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Sequential cyclizations of 2-*iso*thiocyanatobenzonitrile and 2-*iso*cyanatobenzonitrile with α-aminoketones

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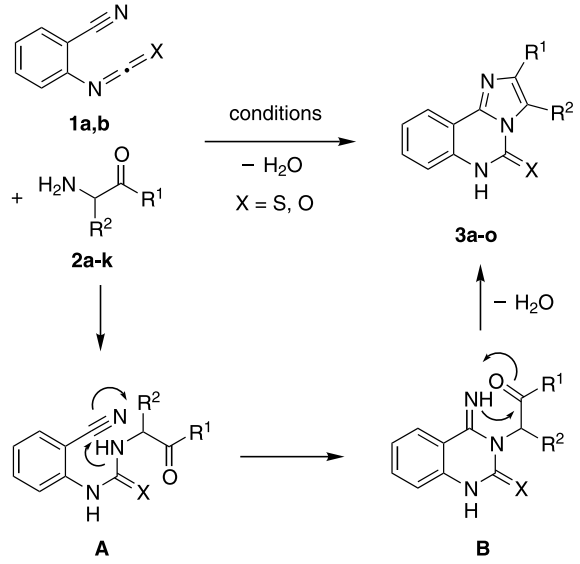
Abstract—Pharmacologically relevant 5-thioxo-6*H*-imidazo[1,2-*c*]quinazolines and 5-oxo-6*H*-imidazo[1,2-*c*]quinazolines were prepared by sequential reactions of α-aminoketones with 2-*iso*thiocyanatobenzonitrile and 2-*iso*cyanatobenzonitrile, respectively.

Domino and sequential reactions represent valuable tools for the efficient synthesis of complex molecules.[1,2] 2-*Iso*thiocyanatobenzonitrile and 2-*iso*cyanatobenzonitrile can be regarded as hetero-enyne-allenes and represent interesting dielectrophilic reagents.[3] We and others have reported the domino cyclization of 2-*iso*thiocyanatobenzonitrile with carboxylic hydrazides to give 1,2,4-triazolo[1,5-*c*]quinazolines.[3b,g,h] These compounds show antihypertonic, antirheumatic, antianaphylactic, antiasthmatic, tranquilizing, neuro-stimulating and benzodiazepine binding activity.[4,5] The stepwise cyclization of 2-*iso*cyanatobenzonitrile with α-aminoacetophenone has been recently reported by Zinner and Thom.[6] Herein, we wish to report the sequential cyclization of 2-*iso*thiocyanatobenzonitrile and 2-*iso*cyanatobenzonitrile with a great variety of α-aminoketones. These transformations allow a chemo- and regioselective synthesis of a variety of 5-thioxo-6*H*-imidazo[1,2-*c*]-quinazolines and 5-oxo-6*H*-imidazo[1,2-*c*]quinazolines.[6,7]

During the optimization of the cyclization of α-aminoacetophenone hydrochloride (**2a**) with 2-*iso*thiocyanatobenzonitrile (**1a**) the choice of the base proved an important parameter. The use of NEt_3 or piperidine (in CH_2Cl_2 or EtOH) resulted in the formation of complex mixtures. In contrast, employment of a two-phase system ($Na_2CO_3/H_2O/CH_2Cl_2$, 10 min, 20°C) resulted in the clean formation of the open-chained condensation product **A** (90% yield). However, extension of the reaction time did not result in cyclization. In contrast, reflux of **A** for 10 min cleanly afforded quinazoline **B** (88%). The second cyclization could again not be realized by extension of the reaction time. A change of the solvent was mandatory: Reflux of an EtOH solution of **B** for 8 h resulted in formation of 5-thioxo-6*H*-imidazo[1,2-*c*]quinazoline **3a** in 85% yield. Based on the optimization outlined above, we developed a sequential reaction of **1a** with **2a** which afforded **3a** in 73% yield.[8] The crude quinazoline **B** has to be isolated during this process. The cyclization involves the formation of three new bonds and proceeds as follows:



Scheme 1. Synthesis of 6*H*-imidazo[1,2-*c*]quinazolines **3a**–**o**. *Conditions*: For **3a**–**k**: (1) Na_2CO_3, H_2O, CH_2Cl_2, 20°C, 10 min; (2) reflux, 10 min, isolation of **B**; (3) EtOH, reflux, 8–24 h. For **3l**–**o**: (1) NEt_3, CH_2Cl_2, 20°C, 10 min; (2) reflux, 40 min, isolation of **A**; (3) *i*PrOH, NH_4OH, reflux, 8–32 h.

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Attack of the amino group onto the central carbon atom of the *iso*thiocyanate gave intermediate **A**. Intermediate **B** was formed by attack of the amino group onto the nitrile. Product **3a** was formed by attack of the imino group onto the ketone and subsequent elimination of a water molecule (Scheme 1). A one-pot procedure (with addition of EtOH during the reaction but without isolation of **B**) was successfully applied to the synthesis of product **3d** (vide infra, Table 1). However, the yield decreased (31%) compared to the overall yield of the corresponding two-step procedure (80%).

The preparative scope of the new cyclization was studied: The cyclization of **1a** with 4-(α-aminoacetyl)-toluene afforded the imidazo[1,2-*c*]quinazoline **3b** in 96% yield. The reaction of **1a** with a variety of functionalized α-aminoacetophenones afforded the methoxy-, bromo-, chloro-, fluoro- and nitro-substituted imidazo[1,2-*c*]quinazolines **3c**–**g**. Quinazoline **3h** was prepared from 2-(α-aminoacetyl)-naphthaline. The cyclization of **1a** with α-amino-acetone and 1-amino-3,3-dimethylbutan-2-one afforded the quinazolines **3i** and **3j**, respectively. Imidazo[1,2-*c*]quinazoline **3k** was prepared from α-amino-α-phenylacetophenone. All cyclizations proceeded with very good chemo- and regioselectivity and afforded the corresponding products in good to very good yields (except for **3g** and **3i**). The 5-thioxoquinazolines **3a**–**k** represent versatile synthetic building blocks as the thioxo group can be functionalized by reactions with nucleophiles and electrophiles.

The reaction of α-aminoketones with *iso*cyanatobenzonitrile (**1b**)—the oxygen analogue of **1a**—was next studied. The conditions developed for the cyclization of aminoketones with *iso*thiocyanatobenzonitrile (**1a**) proved unsatisfactory for **1b**, due to hydrolysis of the *iso*cyanate moiety. After several trial experimentations we have found that optimal results were obtained when a CH_2Cl_2 solution of α-aminoacetophenone (**2a**), **1b** and NEt_3 was (*i*) stirred for 10 min at 20°C and (*ii*) refluxed for 40 min to give intermediate **A** in 90% isolated yield; (*iii*) reflux of a *i*PrOH solution of **A** in the presence of NH_4OH resulted in the formation of 5-oxo-6*H*-imidazo[1,2-*c*]quinazoline **3l** in 74% yield.[9] The protocol developed was successfully applied to the cyclization of **1b** with other α-aminoketones. These transformations afforded the imidazo[1,2-*c*]-quinazolines **3m**–**o** in good yields and with very good chemo- and regioselectivity (Table 1).

Table 1. Products and yields

3	X	R^1	R^2	(%)[a]	Mp (°C)[b]
a	S	C_6H_5	H	73	300–304
b	S	4-MeC_6H_4	H	96	328–330
c	S	4-$(MeO)C_6H_4$	H	67	274–280
d	S	4-BrC_6H_4	H	80	344–346
e	S	4-ClC_6H_4	H	91	342–345
f	S	4-FC_6H_4	H	78	327–332
g	S	4-$(NO_2)C_6H_4$	H	34	350–352
h	S	2-$C_{10}H_7$	H	76	328–335
i	S	Me	H	37	263–273
j	S	*t*Bu	H	53	227–234
k	S	C_6H_5	C_6H_5	79	283–288
l	O	C_6H_5	H	90+74	295–296
m	O	4-MeC_6H_4	H	88+78	302–303
n	O	4-BrC_6H_4	H	78+75	334–336
o	O	4-ClC_6H_4	H	75+61	334–335

[a] Isolated yields for **3a**–**k** (over two steps) and for **A**+**3l**–**o**.
[b] Uncorrected (dec.).

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8. **Typical procedure for the synthesis of 5-thioxo-5,6-dihydro-imidazo[1,2-*c*]quinazolines (3a–j)**: To a CH_2Cl_2 suspension (40 mL) of *iso*thiocyanatobenzonitrile (1.00 g, 6.4 mmol) and 4-(α-aminoacetyl)-1-fluorobenzene hydrochloride (1.21 g, 6.4 mmol) was added an aqueous solution (12 mL) of sodium carbonate (1.38 g) with stirring. The mixture was stirred for 10 min at 20°C and for 10 min under reflux. After cooling to room temperature a colorless precipitate formed (intermediate **B**) which was filtered off. The organic and the aqueous layer of the filtrate were separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were concentrated at reduced pressure. The residue and the precipitate were suspended in EtOH (200 mL) and the mixture was refluxed for 12 h. The product **3f**, which crystallized upon cooling, was filtered off and dried in vacuo. The filtrate was concentrated at reduced pressure to give an additional amount of **3f** (combined yield: 1.48 g, 78%). Data of 2-(*p*-fluorophenyl)-5-thioxo-5,6-dihydro-imidazo[1,2-*c*]-quinazoline (**3f**): Colorless prisms (EtOH), mp 327–332°C (decomp.). IR (KBr, cm^{-1}): $\tilde{\nu}=3179$ (m), 3141 (m), 3113 (m), 3092, 3033 (m, Ar-H, C=CH), 2975 (m), 1634 (s), 1608 (m), 1566 (w), 1540 (s), 1494 (s), 1477 (s), 1467 (w), 1416 (s), 1359 (s), 1316 (s), 1303 (m), 1295 (m), 1283 (w), 1230 (m), 1219 (m), 1208 (w), 1193 (s), 1156 (s), 842 (s), 747 (s). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta=7.49$–7.69 (m, 5H, Ar-H), 8.06–8.31 (m, 3H, Ar-H), 8.73 (s, 1H, 3-H), 13.82 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta=112.6$ (Ar-CH, C-3), 113.5 (10a), 115.7 (d, $J_{C,F}=21$ Hz, C-3′, C-5′), 116.4 (Ar-CH, C-10), 123.1 (Ar-CH, C-9), 125.5 (Ar-CH, C-7), 127.8 (2 d, $J_{C,F}=8$ Hz, C-2′, C-6′), 129.0 (d, $J_{C,F}=3$ Hz, C-1′), 131.0 (Ar-CH, C-8), 134.5 (C-2), 139.9 (C-6a), 142.9 (C=N), 162.1 (d, $J_{C,F}=245$ Hz, C-4′), 166.8 (C=S). MS (EI, 70 eV): m/z [%] = 296 ([M+H]$^+$, 22), 295 (M$^+$, 100), 294 ([M−H]$^+$, 83), 262 ([M−SH]$^+$, 3), 108 (17), 107 (16). UV (CH_3CN, nm): λ_{max} (log ε) = 220 (4.18), 259 (4.60), 283 (4.52), 323 (4.09), 340 (4.09), 354 (3.99). Anal. calcd for $C_{16}H_{10}FN_3S$ (295.34): C, 65.07; H, 3.41; N, 14.23. Found: C, 65.19, H, 3.54, N, 14.14.
9. **Typical procedure 2: 5-Oxo-5,6-dihydro-imidazo[1,2-*c*]quinazolines (3k–n)**: To a CH_2Cl_2 suspension (40 mL) of *iso*cyanatobenzonitrile (325 mg, 2.4 mmol) and 1-(α-aminoacetyl)-4-toluene hydrochloride (520 mg, 2.4 mmol) was added dropwise a CH_2Cl_2 solution (10 mL) of NEt_3 (246 mg). The mixture was stirred for 10 min at 20°C and for 40 min under reflux. Upon cooling to ambient a colorless solid formed (intermediate A) which was filtered off and dried by exposure to air (630 mg, 88%). IR (KBr): $\tilde{\nu}=3322$ (s, NH), 2226 (w, CN), 1682 (s, C=O), 1649 (s, CONH), 1607 (s), 1571 (s, CONH), 1537 (s), 1476 (w), 1450 (m), 1414 (w), 1358 (w), 1298 (m), 1232 (s), 1184 (w) cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta=2.40$ (s, 3H, CH_3), 4.71 (d, $J=5.1$ Hz, 2H, CH_2), 7.09–8.06 (m, 9H, Ar-H, NH), 8.98 (s, 1H, NH). An *i*PrOH (100 mL) suspension of A (360 mg, 1.2 mmol) and of ammonium hydroxide (20 mL) was refluxed for 20 h. The solution was cooled to ambient and concentrated in vacuo to give a colorless precipitate which was filtered off and dried in vacuo. The solid was recrystallized from *i*PrOH to give **3m** (255 mg, 78%) as colorless needles, mp 302–303°C. IR (KBr, cm^{-1}): $\tilde{\nu}=3213$ (w, NH), 3155 (m, NH), 3077, 3064, 3053, 3015 (m, Ar-H, C=CH), 2943, 2923, 2894 (m, CH_3), 1710 (s, C=O), 1599 (s), 1556 (s), 1497 (m), 1483 (m), 1416 (s), 1371 (m), 1330 (w), 1296 (m), 1253 (w), 1147 (w), 830 (w), 822 (m), 747 (s), 737 (m). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta=2.35$ (s, 3H, CH_3), 7.25–8.22 (m, 8H, Ar-H), 8.34 (s, 1H, 3-H), 12.00 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta=20.8$ (CH_3), 108.9 (C-3), 112.0 (10a), 115.8 (Ar-CH, C-10), 122.8 (Ar-CH, C-9), 123.3 (Ar-CH, C-7), 125.4 (Ar-CH, C-3′, C-5′), 129.2 (Ar-CH, C-2′, C-6′), 130.1 (C-1′), 130.4 (Ar-CH, C-8), 135.2 (C-2), 137.0 (C-4′), 143.1 (C-6a), 143.3 (C=N), 144.8 (C=O). MS (EI, 70 eV): m/z [%] = 276 ([M+H]$^+$, 19), 275 (M$^+$, 100), 247 ([M−CO]$^+$, 4), 130 (11). UV (CH_3CN, nm): λ_{max} (log ε) = 242 (4.62), 249 (4.60), 273 (4.30), 312 (4.11), 324 (4.19). Anal. calcd for $C_{17}H_{13}N_3O$ (275.31): C, 74.17; H, 4.76; N, 15.26. Found: C, 74.14, H, 4.78, N, 15.14.