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Reactions of Quaternized Imidazo-Quinazoline and -Pyridopyrimidine with Active Methylene Compounds

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Summary. Syntheses of 1-methylimidazo[1,2-c]quinazolinium iodide (**3**) and 1-methylimidazo-[2,1-f]pyrido[3,2-d]pyrimidinium iodide (**4**) are described. These tricyclic compounds react with nucleophiles derived from active methylene compounds to give the corresponding open-chain enamines.

Keywords. Quaternization of tricyclic azaheterocyclic compounds; Condensed pyrimidine ring opening.

Reaktionen von quaternisierten Imidazo-Chinazolinen und -Pyridopyrimidinen mit Verbindungen mit reaktiven Methylengruppen

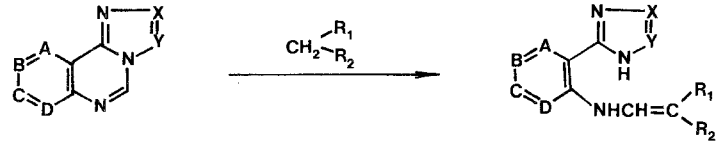
Zusammenfassung. Synthesen von 1-Methylimidazo[1,2-c]chinazoliniumjodid (**3**) und 1-Methyl-imidazo[2,1-f]pyrido[3,2-d]pyrimidiniumjodid (**4**) werden beschrieben. Diese tricyclischen Verbindungen reagieren mit einigen Carbanionen aus Verbindungen mit reaktiven Methylengruppen, wobei die offenkettigen Enamine entstehen.

Introduction

As a continuation of our studies on reactions of condensed pyrimidines [1] we tested whether introduction of a positive charge in a ring by quaternization activates imidazoquinazoline and imidazopyridopyrimidine ring systems sufficiently to enable pyrimidine-ring opening reactions with carbon nucleophiles.

Results and Discussion

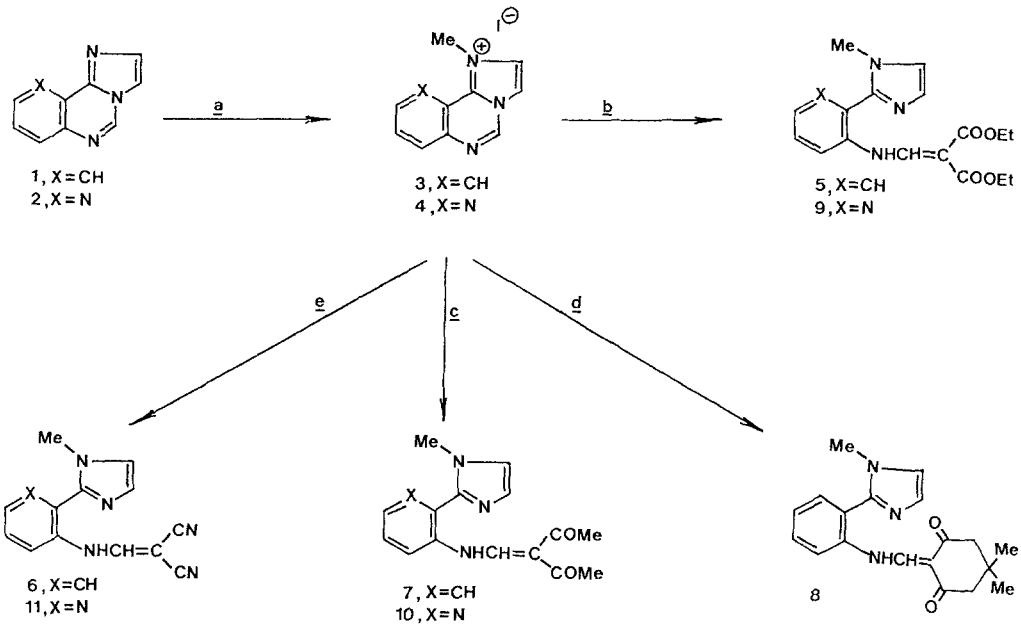
Ring opening of 1,2,4-triazolo- and tetrazolo-fused quinazoline and pyridopyrimidines with active methylene compounds proceeds very easily yielding open-chain products (Scheme 1). Similar reactions of imidazo-fused analogues failed



A, B, C, D = CH or N
X, Y = N or CH

R_1, R_2 = COOEt, COMe, CN, ...

Scheme 1



a: MeI ; b: $CH_2(COOEt)_2$; c: $CH_2(COMe)_2$; d: dimedone ; e: $CH_2(CN)_2$

Scheme 2

(according to our explanation) due to weak ability of the imidazole ring to attract electrons from the π-system as compared to triazole or tetrazole rings [1].

Since quaternization increases the susceptibility of azines for nucleophilic attack [2] we transformed **1** and **2** with methyl iodide into corresponding quaternary salts **3** and **4**. Although there are several possible sites for electrophilic attack only one monomethylated product could be isolated in each case. Methylation occurred at N1 as one would predict on the basis of an analogy with imidazo-fused azines [3]. The structure of the ring-opened products, i.e. N1 methylated imidazoles, also supports the proposed structures.

Both **3** and **4** reacted with sodium salts of diethyl malonate, malonodinitrile, and pentane-2,4-dione furnishing corresponding open-chain products (Scheme 2). Quaternized imidazoquinazoline **3** gave also the corresponding product with sodium salt of 5,5-dimethylcyclohexane-1,3-dione (dimedone). These results confirm that quaternization sufficiently activates imidazoquinazoline and imidazopyridopyrimidine systems for the reaction with nucleophiles derived from a variety of active methylene compounds.

Acknowledgement

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Experimental

Melting points were taken on a Kofler micro hot stage. ^{1}H NMR spectra were obtained on JEOL JNM-C-60-HL or JEOL JNM FX 90 Q spectrometers with *TMS* as internal standard. IR spectra were

obtained on Perkin-Elmer 727 B spectrometer. Elemental analyses for C, H, and N were performed on a Perkin-Elmer CHN Analyzer 240 C.

Imidazo[1,2-c]quinazoline (**1**) and imidazo[2,1-f]pyrido[3,2-d]pyrimidine (**2**) were prepared according to the procedures described in literature [1 b].

1-Methylimidazo[1,2-c]quinazolinium iodide (**3**)

In a sealed glass tube 1.25 g (7.4 mmol) of **1** was heated 3 h with 3 g (21 mmol) of methyl iodide at 100°C. The reaction mixture was suspended in 10 ml of chloroform and the product (1.9 g, 83%) was collected by filtration. For elemental analysis the product was recrystallized from ethanol. M.p. 256–257°C. ^{1}H NMR (*DMSO-d*$_6$): 4.46 (s, CH_3), 7.87–8.25 and 8.67–8.76 (m, H7, H8, H9, H10), 8.32 (d, H2), 8.54 (d, H3), 9.59 (s, H5), $H_{H2-H3} = 2.56$ Hz. Elemental analysis calculated for $C_{11}H_{10}N_3I$: C 42.47, H 3.24, N 13.51. Found: C 42.30, H 3.30, N 13.42.

1-Methylimidazo[2,1-f]pyrido[3,2-d]pyrimidinium iodide (**4**)

Compound **2** (660 mg, 3.9 mmol) and 2 g (14 mmol) methyl iodide were heated in a sealed glass tube at 120°C for 1.5 h. The reaction mixture was suspended in 10 ml of chloroform and the product (1.01 g, 79%) was collected by filtration. M.p. 262–263°C (1-propanol). Elemental analysis calculated for $C_{10}H_9N_4I$: C 38.48, H 2.91, N 17.95. Found: C 38.23, H 2.95, N 17.70.

General procedure for the reactions of **3** *or* **4** *with active methylene compounds*

Active methylene compound (1 mmol) was dissolved in a solution of 1 mmol of sodium in 5–6 ml of anhydrous ethanol. To this solution 1 mmol of **3** or **4** was added. After the reaction was complete the solvent was removed in vacuo. The residue was treated with 5 ml of water and neutralized with 1 *N* HCl. The product was either collected by filtration or isolated by extraction with chloroform.

2-⟨2-{[2,2-Di(ethoxycarbonyl)vinyl]amino}phenyl⟩-1-methylimidazole (**5**)

Reaction conditions: 2 h at room temperature, the product (63 mg, 71%) was collected by filtration. M.p.: 83–85°C (chloroform—cyclohexane). MS (*m/e*): calculated 343.38, found 343 (M^+). ^{1}H NMR ($CDCl_3$) δ: 1.31 (t, CH_2CH_3), 1.35 (t, CH_2CH_3), 3.67 (s, CH_3), 4.22 (q, CH_2CH_3), 4.32 (q, CH_2CH_3), 6.98–7.53 (m, H3, H4, H5, H6, H4′, H5′), 8.44 (d, NHCH), $J_{CH2-CH3} = 7.1$ Hz, $J_{NH-CH} = 14$ Hz. Elemental analysis calculated for $C_{18}H_{21}N_3O_4$: C 62.96, H 6.16, N 12.24. Found: C 62.53, H 6.29, N 12.03.

2-{2-[(2,2-Dicyanovinyl)amino]phenyl}-1-methylimidazole (**6**)

Reaction conditions: 1 h at room temperature, the product (193 mg, 77%) was collected by filtration. M.p. 209–212°C (ethanol). MS (*m/e*): calculated 249.18, found 249 (M^+). ^{1}H NMR (*DMSO-d*$_6$) δ: 3.78 (s, CH_3), 7.0–7.79 (m, H3, H4, H5, H6, H4′, H5′), 8.68 (broad s, NHCH), $J_{H4'-H5'} = 1.4$ Hz. Elemental analysis calculated for $C_{14}H_{11}N_5$: C 67.45, H 4.44, N 28.09. Found: C 67.94, H 4.51, N 28.05.

2-⟨2-{[2,4-Dioxopentyliden-3)methyl]amino}phenyl⟩-1-methylimidazole (**7**)

Reaction conditions: **4** days at room temperature, the product was isolated by extraction with chloroform and recrystallized from chloroform—*n*-hexane (65 mg, 23%). M.p. 154–158°C. ^{1}H NMR ($CDCl_3$) δ: 2.29 (s, $COCH_3$), 2.47 (s, $COCH_3$), 3.61 (s, CH_3), 7.25–7.50 (m, H3, H4, H5, H6, H4′, H5′), 8.10 (d, NHCH), 12.97 (broad d, NHCH), $J_{NHCH} = 13.4$ Hz. Elemental analysis calculated for $C_{16}H_{17}N_3O_2$: C 67.83, H 6.05, N 14.83. Found: C 67.77, H 6.15, N 14.77.

2-⟨2-{[(5,5-Dimethyl-1,3-dioxocyclohexyliden-2)methyl]amino}phenyl⟩-1-methylimidazole (**8**)

Reaction conditions: heating under reflux for 3.5 h, the product (251 mg, 78%) was collected by filtration. M.p. 203–207°C (ethanol—diethylether). ^{1}H NMR ($CDCl_3$) δ: 1.05 [s, $C(CH_3)_2$], 2.38 (s, two CH_2), 3.64 (s, CH_3), 7.2–7.6 (m, H3, H4, H5, H6, H4′, H5′), 8.56 (d, NHC**H**), 13.24 (broad d, N**H**CH), J_{NHCH} = 14.0 Hz. Elemental analysis calculated for $C_{19}H_{21}N_3O_2$: C 70.57, H 6.55, N 12.99. Found: C 70.48, H 6.70, N 12.91.

3-{[2,2-Di(ethoxycarbonyl)vinyl]amino}-2-(1-methylimidazolyl-2)pyridine (**9**)

Reaction conditions: 7 days at room temperature, the product (204 mg, 60%) was collected by filtration. M.p. 108–110°C (ethanol—water). ^{1}H NMR (*DMSO-d*$_6$) δ: 1.25 (t, CH_2CH_3), 1.28 (t, CH_2CH_3), 4.01 (s, CH_3), 4.12 (q, CH_2CH_3), 4.27 (q, CH_2CH_3), 7.11 (d, H4′ or H5′), 7.35 (d, H4′ or H5′), 7.36 (broad d, H5), 7.96 (broad d, H4), 8.30 (d, NHC**H**), 8.33 (broad d, H6), 12.70 (d, N**H**CH), $J_{H4'-H5'}$ = 1.5 Hz, $J_{CH2-CH3}$ = 7.0 Hz, J_{CHNH} = 13.0 Hz, J_{H4-H5} = 8.5 Hz, J_{H5-H6} = 4.5 Hz. Elemental analysis calculated for $C_{17}H_{20}N_4O_4$: C 59.29, H 5.85, N 16.27. Found: C 59.38, H 5.91, N 16.36.

3-{[(2,4-Dioxopentyliden-3)methyl]amino}-2-(1-methylimidazolyl-2)pyridine (**10**)

Reaction conditions: 7 days at room temperature, the product (160 mg, 56%) was collected by filtration. M.p. 174–177°C (ethanol—diethylether). ^{1}H NMR ($CDCl_3$) δ: 2.38 (s, $COCH_3$), 2.54 (s, $COCH_3$), 4.07 (s, CH_3), 7.02 (broad s, H4′ or H5′) and 7.30 (broad s, H4′ or H5′), 7.29 (dd, H5), 7.73 (dd, H4), 8.15 (d, NHC**H**), 8.43 (dd, H6), 14.20 (broad d, N**H**CH), J_{H4-H5} = 8.5 Hz, J_{H4-H6} = 1.5 Hz, J_{H5-H6} = 4.5 Hz, J_{NHCH} = 13.0 Hz. Elemental analysis calculated for $C_{15}H_{16}N_4O_2$: C 63.37, H 5.67, N 19.71. Found: C 62.92, H 5.81, N 19.29.

3-[(2,2-Dicyanovinyl)amino]-2-(1-methylimidazolyl-2)pyridine (**11**)

Reaction conditions: 1 h at room temperature, the product was collected by filtration and recrystallized from ethanol (84 mg, 34%). M.p. 262–265°C. ^{1}H NMR (*DMSO-d*$_6$) δ: 4.07 (s, CH_3), 7.02 (d, H4′ or H5′), 7.35 (dd, H5), 7.36 (d, H4′ or H5′), 8.11 (deg. dd, H4), 8.34 (dd, H6), 8.82 (broad, C**H**NH), 13.50 (broad, CHN**H**), J_{H4-H5} = 8.0 Hz, J_{H5-H6} = 4.5 Hz, J_{H4-H6} = 1.5 Hz, $J_{H4'-H5'}$ = 1.5 Hz. Elemental analysis calculated for $C_{13}H_{10}N_6$: C 62.39, H 4.03, N 33.58. Found: C 62.65, H 4.01, N 33.36.

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