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Mendeleev Commun., 2024, **34**, 129–130

Mendeleev Communications

New synthesis of 6,8-diamino-substituted pyrano[3,4-*c*]pyridines from related pyrano[3,4-*c*]pyridin-6-one

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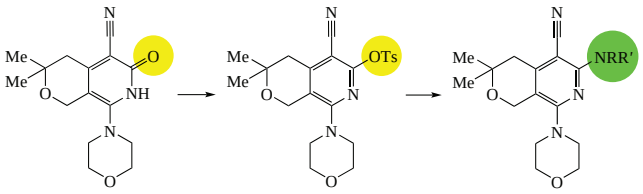
DOI: 10.1016/j.mencom.2024.01.039

The tosylation of 3,3-dimethyl-8-(morpholin-4-yl)-6-oxo-3,4,6,7-tetrahydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitrile with TsCl occurs at the oxo group of the NH-lactam moiety. The subsequent nucleophilic displacement of *O*-tosylate by various amines affords the title compounds in good yields.

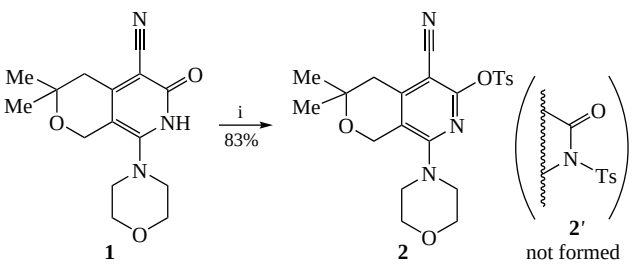


Keywords: pyrano[3,4-*c*]pyridines, *p*-toluenesulfonyl chloride, alkylation, regioselectivity, *O*-tosylate, amines.

Pyranopyridines are of significant interest in organic synthesis and medicinal chemistry due to their unique structural features and diverse biological activities. Various derivatives and analogs of pyranopyridines are frequently synthesized to investigate the relationships between their structure and activity, aiming to enhance their biological effect.[1–7] In drug discovery, pyrano[3,4-*c*]pyridines have been investigated as potential candidates for the development of pharmaceutical agents due to their ability to modulate specific biological targets or pathways. Their presence in natural products has also attracted attention, as they may serve as lead compounds for drug development.[8–13] The presence of specific structural peculiarities contributes to the restricted options for pyrano[3,4-*c*]pyridine synthesis.[14–21] Nonetheless, their synthetically derived counterparts also look as a showcase for a range of biological effects, particularly antimicrobial, anticancer, neurotropic, antiplatelet and vasodilator activities.[17–21]

Previously, we have developed methods for the synthesis of 6,8-diaminopyrano[3,4-*c*]pyridines through the Dimroth and Smiles rearrangements in the pyridine ring.[15,16] This work is dedicated to developing novel and more effective methods for synthesizing derivatives of such compounds.

3,3-Dimethyl-8-(morpholin-4-yl)-6-oxo-3,4,6,7-tetrahydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitrile **1**[22] served herein as the starting material for synthesizing the target compounds and was subjected to tosylation reaction with *p*-toluenesulfonyl chloride. In principle, it was possible to obtain *O*- (compound **2**) and/or *N*-alkylation (compound **2′**) products (Scheme 1). However, the spectroscopic data indicated that the alkylation proceeded regioselectively leading exclusively to *O*-tosylate **2**. IR spectra of compound **2** showed the presence of strong absorption band at 2221 cm^{-1} attributed to the CN group, while the typical absorption band for the C=O group was absent. The ^{13}C NMR spectrum of compound **2** did not contain signal corresponding to the C=O group.



Scheme 1 *Reagents and conditions*: i, TsCl, Et_3N, 1,4-dioxane, reflux, 12 h.

The structure of compound **2** was ultimately confirmed by X-ray analysis (Figure 1). Molecule **2** consists of pyrano[3,4-*c*]-pyridine bicycle, morpholine and tolyl rings. The tolyl and pyridine rings are perfectly planar, the maximum deviation of atoms from mean-squared plane not exceeding 0.0063(4) and 0.0583(4) Å, respectively.† The 1*H*-pyran ring shows well expressed ‘half-chair’ conformation. Its four atoms [C(5), C(6), C(13), C(14)] lie in the same plane and atoms O(1) and C(2) are out of plane with a shift from ‘half-chair’ plane of 0.4725(4) and –0.2787(2) Å, respectively. The morpholine ring shows well expressed ‘chair’ conformation. Its four atoms [C(16), C(17), C(19), C(20)] lie in the same plane and atoms N(15) and O(18) are out of plane with a shift from ‘chair’ plane of 0.5796(4) and –0.6644(4) Å, respectively. In 3D packing of molecules, the van der Waals forces are mainly responsible for intermolecular interactions.

† *Crystal data for* **2**. $C_{22}H_{25}N_3O_5S$ (M = 443.51), triclinic, space group $P\bar{1}$ at 295 K: a = 9.4737(19), b = 10.641(2) and c = 11.724(2) Å, α = 76.33(3)°, β = 67.06(3)°, γ = 82.52(3)°, Z = 2, d_{calc} = 1.394 g cm^{-3}, V = 1056.6(4) Å^3, μ(MoK$_\alpha$) = 0.193, T_{min} = 0.78635, T_{max} = 0.88529 mm^{-1}, F(000) = 468. A total of 6488 reflections were collected (6144 independent reflections, R_{int} = 0.021), GOOF 1.02, final R indices (all data): R_1 = 0.0674 and wR_2 = 0.1989, 283 refined parameters. All diffraction measurements were carried out on an Enraf–Nonius Cad-4 automated diffractometer (graphite monochromator, MoK$_\alpha$ radiation, $\theta/2\theta$-scan). The monoclinic unit cell parameters were measured and refined using the diffraction angles of 24 reflections ($12.05 < \theta < 13.85$). The absorption correction was carried out by psi-scan method.[23] The structure was solved by direct method and refined using the software package SHELXTL.[24] All non-hydrogen atoms were refined anisotropically by full-matrix least squares method. All hydrogen atoms were positioned geometrically and refined using the riding model, with C–H = 0.93–0.97 Å, U_{iso}(H) = 1.2–1.5 U_{eq}(C).

CCDC 2283397 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.

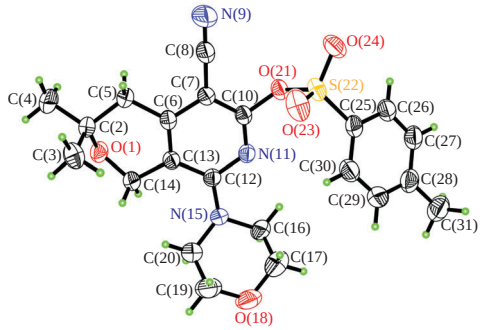
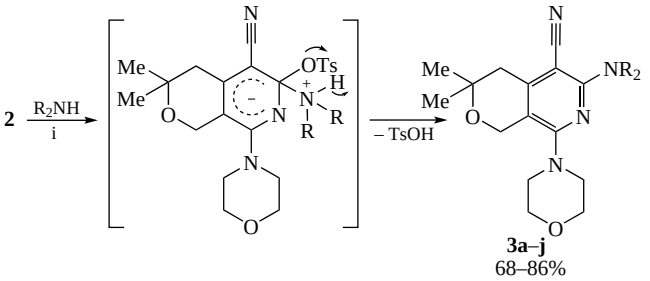


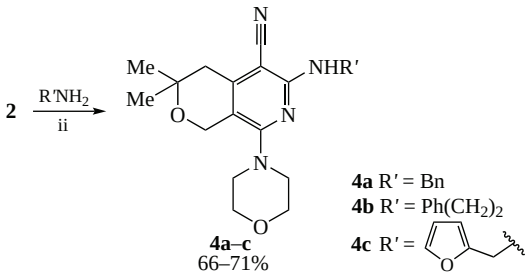
Figure 1 The molecular structure of compound **2** with thermal displacement ellipsoids drawn at the 50% probability level.

The nucleophilic substitution reaction between *O*-tosylate **2** and aliphatic amines has been investigated (Scheme 2). When diethylamine and cyclic secondary amines are used, the reaction occurs in the presence of excess amine in dioxane under mild conditions to produce compounds **3a–j**. With primary amines, in addition to an excess of amine, *N*,*N*-diisopropyl-*N*-ethylamine (DIPEA) was required as a deprotonating reagent (products **4a–c**).

In summary, our study has led to the development of efficient methods for preparing new 6,8-diaminopyrano[3,4-*c*]pyridine derivatives. The regioselective *O*-tosylation of 3,3-dimethyl-8-(morpholin-4-yl)-6-oxo-3,4,6,7-tetrahydro-1*H*-pyrano[3,4-*c*]-pyridine-5-carbonitrile with TsCl has been experimentally proven. The replacement of the tosyloxy group by amino moieties has been fulfilled, the reaction conditions being dependent on the amine type.



3a R + R = $(CH_2)_2O(CH_2)_2$
3b R + R = $(CH_2)_4$
3c R + R = $(CH_2)_5$
3d R + R = $(CH_2)_2NH(CH_2)_2$
3e R + R = $(CH_2)_2NMe(CH_2)_2$
3f R + R = $(CH_2)_2NEt(CH_2)_2$
3g R + R = $(CH_2)_2NBn(CH_2)_2$
3h R + R = $(CH_2)_2N(CHPh_2)(CH_2)_2$
3i R = Et
3j R + R = $(CH_2)_2N(CH_2CH_2OH)(CH_2)_2$



4a R′ = Bn
4b R′ = $Ph(CH_2)_2$
4c R′ =

Scheme 2 *Reagents and conditions*: i, R_2NH, 1,4-dioxane, reflux, 5 h; ii, $R'NH_2$, DIPEA, reflux, 8 h.

This work was supported by the RA MES State Committee of Science (grant no. 21T-1D231).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.01.039.

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Received: 14th August 2023; Com. 23/7226