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# Synthesis of functionalized pyridine derivatives by an amidoalkylation/Staudinger/aza-Wittig sequence

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ABSTRACT

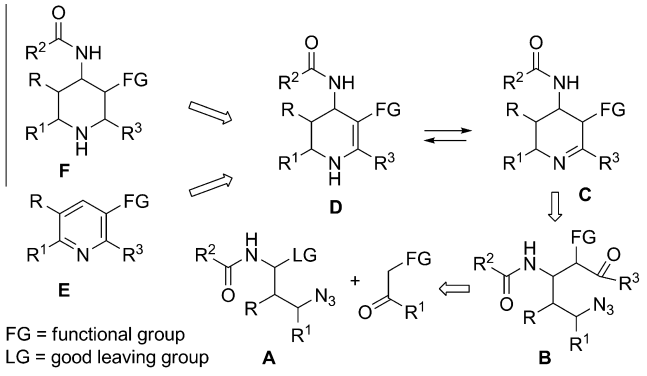
A new efficient methodology for the preparation of 3,4-difunctionalized pyridine derivatives by an amidoalkylation/Staudinger/aza-Wittig sequence has been developed. The synthesis includes condensation of 3-azidopropanal with urea and *p*-toluenesulfinic acid followed by reaction of the *N*-[(3-azido-1-tosyl)propyl]urea obtained with Na-enolates of tosylacetophenone or acetyl acetone to give *N*-[(5-azido-1-oxo-1-phenyl-2-tosyl)pent-3-yl]urea and 5-acetyl-6-(2-azidoethyl)-4-hydroxy-4-methylhexahydropyrimidin-2-one, respectively. These compounds are transformed into 6-phenyl-5-tosyl-4-ureido- and 5-acetyl-6-methyl-4-ureido-1,2,3,4-tetrahydropyridines by treatment with $PPh_3$. The former is aromatized under the action of $MnO_2$ or reduced by $NaBH_4/CF_3COOH$ system to provide 2-phenyl-3-tosylpyridine and 2-phenyl-3-tosyl-4-ureidopiperidine.



The ring system of pyridine and its hydrogenated derivatives occurs in many pharmacologically active natural compounds, including alkaloids, vitamins, cofactors, and antibiotics.[1] Pyridines, piperidines, dihydro-, and tetrahydropyridines have found various applications in medicinal chemistry.[1] Remarkable progress has been achieved in the development of effective approaches to pyridines, including hydrogenated ones.[1e,g,h,2,3] The Staudinger/intramolecular aza-Wittig reaction sequence[4] provides a convenient method for the preparation of tetrahydropyridines that can be easily transformed into piperidines.[5] This protocol uses δ-azido ketones as starting materials. However, the synthesis described for these compounds have some disadvantages, such as the low availability of starting compounds, multi-step synthesis, small-scale preparations, harsh reaction conditions, long reaction times, poor yields, laborious procedures, etc. In addition, it is difficult to obtain δ-azido ketones bearing a functional group at the β-position (e.g., Cl, Br, OH, OR, NHR, etc.). This limits the application of the above approach to the synthesis of 4-functionalized tetrahydropyridines and piperidines as well as aromatic pyridines. Thus, in the context of pyridine synthesis, the development of new general approaches to δ-azido ketones, particularly with additional functional groups at the α- and β-positions, is highly desirable.

We hypothesized that amidoalkylation of enolates of α-functionalized ketones with *N*-(γ-azidoalkyl)amides **A** bearing a leaving group at the position α to nitrogen could give δ-azido ketones **B** which could be transformed into tetrahydropyridines **C** or/and **D** using the Staudinger/intramolecular aza-Wittig reaction sequence (Scheme 1). Subsequent aromatization or reduction of compounds **C** and **D** would give 3-functionalized pyridines **E** or piperidines **F**.

Previously, we demonstrated that the products of the amidoalkylation reaction between enolates of various ketones and readily available *N*-(α-tosyl)alkylureas can serve as versatile precursors for the preparation of functionalized hexahydro-, 1,2,3,4-tetrahydro-, and 1,2-dihydropyrimidin-2-ones, tetrahydro-1*H*-1,3-diazepin-2-ones, 4,5-dihydrofurans, and 1-carbamoyl-1*H*-pyrroles.[6] In continuation of our interest in the development of new methodologies using amidoalkylation we describe herein the synthesis of




**Scheme 1.** Retrosynthesis of functionalized pyridines and their hydrogenated derivatives via amidoalkylation/Staudinger/aza-Wittig reactions.

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δ-azido-β-ureido ketones by the reaction of *N*-[(2-azido-1-tosyl)propyl]urea with enolates of tosylacetophenone and acetyl acetone and their transformation into functionalized 4-ureido-tetrahydropyridines using the Staudinger/aza-Wittig sequence. We also report oxidative aromatization and reduction of one of the tetrahydropyridines to give a pyridine and piperidine derivative, respectively.

The *N*-[(γ-azido-α-tosyl)alkyl]ureas (**A** R = $NH_2$, Scheme 1) required as starting amidoalkylation reagents for the pyridine synthesis can be prepared by the reaction of readily available β-azido aldehydes with *p*-toluenesulfinic acid and urea. In this work, we used 3-azidopropanal (**1**) as an example of a β-azido aldehyde. Aldehyde **1** was obtained according to the literature method[7] by reaction of acrolein (**2**) with $NaN_3$ in aqueous acetic acid (Scheme 2). The product was isolated from reaction mixture as a yellowish oil in 62% yield after extraction with diethyl ether followed by neutralization of the ether extracts with aqueous $Na_2CO_3$, drying and evaporation of the solvent in vacuum. The crude **1** was >95% pure according to $^1$H NMR data and was used in the next stage without additional purification. Reaction of **1** with *p*-toluenesulfinic acid (**3**) and urea (1:1:3 molar ratio, respectively) proceeded in water at room temperature for 24 h to give sulfone **4** in an 86% yield.[8] A threefold excess of urea was used to prevent the formation of the N,N′-disubstituted side product.

The reaction of sulfone **4** with the sodium enolate of tosylacetophenone (**5a**) in dry MeCN proceeded at room temperature for 8 h to give oxoalkylurea **6a** as a mixture of two diastereomers in a ratio of 54:46 in a 93% yield (Scheme 3).[9] No cyclic isomer, the 4-hydroxyhexahydropyrimidin-2-one **7a**, was detected by $^1$H NMR spectroscopy.

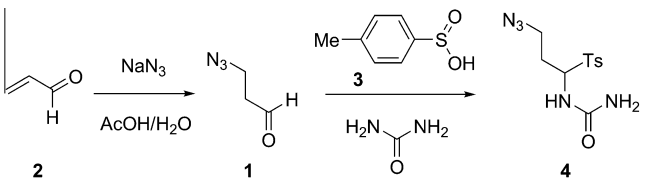
Under similar conditions, the reaction of urea **4** with the Na-enolate of acetyl acetone (**5b**) afforded the 4-hydroxyhexahydropyrimidin-2-one **7b** as a single (4*R**,5*R**,6*R**)-isomer in 75% yield.[10] Based on the values of spin couplings, the orientations of substituents in **7b** were determined as equatorial for the acetyl and azidoethyl groups ($^3J_{5\text{-H},6\text{-H}}$ = 11.7, $^3J_{N(1)H,6\text{-H}}$ ~0 Hz) and axial for the hydroxyl group ($^4J_{5\text{-H,OH}}$ = 0.7 Hz).

The δ-azido ketone **6a** was reacted with $PPh_3$ (1 equiv) in THF (reflux, 3 h) to give 1,2,3,4-tetrahydropyridine **9a** in 90% yield.[11] Under these conditions, the intermediate 2,3,4,5-tetrahydropyridine **8a** was transformed into **9a** via an imine–enamine tautomeric shift. Treatment of pyrimidine **7b** with 1 equiv of $PPh_3$ (THF, reflux, 2 h) produced 1,2,3,4-tetrahydropyridine **9b** in 70% yield through the intermediate formation of the δ-azido ketone **6b**.[12] According to $^1$H NMR spectroscopic data (DMSO-$d_6$ solutions), compounds **9a**,**b** exist in the conformation with a pseudo axial orientation of the ureido group.

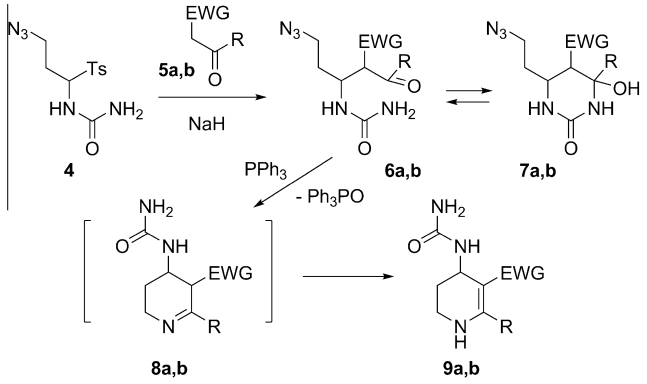
Tetrahydropyridines **9a**,**b** are versatile precursors for preparation of various aromatic and hydrogenated pyridines. Treatment of **9a** with active $MnO_2$ in refluxing toluene resulted in the elimination of urea followed by oxidative aromatization affording 2-phenyl-3-tosylpyridine (**10**) in a 64% yield (Scheme 4).[13]

The structure of **10** was confirmed by IR and NMR spectroscopic data, and an X-ray single crystal analysis (Fig. 1).[14]

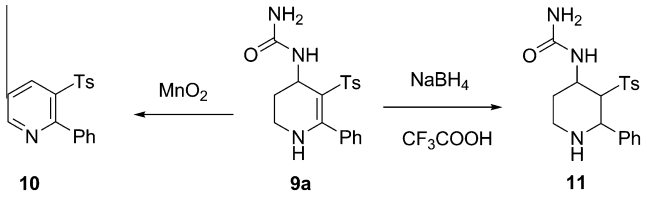
Reduction of **9a** was carried out with the $NaBH_4/CF_3COOH$ system in THF which previously we successfully used for the




**Scheme 2.** Synthesis of the starting amidoalkylation reagent, *N*-[(3-azido-1-tosyl)propyl]urea (**4**).




**Scheme 3.** Synthesis of 3-functionalized 4-ureido-1,2,3,4-tetrahydropyridines **9a,b** using the amidoalkylation/Staudinger/aza-Wittig sequence.




**Scheme 4.** Reduction and elimination/oxidation of tetrahydropyridine **9a**.

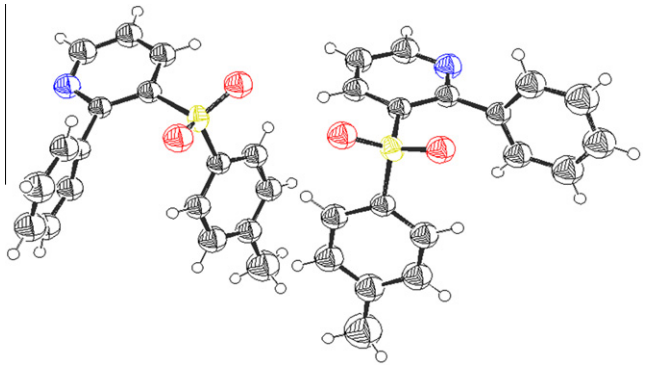


**Figure 1.** The X-ray crystal structure of **10**.

reduction of 1,2,3,4-tetrahydro- and 4-hydroxy- or 4-alkoxyhexahydropyrimidine-2-thiones/ones.[15] The reaction proceeded with high stereoselectivity to give 4-ureidopiperidine **11** as a mixture of three diastereomers with a ratio of 70:25:5 in a 66% combined yield.[16] The major isomer was isolated from the diastereomeric mixture by single crystallization. Its configuration and conformation was determined using $^1$H NMR data and $^1$H,$^1$H-NOESY. The axial orientation of the ureido group and the equatorial orientation of the phenyl group were confirmed by the cross peaks between the NH proton of the ureido fragment and the axial protons 2-H and 6-H in the $^1$H,$^1$H-NOESY. The low values of vicinal coupling between 2-H, 3-H, and 4-H ($^3J_{2\text{-H},3\text{-H}}$ = 3.3, $^3J_{3\text{-H},4\text{-H}}$ = 2.7 Hz) proved the axial orientation of the tosyl group. Thus, the major diastereomer of **11** has the (2*R**, 3*R**, 4*S**)-configuration.

In summary, we have shown that amidoalkylation of Na-enolates of α-functionalized ketones with readily available *N*-[(3-azido-1-tosyl)propyl]urea gives general access to δ-azido-β-ureido ketones or their cyclic isomers, 6-(2-azidoethyl)-4-hydroxyhexahydropyrimidin-2-ones. These compounds can be transformed into 4-ureido-substituted 1,2,3,4-tetrahydropyridines via Staudinger/

aza-Wittig reactions promoted by $PPh_3$. 1,2,3,4-Tetrahydropyridines were reduced by the $NaBH_4/CF_3COOH$ system or aromatized under the action of $MnO_2$ with the loss of urea to give 3-functionalized 4-ureidopiperidines and pyridines, respectively. We envisage that the synthesis of functionalized pyridine derivatives described herein is an attractive alternative to classical procedures. This synthesis is flexible and can be adapted to the preparation of a library of 3-functionalized 4-ureido-1,2,3,4-tetrahydopyridines and 4-ureido-piperidines which are of great interest as potential pharmacologically active compounds (see Ref. 1).

## Acknowledgments

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## Supplementary data

Supplementary data (IR, $^1H$ and $^{13}C$ NMR spectra of **4**, **6a**, **7b**, **9a**,**b**, **10**, (2*R**,3*R**,4*S**)-**11**, 2-D NMR spectra of (2*R**,3*R**,4*S**)-**11** ($^1H,^1H$-COSY, $^1H,^{13}C$-HSQC, $^1H,^1H$-NOESY) in DMSO-$d_6$ and X-ray structural data for **10**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.022.

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8. *Synthesis of N-[(3-azido-1-tosyl)propyl]urea* (**4**): To a stirred emulsion of 3-azidopropanal (**1**) (8.81 g, 88.91 mmol) in $H_2O$ (50 mL) was added *p*-toluenesulfinic acid (**3**) (13.88 g, 88.86 mmol) under vigorous stirring for 1 min followed by the addition of $H_2O$ (80 mL). After 23 min to the obtained suspension were added urea (16.01 g, 266.59 mmol) and $H_2O$ (90 mL). The reaction mixture was stirred at rt for 24 h, cooled to 0 °C, the precipitate was filtered, washed with ice-cold water, petroleum ether, and dried to give 22.75 g (86%) of **4**, which was used further without additional purification. Mp 108.5–110 °C (decomp., MeCN). IR (Nujol): $\nu$ = 3461 (s), 3348 (s), 3330 (br m) ($\nu$ NH), 3065 (w) ($\nu$ $CH_{arom}$), 2161 (m), 2122 (s), 2105 (vs) ($\nu$ $N_3$), 1666 (vs) (amide-I), 1592 (m) ($\nu$ $CC_{arom}$), 1522 (s) (amide-II), 1283 (s) ($\nu_{as}$ $SO_2$), 1142 (s) ($\nu_s$ $SO_2$), 813 (m) ($\delta$ $CH_{arom}$) $cm^{-1}$. $^1H$ NMR (300.13 MHz, DMSO-$d_6$): $\delta$ = 7.67–7.72 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in 4-$MeC_6H_4$), 7.39–7.45 (2H, m, $C_{(3)}H$ and $C_{(5)}H$ in 4-$MeC_6H_4$), 6.97 (1H, d, $^3J_{NH,CH}$ = 10.2 Hz, NH), 5.72 (2H, s, $NH_2$), 5.01 (1H, ddd, $^3J_{CH,CH(D)}$ = 11.1, $^3J_{CH,NH}$ = 10.2, $^3J_{CH,CH(C)}$ = 3.2 Hz, $CHSO_2$), 3.54 (1H, ddd, $^2J_{CH(A),CH(B)}$ = 12.4, $^3J_{CH(A),CH(C)}$ = 6.5, $^3J_{CH(A),CH(D)}$ = 4.7 Hz, $CH_{(A)}$ in $CH_{(A)}H_{(B)}N_3$), 3.31 (1H, ddd, $^2J_{CH(B),CH(A)}$ = 12.4, $^3J_{CH(B),CH(C)}$ = 9.2, $^3J_{CH(B),CH(D)}$ = 5.8 Hz, $CH_{(B)}$ in $CH_{(A)}H_{(B)}N_3$), 2.19 (1H, dddd, $^2J_{CH(C),CH(D)}$ = 14.0, $^3J_{CH(C),CH(B)}$ = 9.2, $^3J_{CH(C),CH(A)}$ = 6.5, $^3J_{CH(C),CH}$ = 3.2 Hz, $CH_{(C)}$ in $CH_{(C)}H_{(D)}CH_2N_3$), 2.40 (3H, s, $CH_3$ in Ts), 1.76 (1H, dddd, $^2J_{CH(D),CH(C)}$ = 14.0, $^3J_{CH(D),CH}$ = 11.1, $^3J_{CH(D),CH(B)}$ = 5.8, $^3J_{CH(D),CH(A)}$ = 4.7 Hz, $CH_{(D)}$ in $CH_{(C)}H_{(D)}CH_2N_3$). $^{13}C$ NMR (75.48 MHz, DMSO-$d_6$): $\delta$ = 156.6 (C=O), 144.5 (C-4 in 4-$MeC_6H_4$), 133.9 (C-1 in 4-$MeC_6H_4$), 129.7 (C-3 and C-5 in 4-$MeC_6H_4$), 129.0 (C-2 and C-6 in 4-$MeC_6H_4$), 67.9 ($CHSO_2$), 46.9 ($CH_2CH_2N_3$), 26.6 ($CH_2CH_2N_3$), 21.2 ($CH_3$). Anal. Calcd for $C_{11}H_{15}N_5O_3S$: C, 44.44; H, 5.09; N, 23.55. Found: C, 44.60; H, 5.41; N, 23.38.
9. *Synthesis of N-[(5-azido-1-oxo-1-phenyl-2-tosyl)pent-3-yl]urea* (**6a**): To a mixture of tosylacetophenone (**5a**)[17] (3.922 g, 14.30 mmol) and NaH (0.343 g, 14.29 mmol) was added dry MeCN (14 mL), the obtained mixture was stirred for 15 min and to the resulting dense enolate suspension were added sulfone **4** (4.245 g, 14.28 mmol) and dry MeCN (6 mL). The formed suspension was stirred at rt for 8 h, and the solvent was removed in vacuum. To the white solid residue was added a saturated aqueous solution of $NaHCO_3$ (22 mL). The obtained mixture was left for 2 h in a water bath (40 °C), overnight at rt, and cooled (0 °C). The precipitate was filtered, washed with ice-cold water, petroleum ether, cold (−10 °C) $Et_2O$, and dried to give **6a** (5.492 g, 93%) as a mixture of two diastereomers in a ratio of 54:46. After crystallization from EtOH the diastereomeric ratio changed to 51:49. Mp 166 °C (decomp., EtOH). IR (Nujol): $\nu$ = 3450 (s), 3374 (s), 3332 (s), 3224 (s) ($\nu$ NH), 3087 (w), 3066 (w), 3054 (w), 3039 (w) ($\nu$ $CH_{arom}$), 2167 (m), 2104 (vs) ($\nu$ $N_3$), 1673 (s), 1661 (s), 1627 (m) ($\nu$ C=O, amide-I), 1595 (m), 1579 (w), 1489 (w) ($\nu$ $CC_{arom}$), 1550 (s) (amide-II), 1294 ($\nu_{as}$ $SO_2$), 1141 ($\nu_s$ $SO_2$), 813 (m) ($\delta$ $CH_{arom}$ in Ts), 744 (s), 691 (m) ($\delta$ $CH_{arom}$ in Ph) $cm^{-1}$. $^1H$ NMR of the 51:49 diastereomeric mixture (300.13 MHz, DMSO-$d_6$): $\delta$ = 7.29–7.90 (9H, m, Ph and $C_6H_4$ in both isomers), 6.160 (0.51H, d, $^3J_{CH,CH}$ = 8.9 Hz, $CHSO_2$ in major isomer), 6.159 (0.49H, d, $^3J_{CH,CH}$ = 8.0 Hz, $CHSO_2$ in minor isomer), 5.98 (0.49H, d, $^3J_{NH,CH}$ = 7.1 Hz, NH in minor isomer), 5.93 (0.51H, d, $^3J_{NH,CH}$ = 7.0 Hz, NH in major isomer), 5.56 (1.02H, s, $NH_2$ in major isomer), 5.51 (0.98H, s, $NH_2$ in minor isomer), 4.39 (0.51H, dddd, $^3J_{CH(A)}$ = 10.5, $^3J_{CH,CH}$ = 8.9, $^3J_{CH,NH}$ = 7.0, $^3J_{CH,CH(B)}$ = 3.3 Hz, CHN in major isomer), 4.25 (0.49H, dddd, $^3J_{CH(A)}$ = 8.5, $^3J_{CH,CH}$ = 8.0, $^3J_{CH,NH}$ = 7.1, $^3J_{CH,CH(B)}$ = 5.3 Hz, CHN in minor isomer), 3.33–3.43 (0.98H, m, $CH_2N_3$ in minor isomer), 3.16–3.30 (1.02H, m, $CH_2N_3$ in major isomer), 2.36 (1.47H, s, $CH_3$ in minor isomer), 2.33 (1.53H, s, $CH_3$ in major isomer), 2.00–2.11 (0.51H, m, CH(B) in $CH_2CH_2N_3$ of major isomer), 1.75–1.89 (1.49H, m, CH(A) in

$CH_2CH_2N_3$ of major isomer, CH(A) and CH(B) in $CH_2CH_2N_3$ of minor isomer). $^{13}C$ NMR of the 51:49 diastereomeric mixture (75.48 MHz, DMSO-$d_6$): $\delta$ = 192.9, 192.3 (C=O in Bz), 157.8 ($CONH_2$), 144.9, 144.8 (C-4 in 4-$MeC_6H_4$), 137.1, 136.9 (C-1 in Ph), 135.8, 135.2 (C-1 in 4-$MeC_6H_4$), 134.2, 134.0 (C-4 in Ph), 129.6, 129.5; 128.99, 128.95; 128.8; 128.6, 128.5 (C-2, C-3, C-5, C-6 in Ph and 4-$MeC_6H_4$), 70.5, 69.7 ($CHSO_2$), 47.6, 47.5 ($CH_2CH_2N_3$), 47.2 (CHNH), 30.7, 32.4 ($CH_2CH_2N_3$), 21.10, 21.06 ($CH_3$). Anal. Calcd for $C_{19}H_{21}N_5O_4S$: C, 54.93; H, 5.09; N, 16.86. Found: C, 54.88; H, 5.22; N, 16.88.

10. *Synthesis of 5-acetyl-6-(2-azidoethyl)-4-hydroxy-4-methylhexahydropyrimidin-2-one* (**7b**): To a stirred, cooled in an ice bath suspension of NaH (0.289 g, 12.04 mmol) in dry MeCN (8 mL) was added dropwise the solution of acetyl acetone (**5b**) (1.218 g, 12.17 mmol) in dry MeCN (10 mL) and the resulting suspension was stirred for 25 min. To the formed suspension were added sulfone **4** (3.252 g, 10.94 mmol) and dry MeCN (3 mL). The reaction mixture was stirred at rt for 7 h 45 min, and the solvent was removed in vacuum. The residue was triturated with petroleum ether (4 × 10 mL), after decantation of the last portion of petroleum ether saturated aqueous solution of $NaHCO_3$ (9 mL) and petroleum ether (10 mL) were added, the obtained suspension was left overnight at rt, and cooled (0 °C). The precipitate was filtered, washed with ice-cold water, petroleum ether, cold (−10 °C) $Et_2O$ (2 × 10 mL), and dried to give compound **7b** (1.974 g, 75%) as a single (4*R**,5*R**,6*R**)-diastereomer. Mp 160.5 °C (decomp., EtOH). IR (Nujol): $\nu$ = 3298 (s), 3266 (s), 3100 (br s) ($\nu$ OH, NH), 2148 (m), 2108 (s), 2088 (s) ($\nu$ $N_3$), 1714 (s) ($\nu$ C=O in Ac), 1653 (vs) (amide-I), 1501 (s) (amide-II), 1135 (s) ($\nu$ C-O) $cm^{-1}$. $^1H$ NMR (300.13 MHz, DMSO-$d_6$): $\delta$ = 7.07 (1H, d, $^4J_{N(3)H,N(1)H}$ = 1.8 Hz, $N_{(3)}H$), 6.55 (1H, d, $^4J_{N(1)H,N(3)H}$ = 1.8 Hz, $N_{(1)}H$), 5.71 (1H, d, $^4J_{OH,5\text{-}H}$ = 0.7 Hz, OH), 3.92 (1H, ddd, $^3J_{6\text{-}H,5\text{-}H}$ = 11.7, $^3J_{6\text{-}H,CH(A)}$ = 7.4, $^3J_{6\text{-}H,CH(B)}$ = 2.9 Hz, 6-H), 3.41–3.57 (2H, m, $CH_2N_3$), 2.45 (1H, dd, $^3J_{5\text{-}H,6\text{-}H}$ = 11.7, $^4J_{5\text{-}H,OH}$ = 0.7 Hz, 5-H), 2.18 (3H, s, $CH_3$ in Ac), 1.40–1.66 (2H, m, $CH_2CH_2N_3$), 1.28 (3H, s, 4-$CH_3$). $^{13}C$ NMR (75.48 MHz, DMSO-$d_6$): $\delta$ = 207.6 (C=O in Ac), 154.5 (C-2), 78.0 (C-4), 61.0 (C-5), 46.4 ($CH_2CH_2N_3$), 45.9 (C-6), 32.0 ($CH_2CH_2N_3$), 30.4 ($CH_3$ in Ac), 27.5 (4-$CH_3$). Anal. Calcd for $C_9H_{15}N_5O_3$: C, 44.81; H, 6.27; N, 29.03. Found: C, 45.01; H, 6.26; N, 29.16.
11. *Synthesis of 6-phenyl-5-tosyl-4-ureido-1,2,3,4-tetrahydropyridine* (**9a**): To a mixture of **6a** (0.360 g, 0.87 mmol) and $PPh_3$ (0.231 g, 0.88 mmol) was added dry THF (4 mL) and the obtained mixture was refluxed under stirring for 3 h. The clear solution formed at the beginning of reflux and after 20 min the product precipitated to give the dense suspension. After the reaction was complete, the mixture was cooled (−10 °C), the precipitate was filtered on cold (−10 °C) filter, washed with cold (−10 °C) THF (3 × 2 mL), cold (−10 °C) $Et_2O$ (4 × 4 mL), petroleum ether, and dried to give **9a** (0.291 g, 90%). Mp 131–132 °C (decomp., MeCN). IR (Nujol): $\nu$ = 3434 (s), 3382 (sh), 3364 (br s), 3303 (sh), 3185 (s) ($\nu$ NH), 1667 (vs) (amide-I), 1617 (m), 1607 (m) ($\nu$ $CC_{arom}$), 1569 (s) ($\nu$ C=C), 1515 (s), 1500 (vs) (amide-II), 1294 (s) ($\nu_{as}$ $SO_2$), 1139 (vs) ($\nu_s$ $SO_2$), 809 (m) ($\delta$ $CH_{arom}$ in Ts), 762 (s), 701 (s) ($\delta$ CH in Ph) $cm^{-1}$. $^1H$ NMR (300.13 MHz, DMSO-$d_6$): $\delta$ = 7.17–7.40 (7H, m, $C_6H_4$ and $C_{(3)}H$, $C_{(4)}H$, $C_{(5)}H$ in Ph), 7.18 (1H, d, $^3J_{1\text{-}H,2\text{-}He}$ = 4.6 Hz, 1-H), 7.03–7.09 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in Ph), 6.07 (1H, d, $^3J_{NH,4\text{-}H}$ = 6.6 Hz, NH), 5.40 (2H, s, $NH_2$), 4.71 (1H, dddd, $^3J_{4\text{-}H,NH}$ = 6.6, $^3J_{4\text{-}H,3\text{-}Ha}$ = 3.3, $^3J_{4\text{-}H,3\text{-}He}$ = 2.8, $^4J_{4\text{-}H,2\text{-}He}$ = 1.3 Hz, 4-H), 3.17–3.27 (1H, m, 2-He), 3.07 (1H, ddd, $^3J_{2\text{-}Ha,3\text{-}Ha}$ = 13.6, $^2J_{2\text{-}Ha,2\text{-}He}$ = 12.9, $^3J_{2\text{-}Ha,3\text{-}He}$ = 3.6 Hz, 2-Ha), 2.33 (3H, s, $CH_3$), 1.83–1.92 (1H, m, 3-He), 1.38 (1H, dddd, $^3J_{3\text{-}Ha,2\text{-}Ha}$ = 13.6, $^2J_{3\text{-}Ha,3\text{-}He}$ = 12.9, $^3J_{3\text{-}Ha,2\text{-}He}$ = 4.9, $^3J_{3\text{-}Ha,4\text{-}H}$ = 3.3 Hz, 3-Ha). $^{13}C$ NMR (75.48 MHz, DMSO-$d_6$): $\delta$ = 157.4 (C=O), 155.6 (C-6), 142.7 (C-4 in 4-$MeC_6H_4$), 141.3 (C-1 in 4-$MeC_6H_4$), 136.2 (C-1 in Ph), 128.9, 128.6 (br), 127.2, 126.0 (C-2, C-3, C-5, C-6 in Ph and 4-$MeC_6H_4$), 128.5 (C-4 in Ph), 99.1 (C-5), 42.5 (C-4), 36.0 (C-2), 27.3 (C-3), 20.9 ($CH_3$). Anal. Calcd for $C_{19}H_{21}N_3O_3S$: C, 61.44; H, 5.70; N, 11.31. Found: C, 61.07; H, 6.07; N, 11.55.
12. *Synthesis of 5-acetyl-6-methyl-4-ureido-1,2,3,4-tetrahydropyridine* (**9b**): To a mixture of **7b** (0.268 g, 1.11 mmol) and $PPh_3$ (0.294 g, 1.12 mmol) was added dry THF (4 mL), the obtained mixture was refluxed under stirring for 2 h, and the solvent was removed in vacuum. The solid residue was triturated with diethyl ether until the crystallization was complete, the precipitate was filtered, washed with $Et_2O$, $Et_2O$–THF (6 mL, 1:1 v/v), $Et_2O$ (2 × 4 mL), petroleum ether, and dried to give **9b** (0.153 g, 70%). *Note*: filtration and washings were performed without cooling to remove $POPh_3$ completely. Mp 168–168.5 °C (decomp., EtOH). IR (Nujol): $\nu$ = 3417 (s), 3344 (s), 3270 (vs), 3217 (sh), 3100 (s) ($\nu$ NH), 1646 (s) ($\nu$ C=O and amide-I), 1591 (s) ($\nu$ C=C), 1516 (vs) (amide-II) $cm^{-1}$. $^1H$ NMR (300.13 MHz, DMSO-$d_6$): $\delta$ = 7.22 (1H, d, $^3J_{1\text{-}H,2\text{-}He}$ = 4.6 Hz, 1-H), 5.97 (1H, d, $^3J_{NH,4\text{-}H}$ = 6.9 Hz, NH), 5.32 (2H, s, $NH_2$), 4.48 (1H, dddd, $^3J_{4\text{-}H,NH}$ = 6.9, $^3J_{4\text{-}H,3\text{-}Ha}$ = 3.4, $^3J_{4\text{-}H,3\text{-}He}$ = 2.8, $^4J_{4\text{-}H,2\text{-}He}$ = 1.4 Hz, 4-H), 3.14 (1H, ddddd, $^2J_{2\text{-}He,2\text{-}Ha}$ = 12.8, $^3J_{2\text{-}He,3\text{-}Ha}$ = 4.8, $^3J_{2\text{-}He,1\text{-}H}$ = 4.6, $^3J_{2\text{-}He,3\text{-}He}$ = 2.1, $^4J_{2\text{-}He,4\text{-}H}$ = 1.4 Hz, 2-He), 2.95 (1H, ddd, $^3J_{2\text{-}Ha,3\text{-}Ha}$ = 13.3, $^2J_{2\text{-}Ha,2\text{-}He}$ = 12.8, $^3J_{2\text{-}Ha,3\text{-}He}$ = 3.4 Hz, 2-Ha), 2.15 (3H, s, $CH_3$ in Ac), 1.99 (3H, s, 6-$CH_3$), 1.79 (1H, dddd, $^2J_{3\text{-}He,3\text{-}Ha}$ = 13.1, $^3J_{3\text{-}He,2\text{-}Ha}$ = 3.4, $^3J_{3\text{-}He,4\text{-}H}$ = 2.8, $^3J_{3\text{-}He,2\text{-}He}$ = 2.1 Hz, 3-He), 1.38 (1H, dddd, $^3J_{3\text{-}Ha,2\text{-}Ha}$ = 13.3, $^2J_{3\text{-}Ha,3\text{-}He}$ = 13.1, $^3J_{3\text{-}Ha,2\text{-}He}$ = 4.8, $^3J_{3\text{-}Ha,4\text{-}H}$ = 3.4 Hz, 3-Ha). $^{13}C$ NMR (75.48 MHz, DMSO-$d_6$): $\delta$ = 193.4 (C=O in Ac), 157.6 ($NH_2C$=O), 155.5 (C-6), 101.6 (C-5), 43.1 (C-4), 35.7 (C-2), 27.6 ($CH_3$ in Ac), 27.6 (C-3), 21.9 (6-$CH_3$). Anal. Calcd for $C_9H_{15}N_3O_2$: C, 54.81; H, 7.67; N, 21.30. Found: C, 54.67; H, 7.83; N, 21.16.
13. *Synthesis of 2-phenyl-3-tosylpyridine* (**10**): The suspension of tetrahydropyridine **9a** (0.718 g, 1.93 mmol) and active $MnO_2$ (2.528 g) in toluene (25 mL) was refluxed under stirring for 1.5 h, cooled to room temperature, filtered through a silica gel pad (0.5 cm), the filter cake was washed with acetone (5 × 15 mL), the combined filtrates were evaporated in vacuum. The residue was dried in vacuum and triturated with petroleum ether (3 mL) until crystallization was complete. The precipitate was filtered, washed with petroleum ether (3 × 3 mL), and dried to give **10** (0.384 g, 64%). Mp 140.5–141 °C (EtOH). IR (Nujol): $\nu$ = 3079 (w), 3065 (w) ($\nu$ $CH_{arom}$), 1593 (m), 1567 (m), 1550 (s), 1510 (w) ($\nu$ $CN_{arom}$, $\nu$ $CC_{arom}$), 1322 (s) ($\nu_{as}$ $SO_2$), 1160 (s) ($\nu_s$ $SO_2$), 817 (s) ($\delta$ $CH_{arom}$ in Ts), 764 (s), 702 (s) ($\delta$ $CH_{arom}$ in Ph) $cm^{-1}$. $^1H$ NMR (600.13 MHz, DMSO-$d_6$): 8.86 (1H, dd, $^3J_{6\text{-}H,5\text{-}H}$ = 4.8, $^4J_{6\text{-}H,4\text{-}H}$ = 1.6 Hz, 6-H), 8.62 (1H, dd, $^3J_{4\text{-}H,5\text{-}H}$ = 8.2, $^4J_{4\text{-}H,6\text{-}H}$ = 1.6 Hz, 4-H), 7.73 (1H, dd, $^3J_{5\text{-}H,4\text{-}H}$ = 8.2, $^3J_{5\text{-}H,6\text{-}H}$ = 4.8 Hz, 5-H), 7.39–7.43 (1H, m, $C_{(4)}H$ in Ph), 7.27–7.31 (2H, m, $C_{(3)}H$ and $C_{(5)}H$ in Ph), 7.15–7.19 (4H, m, $C_6H_4$), 7.06–7.09 (2H, m, $C_{(2)}H$ and $C_{(6)}H$ in Ph), 2.31 (3H, s, $CH_3$). $^{13}C$ NMR (150.90 MHz, DMSO-$d_6$): $\delta$ = 157.8 (C-2), 152.9 (C-6), 144.2 (C-4 in 4-$MeC_6H_4$), 137.9 (C-1 in 4-$MeC_6H_4$), 137.0 (C-4), 136.7, 136.6 (C-1 in Ph, C-3), 129.4, 129.2, 127.4, 127.1 (C-2, C-3, C-5, C-6 in Ph and 4-$MeC_6H_4$), 128.5 (C-4 in Ph), 123.1 (C-5), 20.9 ($CH_3$). Anal. Calcd for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89; N, 4.53. Found: C, 69.76; H, 5.01; N, 4.75.
14. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 891696. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).
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16. *Synthesis of 2-phenyl-3-tosyl-4-ureidopiperidine* (**11**): To a stirred, cooled in an ice-bath suspension of finely powdered $NaBH_4$ (0.621 g, 16.41 mmol) and tetrahydropyridine **9a** (0.777 g, 2.09 mmol) in dry THF (6 mL), was added $CF_3COOH$ (13 mL) dropwise over 25 min with protection from air moisture ($CaCl_2$-tube). The obtained solution was stirred at rt for 6 h, the solvents were removed in vacuum (temperature of bath about 40–45 °C), the resulting oil was co-evaporated with toluene (2 × 10 mL). The residue was dissolved in $H_2O$ (5 mL), neutralized with solid $Na_2CO_3$, the resulting solution was extracted with $CHCl_3$ (6 × 10 mL), the combined extracts were washed with water to pH 7, brine, and dried over $Na_2SO_4$. The solvent was removed in vacuum, the residual foam was triturated with cold $Et_2O$ (3 mL) until crystallization was complete. The obtained suspension was cooled (−10 °C), the precipitate was filtered, washed with cold (−10 °C) $Et_2O$ (3 × 5 mL), petroleum ether, and dried to give **11** (0.512 g, 66%) as a mixture of three diastereomers in a ratio of 70:25:5. After crystallization from MeCN, the major isomer with (2*R**,3*R**,4*S**)-configuration was obtained. Mp 204–204.5 °C (decomp., MeCN). IR (Nujol): $\nu$ = 3468 (s), 3407 (s), 3356 (br m), 3339 (s), 3213 (m) ($\nu$ NH), 3057 (w), 3037 (w), 3018 (w) ($\nu$ $CH_{arom}$), 1646 (s), 1620 (s) (amide-I), 1594 (w) ($\nu$ $CC_{arom}$), 1514 (s) (amide-II), 1295 (s) ($\nu_{as}$ $SO_2$), 1130 (s) ($\nu_s$ $SO_2$), 811 (m) ($\delta$ $CH_{arom}$ in Ts), 754 (s), 701 (s) ($\delta$ $CH_{arom}$ in Ph) $cm^{-1}$. $^1H$ NMR of (2*R**,3*R**,4*S**)-**11** (600.13 MHz, DMSO-$d_6$): $\delta$ = 6.97–7.07 (9H, m, Ph and $C_6H_4$), 6.75 (1H, d, $^3J_{NH,4\text{-}H}$ = 7.1 Hz, NH), 5.55 (2H, s, $NH_2$), 4.72 (1H, dddd, $^3J_{4\text{-}H,NH}$ = 7.1, $^3J_{4\text{-}H,5\text{-}Ha}$ = 4.2, $^3J_{4\text{-}H,5\text{-}He}$ = 3.1, $^3J_{4\text{-}H,3\text{-}H}$ = 2.7 Hz, 4-H), 4.34 (1H, d, $^3J_{2\text{-}H,3\text{-}H}$ = 3.3 Hz, 2-H), 3.88 (1H, ddd, $^3J_{3\text{-}H,2\text{-}H}$ = 3.3, $^3J_{3\text{-}H,4\text{-}H}$ = 2.7, $^4J_{3\text{-}H,5\text{-}He}$ = 1.0 Hz, 3-H), 3.16 (1H, ddd, $^2J_{6\text{-}He,6\text{-}Ha}$ = 14.0, $^3J_{6\text{-}He,5\text{-}Ha}$ = 5.1, $^3J_{6\text{-}He,5\text{-}He}$ = 1.9 Hz, 6-He), 2.92 (1H, ddd, $^2J_{6\text{-}Ha,6\text{-}He}$ = 14.0, $^3J_{6\text{-}Ha,5\text{-}Ha}$ = 13.2, $^3J_{6\text{-}Ha,5\text{-}He}$ = 2.8 Hz, 6-Ha), 2.58 (1H, br s, 1-H), 2.28 (3H, s, $CH_3$), 1.99 (1H, dddd, $^2J_{5\text{-}Ha,5\text{-}He}$ = 14.1, $^3J_{5\text{-}Ha,6\text{-}Ha}$ = 13.2, $^3J_{5\text{-}Ha,6\text{-}He}$ = 5.1, $^3J_{5\text{-}Ha,4\text{-}H}$ = 4.2 Hz, 5-Ha), 1.53 (1H, ddddd, $^2J_{5\text{-}He,5\text{-}Ha}$ = 14.1, $^3J_{5\text{-}He,4\text{-}H}$ = 3.1, $^3J_{5\text{-}He,6\text{-}Ha}$ = 2.8, $^3J_{5\text{-}He,6\text{-}He}$ = 1.9, $^4J_{5\text{-}He,3\text{-}H}$ = 1.0 Hz, 5-He). $^{13}C$ NMR of (2*R**,3*R**,4*S**)-**11** (150.90 MHz, DMSO-$d_6$): $\delta$ = 157.8 (C=O), 142.9 (C-4 in 4-$MeC_6H_4$), 139.3 (C-1 in 4-$MeC_6H_4$), 138.5 (C-1 in Ph), 129.0, 127.4, 126.6, 126.3 (C-2, C-3, C-5, C-6 in Ph and 4-$MeC_6H_4$), 126.1 (C-4 in Ph), 64.5 (C-3), 54.9 (C-2), 43.9 (C-4), 41.0 (C-6), 27.8 (C-5), 20.9 ($CH_3$). Anal. Calcd for $C_{19}H_{23}N_3O_3S$: C, 61.10; H, 6.21; N, 11.25. Found: C, 61.08; H, 6.44; N, 11.32.
17. Arndt, F.; Martius, C. *Liebigs Ann. Chem.* **1932**, *499*, 228–287.