An expedient synthesis of a picolinamide-based betain bearing a 3-sulfonatopropyl substituent

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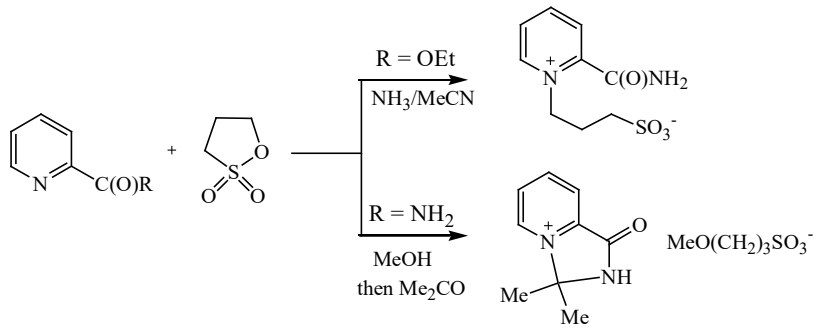
3-[2-(Aminocarbonyl)pyridinium-1-yl]propane-1-sulfonate, a promising medicinal betain, was prepared by a one-pot synthesis with a 89% yield by *N*-alkylation of ethyl picolinate with 1,3-propanesultone in MeCN followed by ammonolysis. A similar reaction in MeOH followed by the treatment with acetone afforded a novel 3,3-dimethyl-1-oxo-2,3-dihydro-1*H*-imidazo[1,5-*a*]pyridin-4-ium 3-methoxypropane-1-sulfonate.



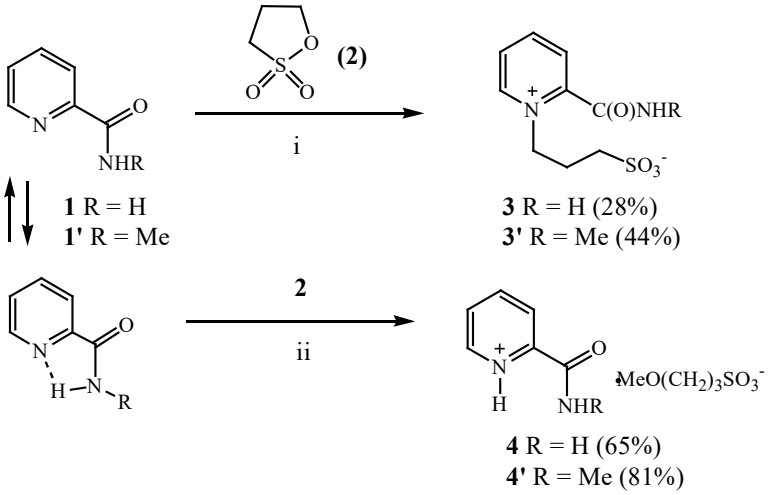
Keywords: picolinic acid derivatives, sulfobetains, sultones, alkylation, pyridinium salts, imidazo[1,5-*a*]pyridin-4-ium salts, NMR and FT–IR spectroscopy; X-ray study.

Over the last decade, the development of multi-target drugs has raised considerable interest because of their advantages in the treatment of multifactor diseases and health conditions.[1–3] The main direction of our work is the design of drugs for the treatment of neurodegenerative disorders [4–

[6], which remain among the top-ranked causes of mortality worldwide.[7] The potential building blocks for these drugs include pyridinecarboxylic acids and their functional derivatives, in particular, the products of the reaction of picolinamide **3** with 1,3-propanesultone.[8]

Although the biological functions of picolinic acid are not fully understood, its derivatives show a broad range of biological activity, including antimicrobial, neuroprotective, immunomodulatory and antiproliferative action.[9–15]

In our previous work, it was shown that the direct reaction of picolinamides **1** and **1'** with 1,3-propanesultone **2** afforded betains **3** and **3'**, respectively. The reaction yields were moderate, which could be a result of intramolecular hydrogen bonding in the substrate (Scheme 1).[8] Higher temperatures favored the formation of by-products **4** and **4'**.

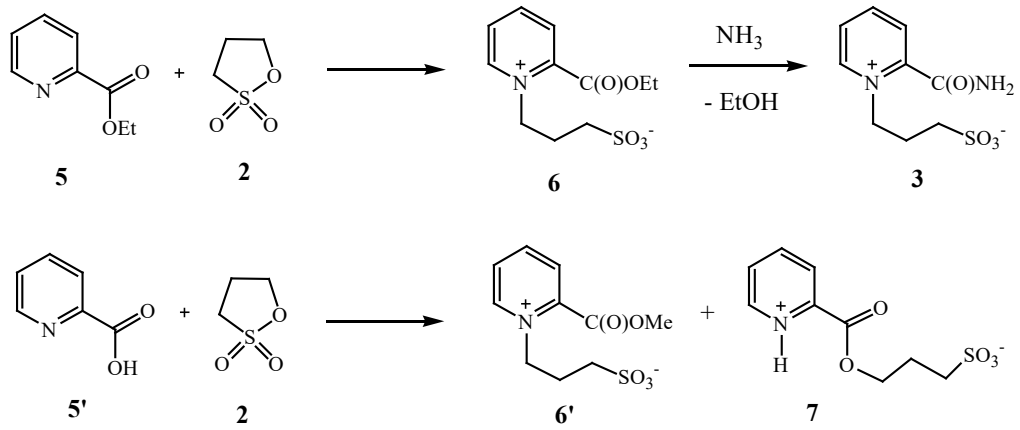


Scheme 1 *Reagents and conditions:* i, MeOH, room temperature, 4 h; ii, MeOH, 40 °C, 4 h

The higher yields of isomeric sulfobetains prepared from nicotinamide and isonicotinamide were attributed to the absence of hydrogen bonding in the substrates.[8]

In order to optimize the synthesis of biologically significant sulfobetains derived from picolinamides, the reactions of compounds **5** and **5'** with 1,3-propanesultone under various conditions (solvents and reaction temperatures) were studied.

The reaction of ethyl picolinate **5** with 1,3-propanesultone **2** in boiling acetonitrile produces propanesulfonate **6** with a yield of 74% (Scheme 2, Table 1, entry 2).



Scheme 2 *Reagents and conditions:* see Table 1.

Table 1 Optimization of synthesis of sulfobetain **3**

Entry	Reactant	Solvent	*T*/°C	Product	Yield, %
1	**1**	MeOH	~20	**3**	28 (Ref. 8)
2	**5**	MeCN	82	**6**	74
3	**6**	NH_3 (aq.)	~20	**3**	64
4[a]	**5**	MeCN, then NH_3 (aq.)	82; ~20	**3**	89
5	**5**	EtOH, then NH_3 (aq.)	78; ~20	**3**	23
6	**5'**	MeOH	~20	**7**	25
7	**5'**	MeOH	64	**6'**+**7**	28+72

[a] One-pot combination of steps of the entries 2 and 3

Salt **6** crystallizes as a 1:1 hydrate (Figure 1).[1] All bond lengths and angles in **6** fall within the ranges typical for pyridine derivatives and aliphatic sulfoacids.

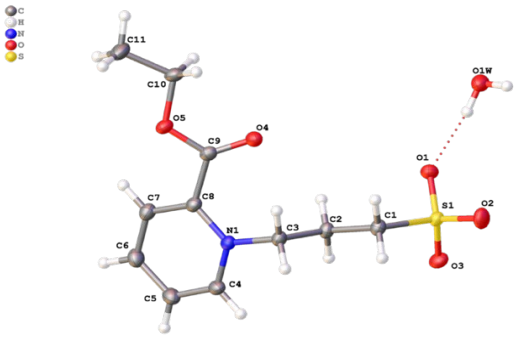


Figure 1 *Molecular structure of monohydrate* **6** *showing thermal ellipsoids at the 50% probability level.*

The pyridine ring and acetate group in **6** are not coplanar, with the angle between corresponding planes of 28.80(5)°. In crystal, the alkylsulfonate groups of compound **6** and solvated

‡ *Crystal data for* **6**. Crystals of **6** ($C_{17}H_{15}NO_5S$, H_2O, M = 291.31) are monoclinic, space group $P2_1/n$, at 100 K: a = 11.644(2), b = 8.1330(16) and c = 15.090(3) Å, V = 1330.5(5) Å^3, Z = 4, d_{calc} = 1.766 g cm^{-3}, μ(MoKα) = 0.308 mm^{-1}, $F(000)$ = 616 reflections were measured, and 11697 independent reflections (R_{int} = 0.0547) were used in a further refinement. The refinement converged to wR_2 = 0.1064 and GOF = 1.038 for all independent reflections [R_1 = 0.097 was calculated against F for 5178 observed reflections with $I > 2\sigma(I)$]. X-ray diffraction datasets for **6** were collected on in Kurchatov Centre for Synchrotron Radiation and Nanotechnology using 'Belok' beamline.

water molecules form centrosymmetric dimers with eight-membered rings via O–H...O bonds (Figure 2).

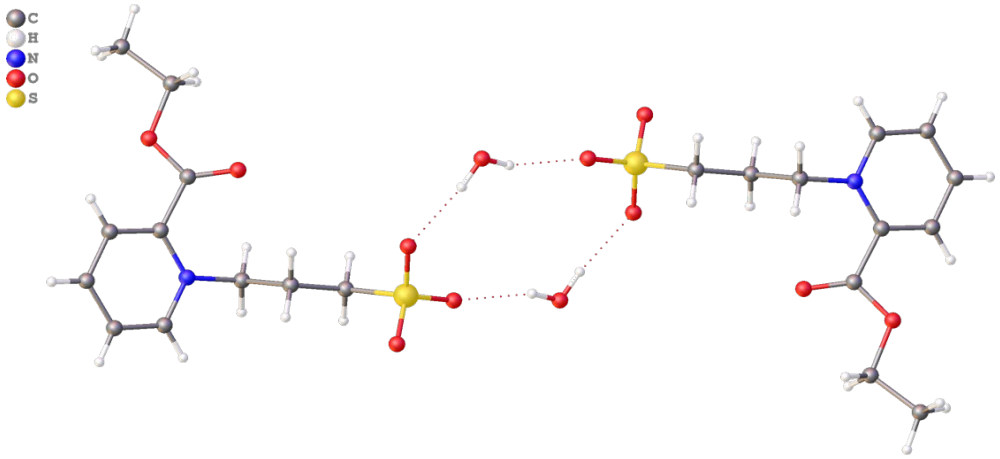


Figure 2. *Centrosymmetric dimers with eight-membered rings formed via O–H...O bonds in crystal of* ***6****.*

The subsequent reaction of propanesulfonate **6** with aqueous ammonia produces carbamoylsulfonate **3** with a 64% yield (Table 1, entry 3), which is significantly higher than that reported earlier (28%, Table 1, entry 1). Finally, the one-pot synthesis of **3** from ethyl picolinate **5**, 1,3-propanesultone and aqueous ammonia gives the highest yield of the target product (89%, Table 1, entries 2 and 3).

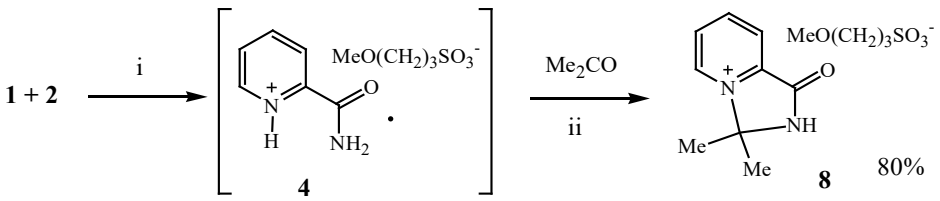
At ambient temperature, picolinic acid **5'** reacts with 1,3-propanesultone in methanol to produce propanoxysulfonate **7** with a 25% yield (Table 1, entry 6).

The formation of **7** is probably caused by the screening effect of an intramolecular H-bond involving hydrogen of the carboxyl group and an endocyclic nitrogen atom. Note that isonicotinic acid, in which such an interaction is impossible, reacts with 1,3-propanesultone to afford the product of *N*-alkylation with a 62% yield.[16]

The same reaction in boiling methanol (Table 1, entry 7) yields a mixture that shows three signals of carbonyl groups (at 159.88, 162.18 and 164.79 ppm) in the ^{13}C NMR spectrum (see Supplementary Materials). The ^{1}H NMR spectrum of that mixture shows one singlet (at 4.07 ppm) of methoxy group. Based on a comparative analysis of experimental and theoretically calculated spectra ^{1}H, ^{13}C NMR, the mixture contains sulfonates **6** and **7** along with unreacted acid **5'** and the open form of 1,3-propanesultone, $CH_3O(CH_2)_3SO_3H$.

This type of chemical transformation is similar to those observed in the reactions of carboxylates with 1,3-propanesultone in methanol or without solvent at 120–150 °C, yielding mixtures of 3-acyloxypropanesulfonic acids with other products.[16]

The addition of acetone to a solution of salt **4** leads to a previously unknown type of heterocyclic salts with a fragment of 4-imidazoline (compound **8**, yield 80%, Scheme 3).



Scheme 3 *Reagents and conditions:* i, MeOH, reflux, 3 h; ii, acetone, reflux, 1.5 h.

In conclusion, the optimization of the synthesis of promising biologically active sulfobetains derived from pyridinecarboxylic acids led to the development of a two-stage synthetic route that afforded picolinamide derivatives with high yields. The treatment of a by-product with acetone afforded the first example of a novel type of heterocyclic salts with a fragment of 4-imidazoline. According to PASS Online[17], the latter compound is likely to demonstrate immunostimulatory and antitumor activity.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.___

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