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Tetrahedron Letters 45 (2004) 8741–8743
Tetrahedron Letters

Efficient synthesis of tricyclic quinazolines by one-pot cyclizations of 2-(dichloroisocyanido)benzonitrile

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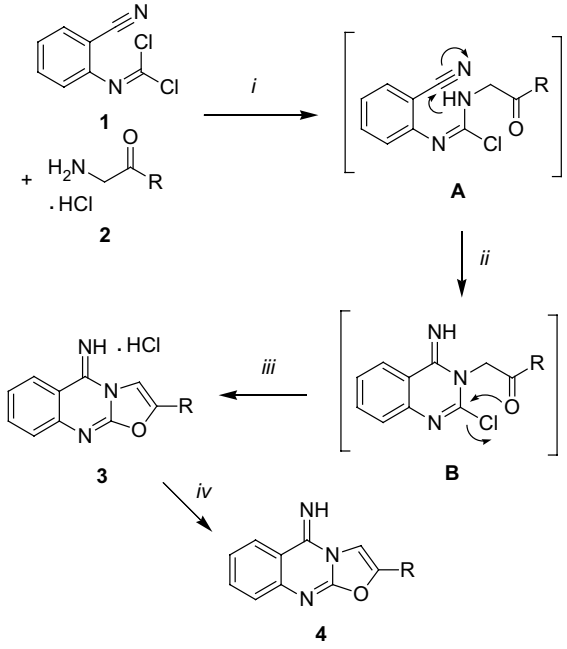
Received 5 August 2004; revised 17 September 2004; accepted 17 September 2004
Available online 2 October 2004

Abstract—The one-pot cyclization of 2-(dichloroisocyanido)benzonitrile with 1,4-dinucleophiles, such as α-aminoketones, afforded 5*H*-oxazolo[2,3-*b*]quinazolin-5-imines and related quinazolines.

Domino and sequential reactions of dinucleophiles with dielectrophiles allow an efficient synthesis of heterocyclic frameworks.[1] In recent years, we have reported a number of one-pot cyclizations of dinucleophiles with oxalic acid-bis(imidoyl)dichlorides—useful 1,2-dielectrophiles, which can be regarded as imino derivatives of oxalyl chloride.[2] Dichloroisocyanides represent imino derivatives of phosgene and have been reacted as 1,1-dielectrophiles with a variety of nucleophiles.[3] Recently, Pazdera et al. have reported an efficient synthesis of 2-(dichloroisocyanido)benzonitrile.[4] This compound represents an interesting 1,1,5-trielectrophilic building block, which combines the functional groups of a dichloroisocyanide and of a nitrile.[5] Herein, we wish to report what are, to the best of our knowledge, the first one-pot cyclizations of 2-(dichloroisocyanido)benzonitrile with α-aminoketones, carboxylic hydrazides and 1,2-diamines. These transformations allow a convenient synthesis of pharmacologically relevant oxazolo[2,3-*b*]quinazolin-5-imines[6] and imidazo[2,1-*b*]quinazolin-5-imines.[7] The products prepared represent analogues of cytotoxic, DNA intercalating natural products, such as luotonine A and B, desoxyvasicinone and camptothecin.[7a] Benzimidazolo[2,3-*b*]quinazolin-5-ones have been shown to possess immunosuppressive activity, again due to their DNA intercalation properties.[7b,c]

The reaction of the hydrochloride of phenacyl amine (**2a**) with 2-(dichloroisocyanido)benzonitrile (**1**) afforded the 5*H*-oxazolo[2,3-*b*]quinazolin-5-imine hydrochloride **3a** (Scheme 1). The best yields were obtained when a CH_2Cl_2 solution of the starting materials was stirred at 20 °C for 10 min, heated at reflux for 1 h and subsequently heated at reflux in *i*-PrOH for 6 h.[8] The hydrochloride **3a** was transformed into the free base **4a** by treatment with sodium bicarbonate. The structures of



Scheme 1. Synthesis of **3** and **4**. Reagents and conditions: (i) 2 equiv NEt_3, CH_2Cl_2, 20 °C, 10 min; (ii) reflux, 1 h; (iii) *i*-PrOH, reflux, 6 h; (iv) $NaHCO_3$, H_2O, *i*-PrOH, 20 °C, 4–12 h.

Keywords: Cyclizations; Dichloroisocyanides; *N*-heterocycles; Imidoyl chlorides; One-pot reactions.
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doi:10.1016/j.tetlet.2004.09.125

heterocycles **3** and **4** were confirmed by spectroscopic methods with comparison of known compounds.[9]

The formation of **3a** can be explained by attack of the amino group of **2a** onto the dichloroisocyanide to provide intermediate **A**, subsequent cyclization by attack of the nitrogen onto the nitrile to give intermediate **B** and subsequent attack of the oxygen onto the imidoyl chloride (Scheme 1).[10] Alternatively, the cyclization could proceed by attack of the oxygen atom onto the imidoyl chloride of **A** and subsequent attack of the nitrogen atom onto the nitrile. Three new bonds were formed in this one-pot reaction. To study the preparative scope of the reaction, the α-aminoketone was varied (Scheme 1, Table 1). The cyclization of **1** with **2b–e** afforded the methyl-, methoxy-, bromo- and chloro-substituted 5*H*-oxazolo[2,3-*b*]quinazolin-5-imines **3b–e** and **4b–e**.

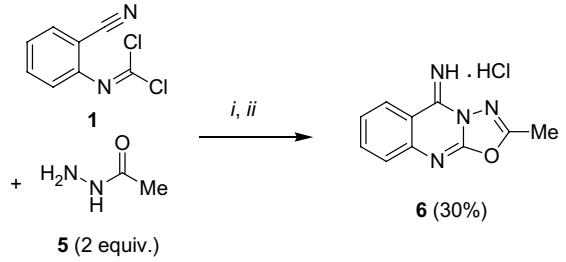
The cyclization of **1** with acetic hydrazide (**5**) gave the 5*H*-oxadiazolo[2,3-*b*]quinazolin-5-imine **6** (Scheme 2). The formation of **6** can be explained by a mechanism related to that depicted in Scheme 1. The formation of an isomeric triazolo[1,5-*c*]quinazoline was excluded by comparison of the spectroscopic data of **6** with those of independently prepared triazolo[1,5-*c*]quinazolines.[11]

The reaction of 2-(dichloroisocyanido)benzonitrile with ethyl glycinate hydrochloride (**7**) resulted in the formation of the 2,3-dihydro-2-oxo-imidazo[1,2-*c*]quinazoline **8** rather than the expected ethoxy-substituted 5*H*-oxazolo[2,3-*b*]quinazolin-5-imine (Scheme 3).[12] The formation of **8** can be explained by attack of two molecules of **7** onto the dichloroisocyanide to provide intermediate **C**, attack of the nitrogen atom onto the nitrile to provide intermediate **D** and final cyclization by attack of the imino nitrogen onto the ester group. In fact, the best yields of **8** were obtained when 2 equiv of **7** were employed.

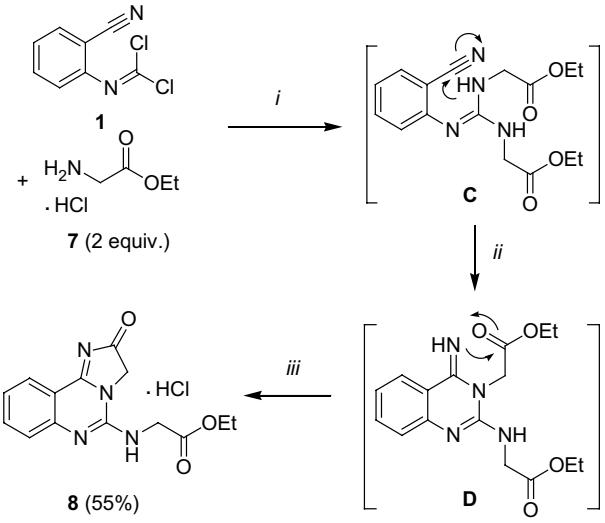
Table 1. Products and yields

3, 4	R	3[a] (%)	4[a] (%)
a	C_6H_5	44	83
b	4-MeC_6H_4	50	68
c	4-$(MeO)C_6H_4$	28	63
d	4-BrC_6H_4	32	65
e	4-ClC_6H_4	47	63

[a] Isolated yields.



Scheme 2. Cyclization of **1** with acetic hydrazide. Reagents and conditions: (i) CH_2Cl_2, reflux, 6 h; (ii) *i*-PrOH, reflux, 8 h.

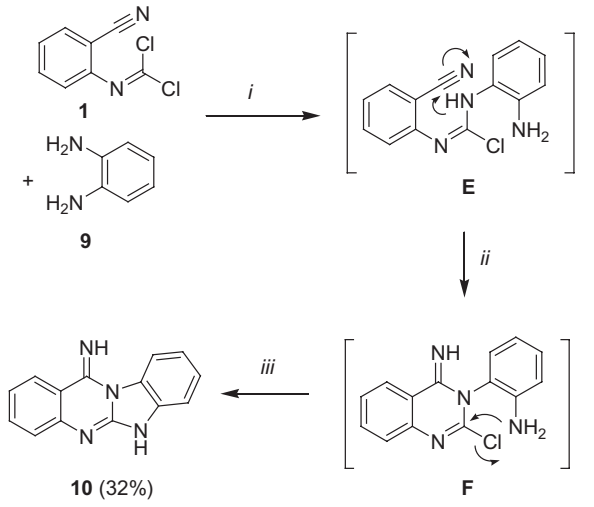


Scheme 3. Cyclization of **1** with ethyl glycinate. Reagents and conditions: (i) 2 equiv NEt_3, CH_2Cl_2, 20 °C, 20 min; (ii) reflux, 1 h; (iii) separation of precipitate, *i*-PrOH, reflux, 1 h.

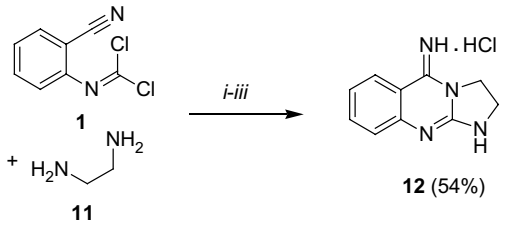
The reaction of 2-(dichloroisocyanido)benzonitrile with 1,2-diamines was studied next. The one-pot cyclization of 1,2-diaminobenzene (**9**) with **1** afforded, under conditions related to those employed for the synthesis of **3**, the benzimidazo[2,1-*b*]quinazolin-5-imine **10**. A possible mechanism for the formation of **10** is depicted in Scheme 4: attack of **9** onto the dichloroisocyanide gave intermediate **E** and subsequent cyclization afforded intermediate **F**. The product was finally formed by attack of the amino onto the imidoyl chloride group.

The cyclization of **1** with 1,2-diaminoethane afforded 2,3-dihydro-5*H*-imidazo[2,1-*b*]quinazolin-5-imine hydrochloride (**12**) (Scheme 5).[13]

The preparative scope of the new one-pot cyclization reactions will be investigated in future studies.



Scheme 4. Cyclization of **1** with 1,2-diaminobenzene. Reagents and conditions: (i) CH_2Cl_2, 20 °C, 10 min; (ii) addition of NEt_3 (1 equiv), reflux, 4 h; (iii) addition of NEt_3 (1 equiv) and of *i*-PrOH, reflux, 6 h.



Scheme 5. Cyclization of **1** with 1,2-diaminoethane. Reagents and conditions: (i) CH_2Cl_2, 20 °C, 10 min; (ii) reflux, 1 h; (iii) addition of *i*-PrOH to the solution, reflux, 6 h.

Acknowledgements

We thank M. Kandt for experimental contributions and Prof. P. Pazdera and Dr. W.-D. Pfeiffer for their support. Financial support from the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

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8. *Typical procedure: synthesis of 2-(p-bromophenyl)-5H-oxazolo[2,3-b]quinazolin-5-imine hydrochloride* **3d**. To a CH_2Cl_2 suspension of 2-amino-1-(*p*-bromophenyl)ethanone hydrochloride (501 mg, 2 mmol) was added a CH_2Cl_2 solution (10 mL) of **1** (400 mg, 2 mmol). A CH_2Cl_2 solution (5 mL) of NEt_3 (404 mg, 4 mmol) was added dropwise and the mixture was stirred at 20 °C for 10 min and under reflux for 1 h. The solvent was removed in vacuo and the residue was heated at reflux in isopropanol (150 mL) for 6–12 h. The solid formed was separated, washed with water (10 mL), dried and recrystallized from isopropanol to give **3d** as colourless prisms (238 mg, 32%), mp 265–285 °C (decomp.). IR (KBr): $\tilde{\nu}$ 3432 (w), 3059, 3034 (w), 2965 (w), 2929 (w), 1673 (s), 1641 (m), 1613 (m), 1471 (m), 1154 (w), 1071 (w), 766 (w). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.71–8.10 (m, 7H, Ar), 8.62–8.65 (m, 1H, Ar), 9.47 (s, 1H, 3-H), 10.94 (br s, 2H, NH, NH$^+$). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 112.0 (CH), 118.4, 128.7, 129.8 (C), 130.4, 131.4, 131.8, 137.6, 140.0 (CH), 149.3, 151.1, 155.9, 156.3 (C). *2-(p-Bromophenyl)-5H-oxazolo[2,3-b]quinazolin-5-imine* **4d**: hydrochloride **3d** (50 mg) was stirred in a mixture of a saturated aqueous solution of $NaHCO_3$ (10 mL) and isopropanol (1 mL) for 4 h at 20 °C. The solid was separated by filtration, washed with water, dried and recrystallized from isopropanol to give **4d** as colourless needles (29 mg, 65%), mp 246 °C (decomp.). IR (KBr): $\tilde{\nu}$ 3427 (w), 3328 (w), 3291 (w), 3067 (w), 1668 (s), 1638 (m), 1612 (s), 1471 (s), 1414 (w), 1170 (w), 1145 (w), 931 (w), 806 (w), 757 (w). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.30–7.78 (m, 7H, Ar), 8.27–8.30 (m, 1H, Ar), 8.65 (s, 1H, 3-H), 9.16 (s, 1H, =NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 106.8 (CH), 116.1, 122.4 (C), 123.9 (CH), 125.5 (C), 125.6 (CH), 125.9, 126.1, 132.1, 132.8 (CH), 142.2, 145.0, 151.2, 152.2 (C). MS (EI, 70 eV): *m/z* (%) 342 ([M]$^+$ (81), 20), 341 (100), 340 ([M]$^+$ (79), 23), 339 (97), 205 (11), 185 (34), 183 (35), 157 (13), 155 (14), 77 (17), 76 (13). Anal. Calcd for $C_{16}H_{10}BrN_3O$ (340.18): C, 56.49; H, 2.96; N, 12.35. Found: C, 56.45; H, 3.22; N, 12.20. All new products gave satisfactory spectroscopic and analytical and/or high resolution mass data.
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13. *Synthesis of 2,3-dihydro-5H-imidazo[2,1-b]quinazolin-5-imine hydrochloride* (**12**): To a CH_2Cl_2 solution (20 mL) of 1,2-diaminoethane (150 mg, 2.5 mmol) was added dropwise a CH_2Cl_2 solution (20 mL) of **1** (500 mg, 2.5 mmol) with stirring. During the addition a colourless precipitate was formed. The mixture was stirred under reflux for 1 h. Isopropanol (100 mL) was added and the mixture was heated at reflux for 6 h. The solid formed was filtered off, dried and recrystallized from isopropanol to give **12** as colourless prisms (300 mg, 54%), mp 306 °C (decomp.). IR (KBr): $\tilde{\nu}$ 3431 (m), 3109 (m), 2998 (m), 2976 (m), 2946 (m), 2913 (m), 2806 (m). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.78 (t, J = 8.7 Hz, 2H, CH_2), 4.33 (t, J = 8.7 Hz, 2H, CH_2), 7.27–7.78 (m, 3H, Ar), 8.35 (d, J = 7.3 Hz, 1H, Ar), 8.54 (s, 1H, =NH), 9.72 (br s, 2H, NH, NH$^+$). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 36.6, 45.2 (CH_2), 109.2 (C), 122.9, 125.0, 125.2, 136.3 (CH), 150.3, 152.1, 154.6 (C). MS (EI, 70 eV): *m/z* (%) 186 ([M]$^+$, 100), 185 ([M−H]$^+$, 85), 129 (15), 102 (14).