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Reactivity of Newly Synthesized N-Substituted α-Halopyridinium Salts with Malonodinitrile Dimer

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Abstract
The present study has investigated the reactivity of various N-derivatives of quaternary 2-halopyridinium salts with malononitrile dimer. The results demonstrate the formation of the corresponding 1,2-dihydropyridines, as well as a complete cascade transformation via the Thorpe–Ziegler reaction leading to pyridoindolizines.

Keywords: 2-Halopyridinium Salts, Malononitrile Dimer, Indolizines, Cyclisation Reaction, Stereoselectivity, Thorpe–Ziegler Reaction, Pyridoindolizines

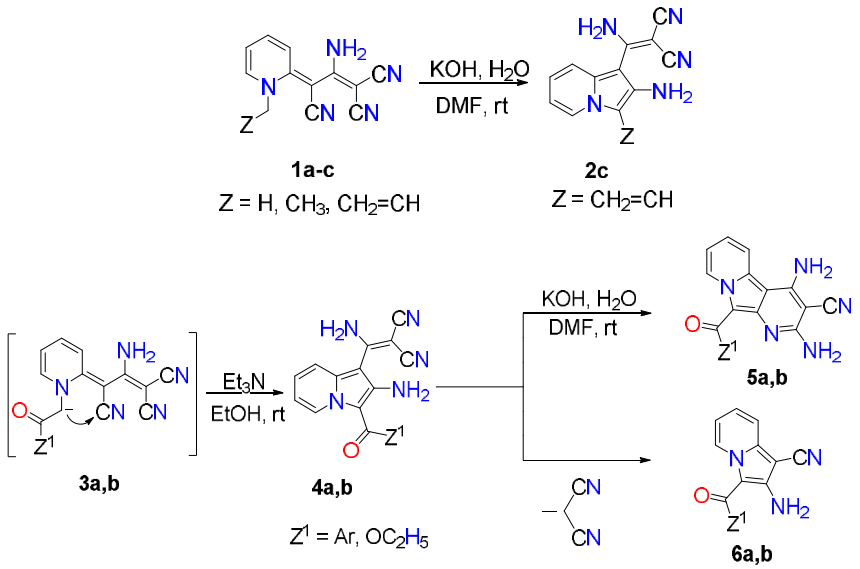
Indolizines represent a class of heterocyclic compounds that have attracted considerable attention in the field of medicinal chemistry, primarily due to their multifaceted biological activities. Despite their structural similarity to indoles, which predominate in numerous commercial pharmaceuticals, indoles have not yet been developed into marketed drugs. Nevertheless, their potential in various therapeutic areas continues to be explored. The chemistry of indolizines has attracted attention for two main reasons. Firstly, the ease with which they can be prepared, and secondly, due to the high physiological activity of the derivatives, particularly in the treatment of Alzheimer's disease [1].

Indolizines derivatives have also demonstrated significant anti-cancer properties [2]. It has been reported that the compounds in question inhibit tubulin polymerization, a process that is crucial for the process of cell division. This inhibition results in the compounds exhibiting potent anticancer activity against a variety of tumor cells. Specific compounds, such as dithiolated indolizine, have been shown to be effective in inducing apoptosis and cell cycle taking in non-small cell lung cancer cells. This highlights their potential as therapeutic agents against cancer [3].

In the continuation of the study of the reactivity of Krönke-Mukayama salts polyfunctional 2-amino-1,1,3-tricyanopropene (malonodinitrile dimer) In the subsequent study, the cascade transformations of Krönke-Mukayama salts with the participation of malonodinitrile dimer were examined [4-9]. It was demonstrated that the interaction of *N*-alkyl-substituted Mukayama salts with the malonodinitrile dimer resulted in the formation of the corresponding 1,2-dihydropyridines 1a-c with a Z-configuration [10]. When attempting to cyclize the formed compounds by Thorpe-Ziegler, only 1c has sufficient CH-acidity, and substituted 2-aminoindolizine is formed. The CH acidity of compounds 1a,b is not sufficient for further intramolecular cyclization [11].

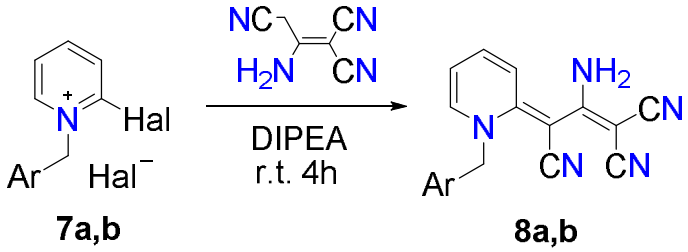
The interaction of Krönke-Mukayama salts, which contain a 1,4-bielectrophilic chain Hal-C=N^+-CH_2-COR, with a malonodinitrile dimer in the presence of triethylamine does not allow the isolation of 1,2-dihydropyridines 3a,b. This is due to their high reactivity. However, further intramolecular interaction occurs with the formation of the corresponding substituted indolizines 4a, b. Treatment of these with an equimolar amount of aqueous KOH solution in high yields leads to facile conversion into pyrido[3,2-a] indolizines 5a, b (Scheme 1). It was found that indolizines 4a,b are unstable and

can easily lose a molecule of malonodinitrile to form compounds. 6a, b. In the present study, the synthetic potential of the N-substituted salts of 2-halogenopyridinium previously obtained was investigated in greater depth. These salts were synthesised with methylenated acetonitrile derivatives, specifically the polyfunctional dimer of malononitrile [12,13].



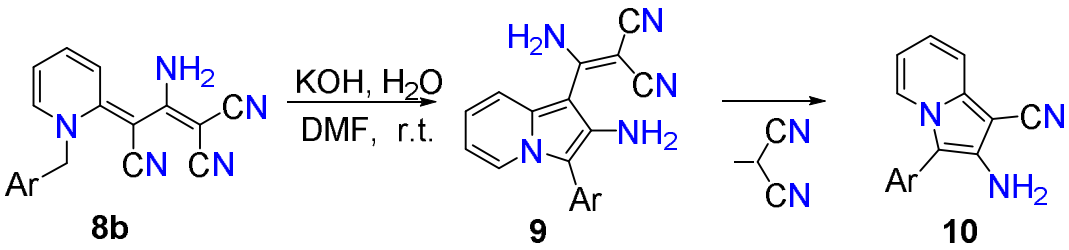
Scheme 1: Transformation of 1,2-Dihydropyridines

Utilising a combination of salts 7a,b (a = Ph, b = 4-BrPh) in the reaction with 2-amino-1,1,3-tricyanopropene, with more selective DIPEA in comparison to triethylamine, we were able to isolate *N*-substituted 1,2-dihydropyridines 8a,b (Scheme 2) [12]. The bright orange colour of compounds 8a,b is indicative of the presence of a relatively extensive chain of conjugated double bonds in the molecule.



Scheme 2: Formation of 1,2-Dihydropyridines

In the H NMR spectra of compounds 8a,b, the signals of methylene protons resonating at 5.46-5.47 ppm are clearly traced, the amino group is shifted to a weaker field and appears as a singlet at 7.32-7.34 ppm [14]. The position of protons H-6 and H-3 of the pyridine cycle should also be emphasized. For H-3, the typical value of J = 8.4-9.2 Hz, while for H-6, J = 5.8-7.2 Hz is characteristic: for compounds 8a,b, H-3 J = 8.2-8.4 Hz, H-6 J = 6.3 Hz [15].

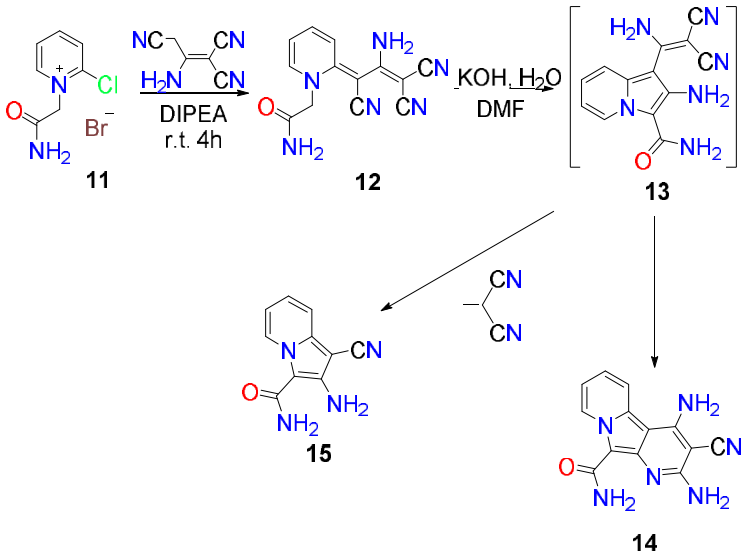


Scheme 3: The formation of Indolizines is Achieved Through the Thorpe Reaction, Concomitant with the Partial Elimination of Malononitrile

During the attempted Thorpe-Ziegler cyclization of 1,2-dihydropyridine 8a, we found out that it was not possible to isolate the corresponding indolizine. This can be explained by the relatively low acidity of the methylene protons. In contrast to compound 8a, the CH acidity of the methylene protons of compound 8b increases, apparently due to the -I effect of the halogen in the para-position. This promotes intramolecular cyclization to form substituted 2-aminoindolizine

9. Concurrently, partial elimination of the malonodinitrile molecule with the formation of 10 is a possibility, as evidenced by the spectral data [12]. (Scheme 3)

The 1H NMR spectrum of 9 reveals significant changes. Firstly, the protons of the methylene group disappear, while the protons of the amino group at position 2 of the formed indoleamine cycle appear in a stronger field and resonate at 4.69 ppm. Secondly, the protons of the amino group of the dicyanoethylene fragment at position 1 appear as two broad ended singlet at 8.23 and 8.31 ppm. Resonance of the protons of H-5 of compound 9 is observed in a stronger field compared to compounds 4a,b, and the protons resonate as a doublet at 8.15 ppm. (J = 6.9 Hz), as is also observed in compound 2c.



Scheme 4: Cascade Transformations Involving Salt 11 and Malonodinitrile Dimer

The salt 11 behaves and reacts with the malonodinitrile dimer in two different ways in reaction [13]. On the one hand, like Mukayama salts, which makes 1,2-dihydropyridine 12. On the other hand, it acts like typical Krönke-Mukayama salts, which makes pyrido[3,2-a]indolizine 14 when it reacts with a water solution of KOH. This probably happens through the formation of an intermediate compound 13 (Scheme 4). It was not possible to separate compound 13 as an individual entity. The transformation of this compound into 14 is only possible under specific conditions, whereas the removal of the malonodinitrile molecule results in the formation of 15. Consequently, the isolation of 14 from 1,2-dihydropyridine 12 using a water-based solution of KOH in DMF also led to the presence of significant amounts of indolizine 15.

The structure of compounds 14 and 15 was successfully deduced through the analysis of the spectral data. A detailed examination of the spectral data reveals that the protons of the amino groups in pyridoindolizine 14 at position 4 resonate at 5.45 ppm and at position 2 at 7.10 ppm, manifesting as two singlets. The amine group is evident in a weaker field, with a resonance of 8.39 ppm. The amino group in indolizine 15 has a resonance of 5.96 ppm, while the protons of the amide fragment appear as a singlet at 7.09 ppm [13].

In summary, the reactivity of the Kroenke-Mukayama salts with the malonodinitrile dimer is dependent upon the electronic nature of the substituent. Thus, the N-benzylpyridinium salt behaves similarly to the N-alkyl-substituted salts, forming only 1,2-dihydropyridine, which is not capable of further Thorpe transformation. The *N*-(4-bromobenzyl) substituted salt reacts similarly to the *N*-allyl substituted salt, forming the corresponding indolizine, which can easily eliminate the malonodinitrile molecule. The N-carboxamidopyridinium salt reacts with the malonodinitrile dimer as a typical Kroenke-Mukayama salt, cascading into pyrido[3,2-a] indolizine.

References

1. Lemercier, G., Fernandez-Montalvan, A., Shaw, J. P., Kugelstadt, D., Bomke, J., Domostoj, M., ... & Leroy, D. (2009). Identification and characterization of novel small molecules as potent inhibitors of the plasmodial calcium-dependent protein kinase 1. Biochemistry, 48(27), 6379-6389.
2. Sardaru, M. C., & Mangalagiu, I. I. (2023). Synthesis and anticancer properties of new indolizinic derivatives. In New frontiers in natural product chemistry (pp. 32-32).
3. Li, G., Wu, X., Sun, P., Zhang, Z., Shao, E., Mao, J., ... & Huang, H. (2021). Dithiolation indolizine exerts viability suppression effects on A549 cells via triggering intrinsic apoptotic pathways and inducing G2/M phase arrest. Biomedicine & Pharmacotherapy, 133, 110961.
4. Babaev, E. V. (2011). 2-halogen-substituted pyridinium-N-phenacylides and their cycloiminium and acyclic analogs: 1. Synthesis of the parent salts, their betaine-ylides, and oxazolium analogs. Review Journal of Chemistry, 1(2), 161-191.

5. Babaev, E. V. (2016). Cyclization reactions of Kröhnke–Mukaiyama salts. Chemistry of Heterocyclic Compounds, 52, 666-674.
6. Khoroshilov, G. E., Tverdokhleb, N. M., Brovarets, V. S., & Babaev, E. V. (2013). Simple stepwise route to 1-substituted 2-amino-3-ethoxycarbonylindolizines. Tetrahedron, 69(21), 4353-4357.
7. Tverdokhleb, N. M., & Khoroshilov, G. E. (2013). Stepwise Synthesis of 2-Amino-3-Vinylindolizines Using a Mixture of N-Allyl-2-Halopyridinium Halides and CH Acid Derived from Acetonitrile. Chemistry of Heterocyclic Compounds, 49(8), 1141-1145.
8. Mittelbach, M. An Improved and Facile Synthesis of 2-Amino-1,1,3-Tricyanopropene. Monatshefte für Chemie - Chemical Monthly 1985, 116 (5), 689–691.
9. Доценко, В. В., & Семенова, А. М. (2018). Реакции гетероциклизации с участием димера малононитрила (2-аминопропен-1, 1, 3-трикарбонитрила). Chemistry of Heterocyclic Compounds, 54(11), 989-1019.
10. Tverdokhleb, N. M., Khoroshilov, G. E., & Dotsenko, V. V. (2014). Cascade synthesis of pyrido [3, 2-a] indolizines by reaction of Kröhnke–Mukaiyama salts with malononitrile dimer. Tetrahedron Letters, 55(48), 6593-6595.
11. Khoroshilov, G., Demchak, I., & Saraeva, T. (2008). Stereoselective synthesis of 2- [1-methylpyridin-2 (1H)-ylidene] malononitrile derivatives. Synthesis, 2008(10), 1541-1544.
12. Kashner, O. Y., Bocharov, K. O., & Khoroshilov, G. E. (2024). The synthesis of 2-amino-3-benzylindolizines with using the mixture of halides N-benzyl-2-halogenpyridines and CH-acids–derivatives acetonitrile. Tetrahedron, 152, 133837.
13. Kashner, O. Y., Bocharov, K. O., & Khoroshilov, G. E. (2024). The synthesis of 2-amino-3-carboxamideindolizines with using pyridinium salt and C-nucleophiles–derivatives acetonitrile. Results in Chemistry, 12, 101861.
14. Pretsch, E., Bühlmann, P., Affolter, C., Pretsch, E., Bhuhlmann, P., & Affolter, C. (2000). Structure determination of organic compounds (p. 108). Berlin: Springer-Verlag.
15. Pauls, H., & Kröhnke, F. (1977). Untersuchungen a 2-Chlorpyridinium-Salzen, III. Umsetzungen mit CH-aciden Verbindungen und übergang in Indolizine. Chemische Berichte, 110(4), 1294-1303.