606, 1556, 1473, 1343, 1270, 1137, 791. ^{1}H-NMR (500 MHz, (D_6)DMSO): 1.14–1.82 (*m*, 5 CH_2); 1.88 (*s*, *Me*NH); 2.49 (*s*, MeN); 4.55–4.58 (*m*, CHN); 5.65 (*d*, ^3J = 6.8, NH); 7.39 (*d*, ^3J = 7.4, CH); 7.63 (*t*, ^3J = 7.5, CH); 7.74 (*t*, ^3J = 7.4, CH); 7.85 (*d*, ^3J = 7.7, CH); 8.15 (*d*, ^3J = 7.3, CH); 8.44 (*d*, ^3J = 8.0, CH); 9.94–9.99 (br. *s*, NH). ^{13}C-NMR (125.7 MHz, (D_6)DMSO): 24.6 (2 CH_2); 25.1 (CH_2); 33.1 (2 CH_2); 33.5 (Me); 54.5 (Me); 57.5 (CHN); 117.9 (CH); 118.1 (CH); 121.5 (C); 122.7 (CH); 122.9 (C); 124.2 (C); 126.9 (CH); 128.0 (CH); 128.6 (CH); 129.4 (C); 129.9 (C). EI-MS: 345 (4, M^+), 226 (100), 113 (35), 155 (63), 129 (48), 77 (43), 44 (63), 39 (35). Anal. calc. for $C_{19}H_{25}ClN_4$ (344.88): C 66.16, H 7.30, N 16.24; found: C 65.89, H 7.12, N 16.54.

*1-(Cyclohexylamino)-2-phenyl-3-(piperidin-1-yl)-2*H-*imidazo[5,1-*a*]isoquinolinium Chloride* (**4f**): Yield 0.36 g (80%). Yellow powder. M.p. 258–260° (dec.). IR (KBr): 3384 (NH), 1651, 1593, 1554, 1497, 1459, 1342, 1263, 1024, 793, 770. ^{1}H-NMR (500 MHz, (D_6)DMSO): 0.89–2.10 (*m*, 8 CH_2); 3.02–3.07 (*m*, 2 CH_2N); 4.60–4.64 (*m*, CHN); 5.16 (*d*, ^3J = 6.1, NH); 7.29 (*d*, ^3J = 7.5, CH); 7.57 (*t*, ^3J = 7.5, CH); 7.60–7.64 (*m*, CH); 7.64–7.76 (*m*, 5 CH); 7.81 (*d*, ^3J = 7.7, CH); 7.85 (*d*, ^3J = 7.5, CH); 8.57 (*d*, ^3J = 8.0, CH). ^{13}C-NMR (125.7 MHz, (D_6)DMSO): 22.8 (2 CH_2); 24.5 (CH_2); 25.0 (CH_2); 33.2 (2 CH_2); 49.9 (2 CH_2); 56.8 (2 CH_2); 57.5 (CHN); 114.9 (CH); 117.3 (CH); 119.0 (C); 122.9 (C); 123.4 (CH); 126.9 (C); 127.8 (C); 128.0 (CH); 128.2 (2 CH); 128.4 (CH); 129.2 (CH); 129.5 (2 CH); 130.6 (CH); 132.4 (C); 136.1 (C). EI-MS: 461 (2, M^+), 346 (100), 233 (55), 155 (70), 129 (62), 77 (38), 39 (43). Anal. calc. for $C_{28}H_{33}ClN_4$ (461.03): C 72.94, H 7.21, N 12.15; found: C 72.65, H 7.14, N 12.45.

*3-(Morpholin-4-yl)-1-{[2-(morphlin-4-yl)ethyl]amino}-2-phenyl-2*H-*imidazo[5,1-*a*]isoquinolinium Chloride* (**4g**): Yield 0.38 g (77%). Pale yellow powder. M.p. 185–188° (dec.). IR (KBr): 3380 (NH), 1648, 1610, 1554, 1439, 1366, 1259, 1107, 971, 795, 745, 689. ^{1}H-NMR (500 MHz, (D_6)DMSO): 2.93–2.98 (*m*, 3 CH_2N); 3.21–3.26 (*m*, 2 CH_2N); 3.33–3.39 (*m*, CH_2N); 3.53–3.58 (*m*, 2 CH_2O); 3.72–3.78 (*m*, 2 CH_2O); 6.11–6.18 (*m*, NH); 7.39 (*d*, ^3J = 7.5, CH); 7.63 (*t*, ^3J = 7.4, CH); 7.64–7.69 (*m*, CH); 7.69–7.90 (*m*, 5 CH); 7.92–7.96 (*m*, CH); 8.06 (*d*, ^3J = 7.5, CH); 8.57 (*d*, ^3J = 7.8, CH). ^{13}C-NMR (125.7 MHz, (D_6)DMSO): 31.7 (2 CH_2N); 32.2 (2 CH_2N); 48.9 (CH_2N); 51.0 (CH_2N); 62.9 (2 CH_2O); 65.7 (2 CH_2O); 116.5 (CH); 117.6 (CH); 119.0 (C); 122.7 (C); 123.0 (CH); 127.0 (C); 127.9 (C); 128.6 (CH); 129.7 (2 CH); 129.8 (CH); 130.3 (CH); 131.0 (2 CH); 131.9 (CH); 134.0 (C); 135.5 (C). EI-MS: 494 (5, M^+), 344 (100), 231 (63), 155 (56), 77 (38), 41 (38). Anal. calc. for $C_{27}H_{32}ClN_5O_2$ (494.02): C 65.63, H 6.52, N 14.17; found: C 65.59, H 6.32, N 14.46.

REFERENCES

[1] L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115.
[2] H. Pellissier, *Tetrahedron* **2006**, *62*, 1619; H. Pellissier, *Tetrahedron* **2006**, *62*, 2143.
[3] R. A. Bunce, *Tetrahedron* **1995**, *51*, 13103.
[4] B. M. Trost, *Science (Washington, DC, U.S.)* **1991**, *254*, 1471.
[5] B. M. Trost, *Angew. Chem., Int. Ed.* **1995**, *34*, 259.
[6] F. J. Swinboune, J. H. Hunt, G. Klinkert, *Adv. Heterocycl. Chem*. **1987**, *23*, 103.
[7] D. E. Kuhla, to *Pfizer Inc.*, U.S. Patent 4163745, August 7, 1979.
[8] J. D. Bower, G. R. Ramage, *J. Chem. Soc.* **1955**, 2834.
[9] D. Blatcher, D. Middlemiss, *Tetrahedron Lett.* **1980**, *21*, 2195.
[10] W. Paudler, P. L. C. Chao, S. L. Helmick, *J. Heterocycl. Chem*. **1972**, *9*, 1157.
[11] K. Sasaki, A. Tsurumori, T. Hirota, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3851.
[12] H. Zimmer, G. D. Glasgow, M. Mcehanahan, T. Novinson, *Tetrahedron Lett.* **1968**, *9*, 2805.
[13] C. J. Berthet, M. Nierlich, M. Ephritikhine, *Eur. J. Org. Chem.* **2002**, 357.
[14] A. Shaabani, E. Soleimani, H. Khavasi, *J. Comb. Chem*. **2008**, *10*, 442.

[15] R. Appel, K.-D. Ziehn, K. Warning, *Chem. Ber.* **1973**, *106*, 2093.
[16] I. Yavari, L. Moradi, *Helv. Chim. Acta* **2006**, *89*, 1942.
[17] I. Yavari, A. Mirzaei, L. Moradi, *Helv. Chim. Acta* **2006**, *89*, 2825.
[18] I. Yavari, M. Sabbaghan, Z. Hossaini, M. Ghazanfarpour-Darjani, *Helv. Chim. Acta* **2008**, *91*, 1144.
[19] I. Yavari, S. Souri, *Synlett* **2008**, 1208.
[20] I. Yavari, Z. Hossaini, S. Seyfi, F. Shirgahi-Talari, *Helv. Chim. Acta* **2008**, *91*, 1177.

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