

Highly diastereoselective multicomponent synthesis of pyridinium-substituted piperidin-2-ones with three stereogenic centres

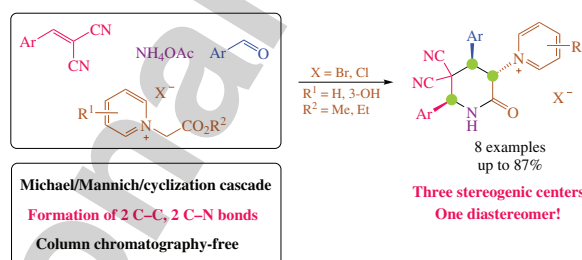
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The Michael–Mannich–cyclization cascade of dicyano olefins, 1-(2-alkoxy-2-oxoethyl)pyridin-1-ium halogenides, aromatic aldehydes and ammonium acetate provides convenient stereoselective formation of (4,6-diaryl-5,5-dicyano-2-oxo-piperidin-3-yl)pyridin-1-ium halogenides with three stereogenic centres. Ammonium acetate plays dual role acting as a base and as a nitrogen source.



Keywords: multicomponent reactions, ylides, pyridinium salts, piperidin-2-ones, ammonium acetate, stereoselectivity.

Dedicated to Academician M. P. Egorov, director of N. D. Zelinsky Institute of Organic Chemistry, on his 70th birthday.

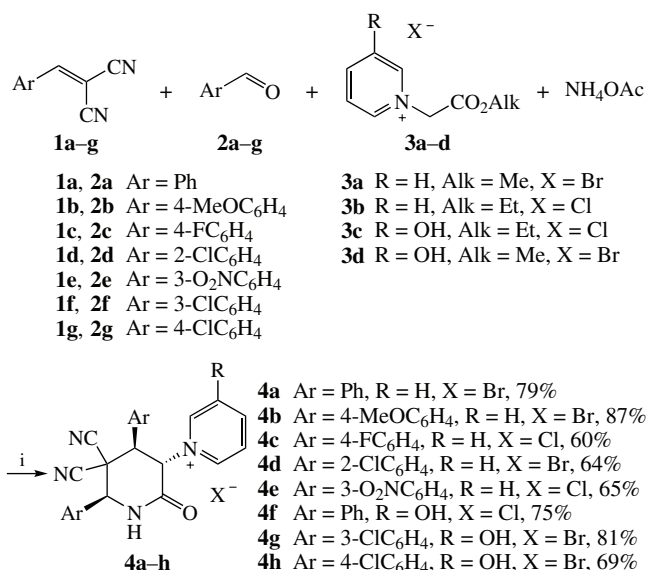
Pyridinium salts represent a preferred group of naturally and synthetically important compounds¹ and exhibit high antibacterial^{2–5} and anticancer⁶ activities. Their derivatives may be potential pharmacophores for the development of new anti-tubercular candidates.⁷ As a result of rational molecular modifications, some pyridinium salt derivatives not only have a remarkable antibacterial capability but demonstrate low toxicity to non-target organisms.⁸ Piperidine derivatives are close analogues of pharmacologically active compounds, mainly antiviral and antitumour. Such molecules have found application as synthetic drugs of wide pharmacological action: analgesics, anesthetics, antipsychotics, antidepressants, opiate receptor agonists or anticancer drugs.^{9–13} Compounds with piperidinone scaffold can inhibit MDM2 protein, which plays a role in tumour development.¹⁴

Over the past ten years, multicomponent reactions have proven to be a convenient and environmentally friendly method for the synthesis of complex molecules including polymers and polysubstituted N-containing heterocycles.^{15–19} Such processes are advantageous compared to multi-step synthesis due to simplicity and availability of reagents, decrease in the number of synthesis stages, simplification of the isolation of final compounds, reduction in solvent consumption. Previously we performed multicomponent syntheses of substituted piperidines with NH₄OAc or aqueous ammonia as a nitrogen source for the formation of the piperidine ring.^{20–22}

Herein, we present a four-component synthesis of novel piperidine-containing pyridinium salts bearing three stereogenic centres. Refluxing of dicyano-substituted olefins **1a–g**, aromatic aldehydes **2a–g** (both with electron-withdrawing and electron-donating substituents), 1-(2-alkoxy-2-oxoethyl)pyridin-1-ium halogenides **3a–d** and ammonium acetate leads to products of type **4** (Scheme 1). The procedure was optimized in the course

of the preparation of polysubstituted 2-hydroxy-2-trifluoromethylpiperidines.²³

The NMR spectra of products **4** showed only one set of signals suggesting stereoselective formation of individual diastereomers. Their structures were confirmed by NMR spectroscopy. The structure of representative compound **4d** was ultimately established by X-ray diffraction study (Figure 1).[†] This study indicated that configuration of three stereogenic centres of **4d**



Scheme 1 Reagents and conditions: i, Michael acceptor **1** (2 mmol), aldehyde **2** (2 mmol), 1-(2-alkoxy-2-oxoethyl)pyridin-1-ium halogenide **3** (2 mmol), NH₄OAc (4 mmol), MeOH (10 ml), reflux, 2 h. Isolated yields are given.

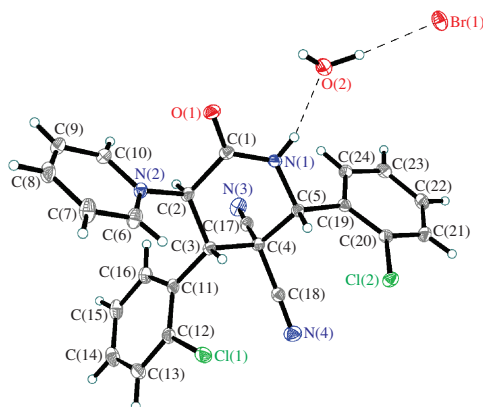
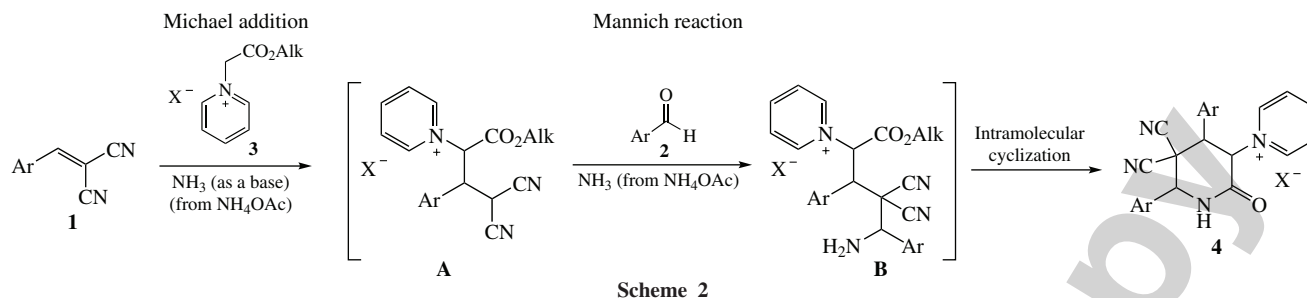


Figure 1 Molecular structure of compound **4d**.

should be assigned as *3SR,4SR,6RS*. In this case, the molecule would acquire conformation when bulky aryl substituents are located in sterically least hindered positions relative to each other.

A possible reaction pathway is shown in Scheme 2. The multicomponent reaction between Michael acceptors **1**, aldehydes **2**, 1-(2-alkoxy-2-oxoethyl)pyridin-1-ium bromide **3** and ammonium acetate is a three-step domino process. The first step of the process is the Michael addition of ylide generated from **3** to the electron-deficient olefin **1** to form the Michael adduct **A**. The subsequent Mannich reaction of **A**, aldehyde **2** and ammonia, which is formed from ammonium acetate, leads to intermediate **B**. The latter would undergo intramolecular cyclization with the formation of (4,6-diaryl-5,5-dicyano-2-oxopiperidin-3-yl)pyridin-1-ium halogenides which were identified and characterized in this work for the first time.

In conclusion, we have developed a four-component stereoselective single-step synthesis of pyridinium salts with piperidin-2-one moieties utilizing Michael acceptors, 1-(2-alkoxy-2-oxoethyl)pyridin-1-ium halogenides, aromatic aldehydes and ammonium acetate as a nitrogen source for the piperidine cycle. Our method allows one to obtain stereo-

selectively (4,6-diaryl-5,5-dicyano-2-oxopiperidin-3-yl)pyridin-1-ium halogenides with three stereogenic centres as single diastereomers. The pure products are isolated by simple filtration, and column chromatography is entirely avoided.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.10.007.

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† Crystal data for **4d**. $C_{24}H_{19}BrCl_2N_4O_2$ ($M = 546.24$), $T = 99.99(10)$ K, $\lambda = 1.54184$ Å, monoclinic, space group $P1_21/c1$, $a = 13.08353(7)$, $b = 10.91141(5)$ and $c = 16.00256(7)$ Å, $\alpha = 90^\circ$, $\beta = 96.2874(4)^\circ$, $\gamma = 90^\circ$, $V = 2270.781(18)$ Å³, $Z = 4$, $d_{calc} = 1.598$ g cm⁻³. Absorption coefficient 4.888 mm⁻¹, $F(000) = 1104$, crystal size $0.19 \times 0.08 \times 0.05$ mm³, θ range for data collection 3.398 to 77.828° , index ranges $-16 \leq h \leq 16$, $-13 \leq k \leq 13$, $-16 \leq l \leq 20$, reflections collected 50661, independent reflections 4846 ($R_{int} = 0.0404$), observed reflections 4801, completeness to θ 67.684° (100.0%). Absorption correction semi-empirical from equivalents, max. and min. transmission 1.00000 and 0.64472, refinement method full-matrix least-squares on F^2 , data/restraints/parameters 4846/0/375, goodness-of-fit on $F^2 = 1.055$. Final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0246$, $wR_2 = 0.0651$, R indices (all data): $R_1 = 0.0247$, $wR_2 = 0.0653$, extinction coefficient 0.00030(7), largest diff. peak and hole 0.557 and -0.371 e Å⁻³.

CCDC 2213725 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk>.