DOI 10.1007/s10593-015-1736-z

Chemistry of Heterocyclic Compounds **2015**, *51*(6), 560–562

Kröhnke's salts and their ester analogs in reactions with ethoxymethylidene derivatives of CH acids

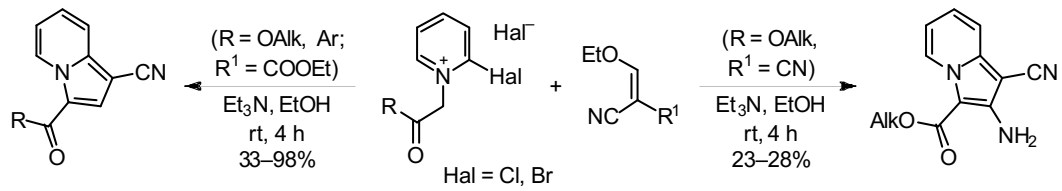
Dmitry A. Ponomarenko[1], Gennadii E. Khoroshilov[1]*, Denis A. Krasnikov[2]

[1] *Taras Shevchenko Lugansk National University, 1 Gogolya Sq., Starobelsk 92700, Lugansk obl., Ukraine; e-mail: khoroshilov@inbox.ru*

[2] *Scientific Manufacturing Enterprise "NIIPAV", 62 Khimikov St., Volgodonsk 347366, Rostov obl., Russia; e-mail: krasnikov.denis@gmail.com*

Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2015, *51*(6), 560–562

Submitted June 4, 2015
Accepted June 28, 2015

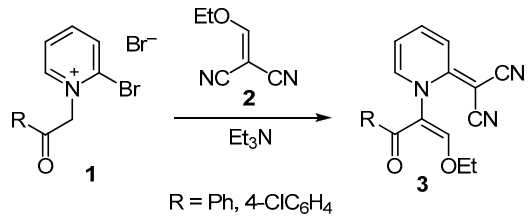


2-Bromo(chloro)-*N*-(2-ethoxy(methoxy)-2-oxoethyl)pyridinium halides react with (ethoxymethylidene)malononitrile and ethyl (ethoxymethylidene)cyanoacetate to afford ethyl(methyl) 2-amino-1-cyanoindolizine-3-carboxylate and ethyl(methyl) 1-cyanoindolizine-3-carboxylate, respectively.

Keywords: methyl 2-amino-1-cyanoindolizine-3-carboxylate, 2-bromo(chloro)-*N*-(2-ethoxy(methoxy)-2-oxoethyl)pyridinium salts, ethyl 1-cyanoindolizine-3-carboxylate, (ethoxymethylidene)malononitrile, ethyl (ethoxymethylidene)cyanoacetate.

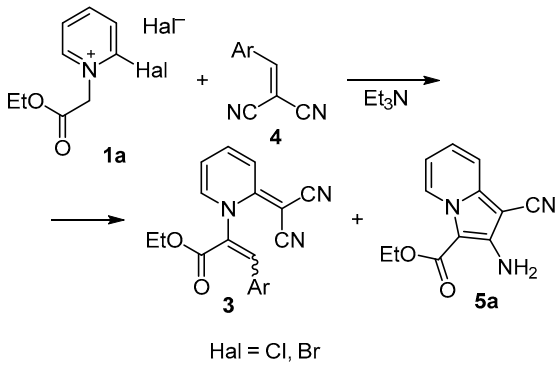
In 1996, I. A. Aitov et al.[1] described two examples of a reaction of a Kröhnke's salt **1** with (ethoxymethylidene) malononitrile (**2**) to form the olefin metathesis product **3**. The structure of the synthesized compounds was confirmed by X-ray structural analysis; in solid state compounds **3** were in the form of *Z*-isomers (Scheme 1).

Scheme 1



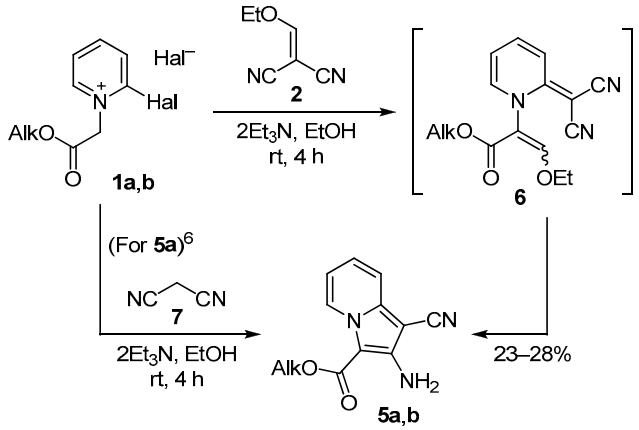
More recently, we have shown[2,3] that a by-product 2-amino-1-cyanoindolizine **5a** may form along with the products of the metathesis **3** in the reaction of (arylmethylidene)malononitriles **4** with Kröhnke's salt **1a** possessing an ester substituent on the nitrogen atom (Scheme 2).

Scheme 2



The reactivity of ester analogs of Kröhnke's salts **1a**,**b**[4,5] with (ethoxymethylidene)malononitrile (**2**) has not been studied, so the aim of this work was to explore these reactions. 2-Amino-1-cyanoindolizines **5a**,**b** were obtained as a result of the reaction of salts **1a**,**b** with compound **2** in low yields (23-28%). Presumably, the reaction proceeds *via* the intermediate **6** (Scheme 3). Indolizine **5a** had previously[6] been prepared by us by reacting salt **1a** with malononitrile (**7**).

Scheme 3

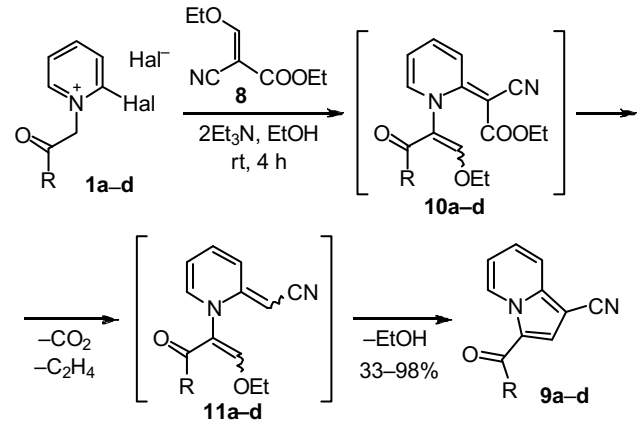


a Alk = Et, **b** Alk = Me; Hal = Cl, Br

The reaction of salts **1a**–**d** with ethyl (ethoxymethylidene)-cyanoacetate **8** afforded 1-cyanoindolizines **9a-d** (Scheme 4).

We assumed that decarboxylation, characteristic to enamine esters,[8] occurs after the stage of formation of metathesis products **10**. As a result, intermediates **11** form,

Scheme 4



a R = OEt, **b** R = OMe, **c** R = Ph, **d** R = 4-MeOC$_6$H$_4$; Hal = Cl, Br

cyclization of which gives indolizines **9a-d** in moderate to high yields.

Characteristic to ^{1}H NMR spectra of indolizines **9a-d** is the downfield shift of the signal of the H-5 proton (9.40–9.89 ppm) by comparison to the analogous signal in the spectra of compounds **5a,b** (9.25 ppm).[4,5] Apparently, this can be explained by an exclusive non-covalent interaction between the H-5 proton of the heterocycle with the oxygen atom of the carbonyl group. The latter is presumptively forming an intramolecular hydrogen bond with the amino group in indolizines **5a**,**b**.

To conclude, a novel convenient method for the synthesis of 3-acyl and 3-alkoxycarbonyl-1-cyanoindolizines and their 2-amino derivatives has been developed based on the reaction of ethyl (ethoxymethylidene)-cyanoacetate or (ethoxymethylidene)malononitrile with Kröhnke's salts possessing an acyl or ester group in the substituent at the nitrogen atom.

Experimental

IR spectra were registered on an IKS-40 spectrometer in petroleum jelly (compounds **9a**,**b**) and a Perkin Elmer Spectrum One spectrometer in KBr pellets (remaining compounds). ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance II-400 (400 and 100 MHz, respectively) in DMSO-d_6, with TMS as internal standard. Mass spectra were recorded on a Varian 1200 L mass spectrometer, EI ionization (70 eV) with direct sample injection. Elemental analysis was performed on a Eurovector EA-3000 Elemental analyzer. Melting points were determined on a Kofler bench. Monitoring of the reaction progress and assessment of the purity of synthesized compounds was done by TLC on Silufol UV-254 plates in acetone–hexane, 3:5 eluent system, visualization with UV or in an iodine chamber.

Synthesis of compounds 5a,b, 9a–d (General method). Nitrile **2** (0.244 g, 2.0 mmol; compounds **5a**,**b**) or ester **8** (0.338 g, 2.0 mmol; compounds **9a**–**d**) and Et$_3$N (0.56 ml, 4.0 mmol) were added to a solution of 2-halopyridinium salts **1a**–**d** (2 mmol) in EtOH (8 ml). The reaction mixture was stirred at room temperature for 4 h, then kept at 0–2°C for 24 h. The formed precipitate was filtered off, washed with MeOH (compounds **5b**, **9b**) or EtOH (remaining compounds), and dried.

Ethyl 2-amino-1-cyanoindolizine-3-carboxylate (5a). Yield 0.105 g (23%), colorless crystals, mp 154–155°C (EtOH) (mp 151 °C (EtOH)[4]).

Methyl 2-amino-1-cyanoindolizine-3-carboxylate (5b). Yield 0.121 g (28%), brown powder, mp 147–149°C (MeOH) (mp 148–150°C (MeOH)[5]).

Ethyl 1-cyanoindolizine-3-carboxylate (9a). Yield 0.295 g (69%), orange needles, mp 70–71°C (EtOH). IR spectrum, ν, cm^{-1}: 1699 (C=O), 2214 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.37 (3H, t, *J* = 7.1, OCH$_2$C<u>H</u>$_3$); 4.35 (2H, q, *J* = 7.1, OC<u>H</u>$_2$CH$_3$); 7.21 (1H, t, *J* = 7.0, H-6); 7.47–7.51 (1H, m, H-7); 7.80–7.82 (2H, m, H-2,8); 9.46 (1H, d, *J* = 7.0, H-5). ^{13}C NMR spectrum, δ, ppm: 14.7 (OCH$_2$<u>C</u>H$_3$); 60.9 (O<u>C</u>H$_2$CH$_3$); 83.0 (C-1); 115.2 (CN); 115.6 (C-3); 116.2; 117.6; 124.9; 127.4; 128.3; 140.4 (C-8a); 160.0 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 214 [M]$^+$ (64), 187 (32), 186 (100). Found, %: C 67.31; H 4.69; N 13.02. $C_{12}H_{10}N_2O_2$. Calculated, %: C 67.28; H 4.71; N 13.08.

Methyl 1-cyanoindolizine-3-carboxylate (9b). Yield 0.132 g (33%), white powder, mp 145–146°C (MeOH). IR spectrum, ν, cm^{-1}: 1692 (C=O), 2218 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.85 (3H, s, OCH$_3$); 7.24 (1H, t, *J* = 7.1, H-6); 7.50–7.53 (1H, m, H-7); 7.83 (1H, d, *J* = 8.9, H-8); 7.95 (1H, s, H-2); 9.40 (1H, d, *J* = 7.1, H-5). ^{13}C NMR spectrum, δ, ppm: 52.2 (CH$_3$); 83.1 (C-1); 115.1 (CN); 115.7 (C-3); 116.3; 117.7; 125.2; 127.5; 128.4; 140.5 (C-8a); 160.5 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 200 [M]$^+$ (58), 168 (56), 141 (53), 49 (100). Found, %: C 66.08; H 4.06; N 13.95. $C_{11}H_8N_2O_2$. Calculated, %: C 66.00; H 4.03; N 13.99.

3-Benzoylindolizine-1-carbonitrile (9c). Yield 0.482 g (98%), white powder, mp 120–122°C (EtOH). IR

spectrum, ν, cm^{-1}: 1601 (C=O), 2225 (CN). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.33 (1H, t, *J* = 7.0, H-6); 7.55 (2H, t, *J* = 7.4, Ar); 7.61–7.65 (2H, m, H-7, H Ph); 7.75–7.80 (3H, m, H-2, H Ph); 7.91 (1H, d, *J* = 8.9, H-8); 9.89 (1H, d, *J* = 7.0, H-5). ^{13}C NMR spectrum, δ, ppm: 83.9 (C-1); 115.2 (CN); 116.6; 117.3; 122.4 (C-3); 128.6 (C Ph); 128.9; 129.0 (C Ph); 129.1; 129.4; 132.1; 138.7; 140.7 (C-8a); 184.2 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 246 $[M]^+$ (100). Found, %: C 78.07; H 4.13; N 11.45. $C_{16}H_{10}N_2O$. Calculated, %: C 78.04; H 4.09; N 11.38.

3-(4-Methoxybenzoyl)indolizine-1-carbonitrile (9d). Yield 0.353 g (64%), beige powder, mp 191–192°C (EtOH). IR spectrum, ν, cm^{-1}: 1620 (C=O), 2222 (C≡N). ^1H NMR spectrum, δ, ppm (*J,* Hz): 3.89 (3H, s, OCH_3); 7.04 (2H, d, *J* = 8.6, H Ar); 7.27 (1H, t, *J* = 7.0, H-6); 7.60 (1H, t, *J* = 7.8, H-7); 7.75 (1H, s, H-2); 7.80 (2H, d, *J* = 8.6, H Ar); 7.86 (1H, d, *J* = 8.9, H-8); 9.81 (1H, d, *J* = 7.0, H-5). ^{13}C NMR spectrum, δ, ppm: 55.6 (OCH_3); 83.4 (C-1); 113.9 (C Ar); 115.4 (CN); 116.2; 117.2; 122.5; 128.4; 128.5; 129.0; 131.0; 131.4 (C Ar); 140.5; 162.6 (C Ar); 183.1 (C=O). Mass spectrum, *m*/*z* (I_{rel},%): 276 $[M]^+$ (90), 135 (100). Found, %: C 73.86; H 4.33; N 10.11. $C_{17}H_{12}N_2O_2$. Calculated, %: C 73.90; H 4.38; N 10.14.

References

1. Aitov, I. A.; Nesterov, V. N.; Sharanin, Yu. A.; Struchkov, Yu. T. *Russ. Chem. Bull.* **1996**, *45*, 417. [*Izv. Akad. Nauk*, *Ser. Khim.* **1996**, 434.]
2. Khoroshilov, G. E. *Chem. Heterocycl. Compd.* **2001**, *37*, 1141. [*Khim. Geterotsikl. Soedin.* **2001**, 1245.]
3. Tverdokhleb, N. M.; Khoroshilov, G. E.; Zubatyuk, R. I.; Shishkin, O. V. *Chem. Heterocycl. Compd.* **2013**, *49*, 720. [*Khim. Geterotsikl. Soedin.* **2013**, 772.]
4. Khoroshilov, G. E.; Tverdokhleb, N. M.; Brovarets, V. S.; Babaev, E. V. *Tetrahedron* **2013**, *69*, 4353.
5. Tverdokhleb, N. M.; Khoroshilov, G. E. *Chem. Heterocycl. Compd.* **2015**, *51*, 56. [*Khim. Geterotsikl. Soedin.* **2015**, *51*, 56.]
6. Tverdokhleb, N. M.; Khoroshilov, G. E. *Chem. Heterocycl. Compd.* **2013**, *49*, 1141. [*Khim. Geterotsikl. Soedin.* **2013**, 1226.]
7. Rigo, B.; Jabre, S.; Maliar, F.; Couturier, D. *Synth. Commun.* **1985**, *15*, 473.