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Cascade synthesis of pyrido[3,2-*a*]indolizines by reaction of Kröhnke–Mukaiyama salts with malononitrile dimer

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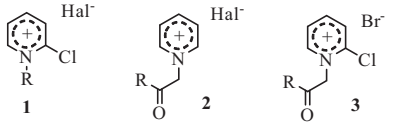
ABSTRACT

An efficient protocol for the synthesis of highly functionalized 2-aminoindolizines and pyrido[3,2-*a*]indolizines has been achieved via the reaction of *N*-RC(O)CH_2-2-chloropyridinium bromides with 2-amino-1,1,3-tricyanopropene in the presence of Et_3N. The reaction of *N*-allyl-2-chloropyridinium bromide with 2-amino-1,1,3-tricyanopropene in the presence of Et_3N gives 3-[1-allylpyridin-2(1*H*)-ylidene]-2-amino-prop-1-ene-1,1,3-tricarbonitrile, which could be cyclized to give [2-amino-(2-amino-3-vinylindolizin-1-yl)methylene]malononitrile upon treatment with KOH–DMF.

Since *N*-alkylpyridinium salts were introduced in the 1930s by Kröhnke,[1] these compounds have attracted the attention of chemists as useful and easily available building blocks for organic synthesis. The Mukaiyama reagents[2] **1** and Kröhnke salts[3,4] **2** are among the most commonly used reagents in heterocyclic synthesis leading to a variety of substances (Scheme 1). Since the Mukaiyama condensation reagent (*N*-methyl-2-chloropyridinium iodide) was first introduced in 1975 for the esterification of carboxylic acids,[5] various *N*-alkyl-2-halopyridinium salts have been widely used as coupling and dehydrating reagents.[1,6] The Kröhnke salts **2** have been recognized as important precursors to pyridinium ylides.[3,4,7–11] The successful synthesis of Kröhnke-type pyridines has also been reported through the reaction of *N*-phenacylpyridinium salts with α,β-unsaturated ketones in the presence of ammonium acetate.[12]

Our interests have been focused on the chemistry of *N*-phenacyl(2-halopyridinium) salts **3** combining both Mukaiyama 2-chloropyridinium and Kröhnke *N*-(β-ketoalkyl)pyridinium functionalities.[13,14] Recently, we reported the reaction of the Kröhnke–Mukaiyama salts **3** with active methylene nitriles[14–19] to form 2-aminoindolizines in good yields. Indolizines are widely represented in nature and have become of particular interest for drug design because of their wide ranging biological activities.[20–22] These points encouraged us to continue our research and we turned our attention to the reaction of the Kröhnke–Mukaiyama salts **3** with malononitrile dimer **4**. Malononitrile dimer (2-amino-1,1,3-tricyanopropene) (**4**) is an easily accessible and cheap active methylene compound which tends to react by cascade mechanisms to give a variety of polyheterocyclic ensembles.[23–25]



Scheme 1. Reactive *N*-alkylpyridinium species.

When the starting compounds were treated with a twofold excess of Et_3N at ambient temperature, indolizines **5a–d** were formed in 53–68% yields as a result of the nucleophilic substitution of Cl with the anion of dimer **4**, followed by a spontaneous Thorpe–Ziegler-type of cyclization (Scheme 2, Table 1). It is noteworthy that ambient conditions are crucial for the successful synthesis of indolizines **5**. Thus, the short-term heating of indolizines **5a–d** with lower alcohols leads to mixtures of the starting compounds **5** and the products of malononitrile elimination, namely

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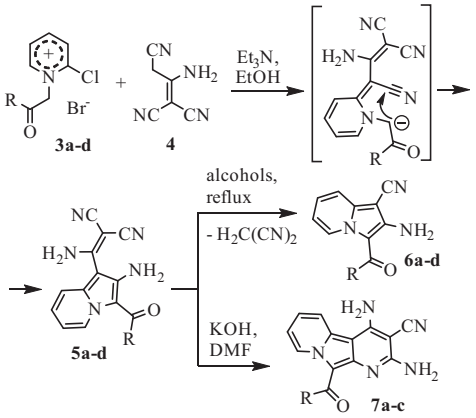


Scheme 2. Synthesis of indolizines **5**, **6**, and pyridoindolizines **7**.

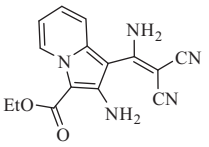
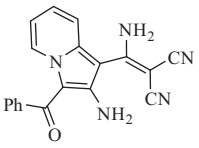
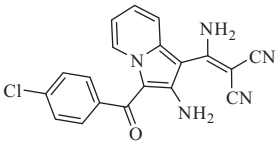
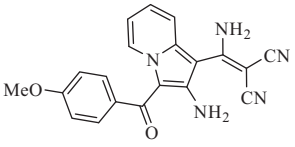
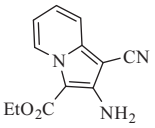
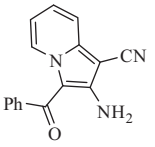
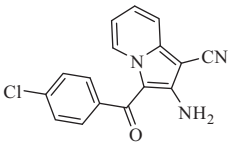
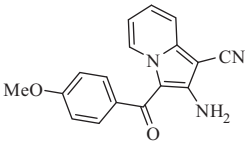
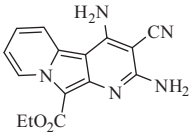
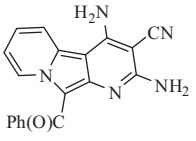
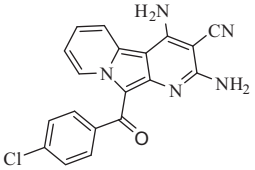
2-amino-3-cyanoindolizines **6a–d**. Moreover, we failed to isolate indolizine **5d** in pure form due to its spontaneous decomposition *in statu nascendi*, even under mild conditions (0 °C). Any sample of compound **5d** obtained by the reaction of dimer **4** with the Kröhnke–Mukaiyama salt **3d** contained significant amount of 2-amino-3-cyanoindolizine **6d**.

Indolizines **6** were also prepared by independent synthesis from malononitrile and 2-chloropyridinium salts **3**.[14] Finally, when treated with one equivalent of KOH (10% aq) in DMF, indolizines **5a–c** underwent the expected *exo-dig*-cyclization to give pyrido[3,2-*a*]indolizines **7a–c** in good yields (83–87%).

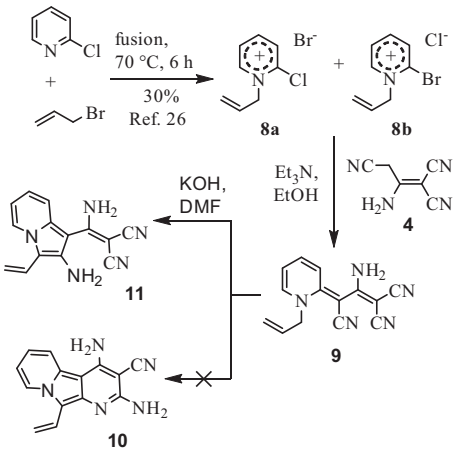
The structures of indolizines **5**, **6** and pyrido[3,2-*a*]indolizines **7** were elucidated on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass (EI) spectra. The IR spectra of indolizines **5** revealed two absorption bands corresponding to nitrile stretches (2192–2198 and 2210–2215 cm^{-1}), while only one band corresponding to C≡N stretching vibrations was observed in the IR spectra of pyrido[3,2-*a*]indolizines **7**. In the IR spectra of compounds **5**, the observed shift of the C=O band frequency to 1658–1662 cm^{-1} clearly indicated strong conjugation of the C=O double bond with the enamine NH_2–C=C moiety. The ^{1}H NMR spectra of compounds **5** showed signals due to the two NH_2 groups at δ 5.24–5.90 for the indolizine C(2)NH_2 and at δ 8.24–8.33 for the H_2NC=C$(CN)_2$ fragment.

Recently, we reported that treatment of 2-chloropyridine with allyl bromide leads to a mixture (~1:1) of chloride **8a** and bromide **8b** in a modest yield (30%).[26] We found that the halide mixture **8a** + **8b** easily reacts with the malononitrile dimer **4** in the presence of two equivalents of Et_3N to form bright-orange polyene intermediate **9** in 75% yield (Scheme 3). In contrast to the Kröhnke–Mukaiyama salts **3**, the spontaneous formation of indolizine Thorpe–Ziegler cyclization products was not observed in this case, probably due to the relatively weak electron-withdrawing effect of the vinyl group. It was believed that polyene **9** existed as the (*Z*)-isomer only. This suggestion could be rationalized by steric reasons, since the less bulky CN group and the allyl fragment were expected to be *cis*-oriented with respect to one another. It can be supposed that the *cis*-orientation would favor the Thorpe–Ziegler cascade cyclization to form the pyrrole ring and the second pyridine ring of the polycyclic ensemble, so we attempted to obtain the pyrido[3,2-*a*]indolizine derivative **10** by the treatment of polyene **9** with stronger bases than Et_3N. However, the only product isolated upon treatment with aqueous KOH in DMF was indolizine **11**. The latter was found to be a quite stable compound and it failed to cyclize into pyridoindolizine **10**, even under harsh conditions. The IR spectrum of **11** showed the same absorption bands at 2189 and 2207 cm^{-1} corresponding to the typical stretches of two conjugated C≡N groups.

Table 1
Structures and yields of compounds **5–7**

Compound	R	Product	Yield (%)
5a	OEt		55
5b	Ph		53
5c	4-ClC$_6$H$_4$		68
5d	4-MeOC$_6$H$_4$		66
6a	OEt		27
6b	Ph		35
6c	4-ClC$_6$H$_4$		43
6d	4-MeOC$_6$H$_4$		38
7a	OEt		87
7b	Ph		89
7c	4-ClC$_6$H$_4$		83

In summary, a simple and efficient protocol for the synthesis of previously unknown [2-amino-(2-aminoindolizin-1-yl)methylene]malononitriles and 2,4-diaminopyrido[3,2-*a*]indolizine-3-carbonitriles



Scheme 3. Synthesis of compounds **9** and **11**.

has been developed, enabling a new approach to functionalized indolizines.[27,28] The indolizines obtained constitute an important structural subunit of a variety of biologically active compounds and could serve as useful building blocks in the construction of polyheterocyclic ensembles.

Supplementary data

Supplementary data (detailed experimental procedures, analytical data and spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.046.

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27. *General procedure for the synthesis of compounds* **5**: Et_3N (0.28 mL, 2.0 mmol) was added to a mixture of 2-chloropyridinium salt **3a–d** and malononitrile dimer **4** (0.132 g, 1.0 mmol) in EtOH (10 mL). The mixture was stirred for 4 h at ambient temperature and then was kept in a refrigerator for 24 h. The precipitate was filtered off and washed with EtOH. Compounds **5a–c** were obtained in analytically pure form. Compound **5d** was found to be relatively unstable and we failed to obtain it in pure form.
Synthesis of 2-amino-1-cyano-3-RC(O)-indolizines (**6a–d**): A suspension of indolizine **5a–d** (1.0 mmol) in *n*-BuOH (15.0 mL) was heated with stirring until a solution formed. The mixture was filtered through a paper filter and left for 24 h at 20 °C. The precipitated solid was filtered off and washed sequentially with *n*-BuOH and EtOH to give indolizines **6a–d**. 2-Amino-1-cyano-3-ethoxycarbonylindolizine (**6a**) was obtained in 27% yield, the physical data and spectra match those data reported earlier.[17] 2-Amino-3-benzoylindolizine-1-carbonitrile (**6b**) and 2-amino-3-(4-chlorobenzoyl)indolizine-1-carbonitrile (**6c**) were obtained in 35% and 43% yields, respectively. Their physical data and spectra were in agreement with previously reported data.[14]
General procedure for the synthesis of 2,4-diaminopyrido[3,2-a]indolizines (**7a–c**). Indolizines **5a–c** (1.0 mmol) were dissolved in DMF (5–7 mL), then 10% aqueous KOH (0.52 mL, 1.0 mmol) was added dropwise to the stirred solution. The mixture was stirred for 4 h at ambient temperature, diluted with H_2O (5–7 mL), and left for 24 h in a refrigerator (0 °C). The precipitate was filtered off and washed with H_2O and EtOH.
28. *Representative compounds synthesized. Ethyl 2-amino-1-(1-amino-2,2-dicyanovinyl)-indolizine-3-carboxylate* (**5a**): Yield 55%, yellow powder, mp 221–222 °C. FTIR (KBr): 3439, 3356, 3205, 2214, 2198, 1658 cm^{-1}. ^1H NMR (400 MHz, CCl_4–DMSO-d_6), δ 1.40 (t, J = 7.0, 3H, CH_3), 4.38 (q, J = 7.0, 2H, OCH_2), 5.90 (br s, 2H, NH_2), 6.92 (m, 1H, H-6), 7.24–7.28 (m, 1H, H-7), 7.36 (d, 1H, J = 8.8, H-8), 8.24 (d, J = 11.2, 2H, NH_2), 9.24 (br pseudo-s, 1H, H-5). ^{13}C NMR (101 MHz, CCl_4–DMSO-d_6), δ 14.5, 48.9, 59.0, 92.4, 99.7, 111.9, 115.6, 116.2, 116.8, 125.5, 127.6, 135.9, 145.1, 160.8, 163.5. MS (EI, 70 eV) m/z (I, %): 295 (64) $[M]^+$, 249 (43), 223 (100) $[M-COOEt]^+$. Anal. Calcd for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 61.04; H, 4.38; N, 23.68.
Ethyl 2,4-diamino-3-cyanopyrido[3,2-a]indolizine-10-carboxylate (**7a**): Yield 87%, off-white powder, mp 246 °C. ^1H NMR (400 MHz, CCl_4–DMSO-d_6), δ 1.47 (t, J = 7.1, 3H, CH_3), 4.38 (q, J = 7.1, 2H, OCH_2), 6.00 (br s, 2H, NH_2), 6.97 (br s, 2H, NH_2), 7.17–7.23 (m, 1H, H-7), 7.39–7.45 (m, 1H, H-6), 8.44 (d, J = 8.6, 1H, H-5), 9.86 (d, J = 6.9, 1H, H-8). ^{13}C NMR (101 MHz, CCl_4–DMSO-d_6), δ 15.1, 59.6, 93.0, 96.1, 100.3, 112.5, 116.2, 116.8, 117.4, 126.1, 128.1, 136.5, 154.8, 161.5, 164.1. MS (EI, 70 eV) m/z (I, %): 295 (69) $[M]^+$, 223 (100) $[M-COOEt]^+$. Anal. Calcd for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 61.05; H, 4.46; N, 23.70.