Chemistry of Heterocyclic Compounds, Vol. 43, No. 8, 2007

HALOHETEROCYCLIZATION OF 2-ALLYL(PROPARGYL)OXY-QUINOLINE-3-CARBALDEHYDES

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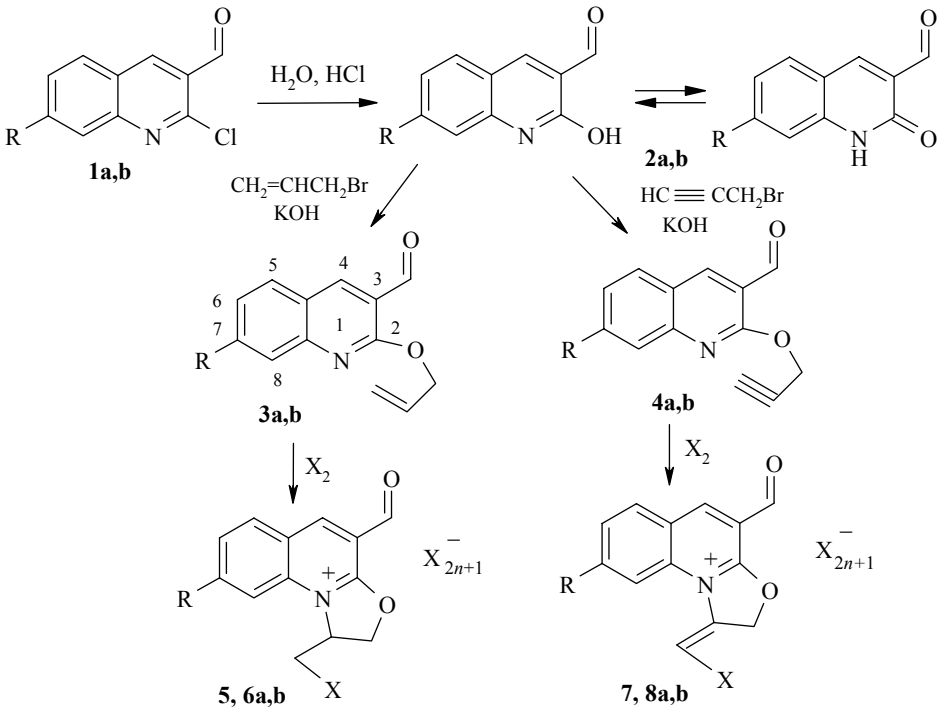
The reaction of 2-allyl(propargyl)oxyquinoline-3-carbaldehydes with halogens gives 1-bromomethyl(bromomethylidene)-4-formyl-1,2-dihydrooxazolo[3,2-a]quinolinium halides.

Keywords: 2-allyloxy-3-formylquinoline, 3-formyl-2-propargylquinoline, haloheterocyclization.

There are literature reports of the haloheterocyclization reactions of unsaturated quinoline ethers and thioethers [1] to give heterocyclic systems with oxa(thia)zolinium rings. In continuation of these studies we have selected the 2-allyl(propargyl)oxyquinoline-3-carbaldehydes **3, 4** as model compounds for this haloheterocyclization. These substrates were prepared by conversion of 2-chloro-3-formylquinolines **1** to the corresponding quinolones **2** by treatment with hydrochloric acid and subsequent alkylation using allyl(propargyl) bromides.



1–8 a R = H, **b** R = Me; **5**, **7** X = Br, n = 0; **6**, **8** X = I , n = 1

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Bromine and iodine were selected as electrophilic agents for the haloheterocyclization. The reactions of the allyl ethers **3** were carried out in acetic acid or methylene chloride with a twofold excess of the halogen. The resulting 3-halomethyl-2,3-dihydrooxazolo[3,2-*a*]quinolinium halides **5, 6** were treated with acetone to give the monobromide **5** and the triiodide **6**. Similar halogenation of the propargyl ethers **4** and work up of the precipitates obtained with acetone gave compounds **7** and **8**.

The ^{1}H NMR spectra of compounds **5** and **6** showed proton signals for the OCH_2 and CH_2Br groups as doublets at 5.2-5.4 and 4.1-4.3 ppm in good agreement with literature data [2]. The ^{1}H NMR spectra of compounds **7** and **8** showed doublet signals at 7.05-7.13 corresponding to the =CHX protons and multiplet signals for the OCH_2 protons at 5.36-5.60 ppm. This spectroscopic data agreed with that in the literature [3] and pointed to the formation of tricyclic condensed systems with an exocyclic double bond.

It was interesting to note that the haloheterocyclization of the propargyl ethers **4** did not proceed stereospecifically but gave a mixture of the geometric isomers **7** and **8**. According to ^{1}H NMR data the isomer ratio was 7:1. It is likely that the *E*-somer is principally formed, governed by a haloheterocyclization mechanism *via* a stage of electrophilic *trans* addition of halogen to the multiple carbon-carbon bond and subsequent cyclization at the nucleophilic center. The principal formation of the *E*-isomer is also explained by its high thermodynamic stability as shown by quantum-chemical calculations. The ^{1}H NMR spectrum also confirms the major formation of the *E*-isomer since the signal for the proton *cis* to the heteroatom resonates at lower field than that in the *trans* position, in agreement with literature data [4-6].

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian VXR-300 (300 MHz) instrument using a mixture of DMSO-d_6 and CCl_4 as solvent and TMS as internal standard.

2-Chloro-3-formylquinoline (1a) and **2-Chloro-3-formyl-7-methylquinoline (1b)** were sinthesized as reported in [7], **3-Formylquinol-2-one (2a)** and **3-Formyl-7-methylquinol-2-one (2b)** as in [8].

Preparation of Ethers 3, 4 (General Method). A mixture of the quinolone **2a,b** (1 mmol), NaOH (1.2 mmol) in water (3 ml), and 2-propanol (30 ml) was refluxed for 1 h. The solution obtained was treated with the alkyl bromide (1.5 mmol) (80% solution of propargyl bromide in toluene) and refluxed for 2 h. The precipitate was filtered off and recrystallized from ethanol or DMF.

2-Allyloxy-3-formylquinoline (3a). Yield 42%; mp 110-113ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.9 (2H, d, *J* = 2, OCH_2); 5.1 (2H, dd, *J* = 15, *J* = 9, $=CH_2$); 5.9 (1H, m, =CH); 7.3 (1H, t, *J* = 7, H-6); 7.46 (1H, d, *J* = 7, H-5); 7.68 (1H, t, *J* = 8, H-7); 7.9 (1H, d, *J* = 8, H-8); 8.5 (1H, s, H-4); 10.3 (1H, s, CHO). Found, %: N 6.43. $C_{13}H_{11}NO_2$. Calculated, %: N 6.57.

2-Allyloxy-3-formyl-7-methylquinoline (3b). Yield 33%; mp 121-123ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.65 (3H, d, CH_3); 4.7 (2H, d, *J* = 2, OCH_2); 5.0 (2H, dd, *J* = 15, *J* = 8, $=CH_2$); 6.01 (1H, m, =CH); 7.55 (1H, d, *J* = 8, H-6); 7.8 (1H, d, *J* = 8, H-5); 8.05 (1H, s, H-8); 8.85 (1H, s, H-4); 10.3 (1H, s, CHO). Found, %: N 6.09. $C_{14}H_{13}NO_2$. Calculated, %: N 6.17.

3-Formyl-2-propargyloxyquinoline (4a). Yield 58%; mp 193-195ºC (DMF). ^{1}NMR spectrum, δ, ppm (*J*, Hz): 3.0 (1H, s, ≡CH); 5.1 (2H, s, CH_2); 7.35 (1H, t, *J* = 7, H-6); 7.6 (1H, d, *J* = 7, H-5); 7.75 (1H, t, *J* = 8, H-7); 7.9 (1H, d, *J* = 8, H-8); 8.4 (1H, s, H-4); 10.25 (1H, s, CHO). Found, %: N 6.55. $C_{13}H_{11}NO_2$. Calculated, %: N 6.64.

3-Formyl-7-methyl-2-propargyloxyquinoline (4b). Yield 57%; mp 215-217ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.65 (3H, s, CH_3); 2.9 (1H, s, ≡CH); 5.0 (2H, s, CH_2); 7.45 (1H, d, *J* = 8, H-6); 7.65 (1H, d, *J* = 8, H-5); 8.05 (1H, s, H-8); 8.45 (1H, s, H-4); 10.20 (1H, s, CHO). Found, %: N 6.19. $C_{14}H_{11}NO_2$. Calculated, %: N 6.22.

Preparation of Bromides 5, 7 (General Method). A solution of bromine (2 mmol) in methylene chloride (5 ml) was added with constant stirring to a solution of the allyl ether **3** or propargyl ether **4** (1 mmol) in methylene chloride (10 ml) and DMF (1 ml). After 2 h the precipitate was filtered off, treated with acetone, and again filtered.

1-Bromomethyl-4-formyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium Bromide (5a). Yield 70%; mp 220-222ºC . ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.1 (2H, d, *J* = 7, CH_2Br); 5.3 (2H, d, *J* = 8, OCH_2); 6.1 (1H, m, CH); 7.45 (1H, t, *J* = 7, H-7); 7.55 (1H, d, *J* = 7, H-6); 7.75 (1H, t, *J* = 8, H-8); 8.05 (1H, d, *J* = 8, H-9); 8.7 (1H, s, H-5); 10.45 (1H, s, CHO). Found, %: N 3.69. $C_{13}H_{11}Br_2NO_2$. Calculated, %: N 3.75.

1-Bromomethyl-4-formyl-8-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium Bromide (5b). Yield 65%; mp 228-230ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.80 (3H, s, CH_3); 4.2 (2H, d, *J* = 6, CH_2Br); 5.35 (2H, d, *J* = 8, OCH_2); 6.0 (1H, m, CH); 7.5 (1H, d, *J* = 7, H-7); 7.75 (1H, d, *J* = 7, H-6); 8.15 (1H, s, H-9); 8.65 (1H, s, H-5); 10.35 (1H, s, CHO). Found, %: N 3.55. $C_{14}H_{13}Br_2NO_2$. Calculated, %: N 3.62.

1-Bromomethylidene-4-formyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium Bromide (7a). Yield 59%; mp 137-138ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.35 (2H, m, OCH_2); 7.05 (1H, 2s, =CHBr); 7.40 (1H, t, *J* = 7, H-7); 7.50 (1H, d, *J* = 7, H-6); 7.75 (1H, t, *J* = 8, H-8); 8.05 (1H, d, *J* = 8, H-9); 8.55 (1H, s, H-5); 10.35 (1H, s, CHO). Found, %: N 3.69. $C_{13}H_9Br_2NO_2$. Calculated, %: N 3.77.

1-Bromomethylidene-4-formyl-8-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium Bromide (7b). Yield 55%; mp 141-143ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.75 (3H, s, CH_3); 5.40 (2H, m, OCH_2); 7.08 (1H, 2s, =CHBr); 7.45 (1H, d, *J* = 8, H-7); 7.65 (1H, d, *J* = 8, H-6); 8.15 (1H, s, H-9); 8.5 (1H, s, H-5); 10.45 (1H, s, CHO). Found, %: N 3.60. $C_{14}H_{11}Br_2NO_2$. Calculated, %: N 3.64.

Preparation of Iodides 6, 8 (General Method). A solution of iodine (2 mmol) in acetic acid (20 ml) was added with constant stirring to a solution of the allyl ether **3** or propargyl ether **4** (1 mmol) in acetic acid (10 ml). After 2-3 h the precipitate was filtered off, treated with acetone, and again filtered.

4-Formyl-1-iodomethyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium Triiodide (6a). Yield 52%; mp 172-174ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.35 (2H, d, *J* = 8, CH_2I); 5.45 (2H, d, *J* = 6, OCH_2); 6.1 (1H, m, CH); 7.45 (1H, t, *J* = 7, H-7); 7.65 (1H, d, *J* = 7, H-6); 7.75 (1H, t, *J* = 8, H-8); 7.95 (1H, d, *J* = 8, H-9); 8.7 (1H, s, H-5); 10.5 (1H, s, CHO). Found, %: N 1.88. $C_{13}H_{11}I_4NO_2$. Calculated, %: N 1.94.

4-Formyl-1-iodomethyl-8-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium Triiodide (6b). Yield 45%; mp 178-180ºC.

1-Bromomethylidene-4-formyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium Triiodide (8a). Yield 59%; mp 137-138ºC.

1-Bromomethylidene-4-formyl-8-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium Triiodide (8b). Yield 57%; mp 225-227ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.73 (3H, s, CH_3); 5.60 (2H, m, OCH_2); 7.13 (1H, 2s, =CHI); 7.25 (1H, d, *J* = 8, H-7); 7.45 (1H, d, *J* = 8, H-6); 8 15 (1H, s, H-9); 8.55 (1H, s, H-5); 10.24 (1H, s, CHO). Found, %: N 2.00. $C_{14}H_{11}I_4NO_2$. Calculated, %: N 1.91.

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