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

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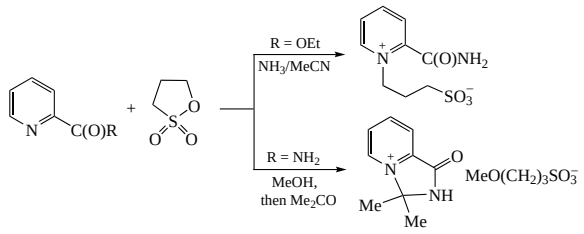
3-[2-(Aminocarbonyl)pyridinium-1-yl]propane-1-sulfonate, a promising medicinal betain, was prepared by a one-pot synthesis with a 89% yield *via N*-alkylation of ethyl picolinate with 1,3-propanesultone in MeCN followed by ammonolysis. The reaction involving picolinamide in MeOH followed by the treatment 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.

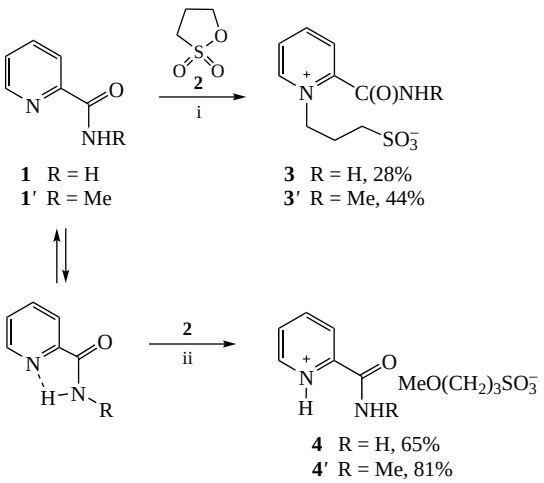


Keywords: picolinic acid derivatives, sulfobetains, sultones, alkylation, pyridinium salts, imidazo[1,5-*a*]pyridin-4-ium salts, NMR and FT–IR spectroscopy, X-ray study.

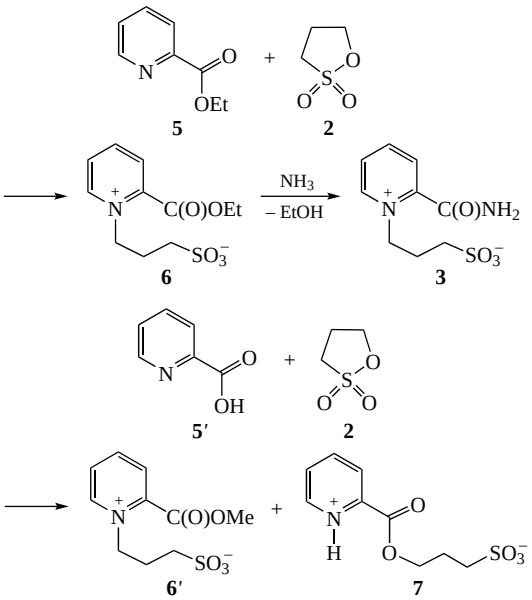
Over the last decade, the development of multi-target drugs became of considerable interest because of their advantages in the treatment of multifactor diseases and health conditions.[1–3] The main direction of our works was the design of drugs for the treatment of neurodegenerative disorders[4–6] which 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 between picolinamide **1** and 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] Previously,[8] we have shown that the direct reaction of picolinamides **1** and **1′** with 1,3-propanesultone **2** afforded betains **3** and **3′**, respectively (Scheme 1). The product yields were moderate, which could be a result of intramolecular hydrogen bonding in the substrate. Higher temperatures favored the formation of *H*-pyridinium by-products **4** and **4′**. 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



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



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.

compounds **5** and **5′** with 1,3-propanesultone under various conditions (solvents and reaction temperatures) were studied. In fact, the reaction of ethyl picolinate **5** with 1,3-propanesultone **2** in boiling acetonitrile produced propanesulfonate **6** with a yield of 74% (Scheme 2, Table 1, entry 2).

Salt **6** crystallizes as a 1:1 hydrate (Figure 1).† All bond lengths and angles in **6** fall within the ranges typical of pyridine derivatives and aliphatic sulfo acids. The pyridine ring and carboxy group in **6** are not coplanar, with the angle between corresponding planes being 28.80(5)°. In the crystal, its alkylsulfonate groups and solvated water molecules form centrosymmetric dimers with eight-membered rings *via* O–H···O bonds (Figure 2).

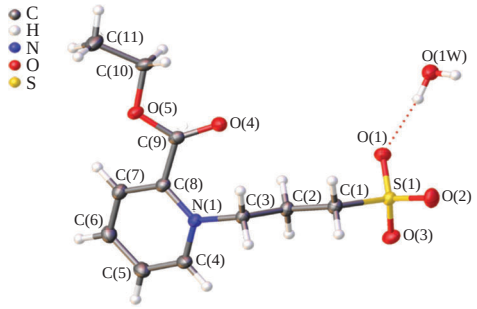


Figure 1 Molecular structure of monohydrate **6** showing thermal ellipsoids at the 50% probability level.

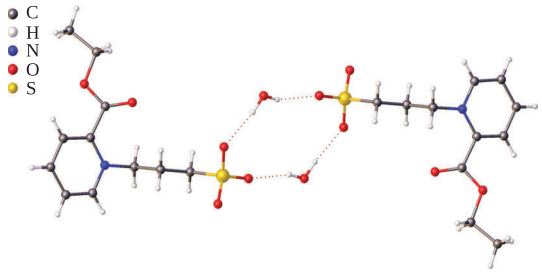


Figure 2 Centrosymmetric dimers with eight-membered rings formed *via* O–H···O bonds in crystal of **6**.

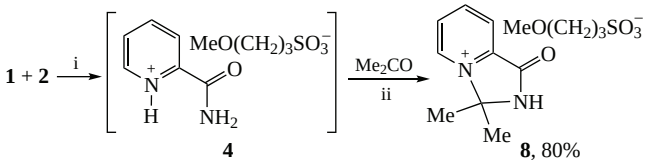
† *Crystal data for* **6**. Crystals of **6** ($C_{17}H_{15}NO_5S$, H_2O, M = 291.31) are monoclinic, space group $P2_1/n$, at 100 K, a = 11.644(2), b = 8.1330(16) and c = 15.090(3) Å, V = 1330.5(5) Å^3, Z = 4, d_{calc} = 1.454 g cm^{-3}, μ = 0.308 mm^{-1}, $F(000)$ = 616, 11697 reflections were measured, and 3404 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 = 0.0388 was calculated against F for 3113 observed reflections with $I > 2\sigma(I)$]. X-ray diffraction dataset for **6** was collected in Kurchatov Centre for Synchrotron Radiation and Nanotechnology using 'Belok' beamline (Si111 monochromator, ω scan mode, λ = 0.75027 Å).

CCDC 2300128 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.

The subsequent reaction of ester **6** with aqueous ammonia affords the target carbamoyl derivative **3** with a 64% yield (see Table 1, entry 3), which is significantly higher than that reported earlier (28%, entry 1). Finally, the one-pot synthesis of **3** from ethyl picolinate **5** and 1,3-propanesultone followed by ammonolysis provides the highest yield of the target product (89%, entries 2 and 3).

At ambient temperature, picolinic acid **5′** reacts with 1,3-propanesultone **2** in methanol to produce 3-acyloxypropanesulfonate **7** with a 25% yield (see Scheme 2 and Table 1, entry 6). The formation of **7** is probably caused by the shielding effect of an intramolecular H-bond involving hydrogen of the carboxy 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 (entry 7) yields a mixture that shows three signals for carbonyl groups (at 159.88, 162.18 and 164.79 ppm) in the ^{13}C NMR spectrum (see Online Supplementary Materials). The ^{1}H NMR spectrum of this mixture shows one singlet (at 4.07 ppm) for 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 sulfonic acid $MeO(CH_2)_3SO_3H$, the product of methanolysis of sultone **2**. This type of chemical transformation is similar to those observed in the reactions of carboxylates with 1,3-propanesultone **2** 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 novel heterocyclic salt **8** with a fragment of imidazolin-4-one (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 resulted in the two-stage one-pot procedure that furnished picolinamide derivatives with high yields. The treatment of N-protonated picolinamide by-product with acetone afforded the first example of a novel type of heterocyclic salts with a fragment of imidazolin-4-one. 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.2024.01.038.

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