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Simple and highly diastereoselective synthesis of trifluoromethyl-containing myosmines via reaction between 2-(aminomethyl)pyridine and 1,1,1,5,5,5-hexafluoro-2,4-pentanedione

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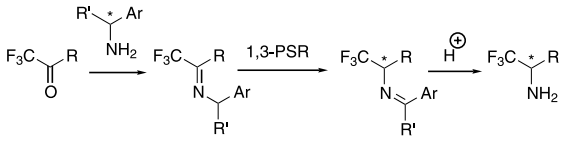
Abstract—The reaction between 1,1,1,5,5,5-hexafluoro-2,4-pentanedione and 2-(aminomethyl)pyridine, or its salts with carboxylic acids, was found to produce a mixture of diastereomeric 2-(2′-pyridyl)-3-hydroxy-3,5-bis-trifluoromethyl-1-pyrrolines with high (up to 85% de) of kinetic (3*R**,5*S**)-diastereoselectivity. The thermodynamic (3*R**,5*R**) diastereomer was prepared as a major product (90% de) by epimerization of the kinetic (3*R**,5*S**) diastereomer with triethylamine.

A naturally occurring 2-(2-pyridyl)-1-pyrroline (*o*-myosmines) is a unique structural unit found in a number of big groups of antibiotics such as myosmines,[1] siderochelins[2] as well as in proferrorosamines, belonging to the family of the rare microbial iron(II) chelators.[3] Besides the biological activity of this type of compounds, chiral derivatives of 2-(2-pyridyl)-1-pyrroline have drawn a great deal of synthetic interest being used as an effective α-diimine ligands for transition metal-catalyzed enantioselective reactions.[3] In this communication, we report our unexpected results that allow for a experimentally simple and highly diastereoselective preparation of a hitherto unknown type of these versatile molecules, fluorine-containing derivatives of 2-(2′-pyridyl)-1-pyrroline, to study their biological activity as well as potential synthetic applications.



Scheme 1.

Keywords: kinetic/thermodynamic diastereoselectivity; epimerization; fluorine-containing compounds; 1,3-proton shift.

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For quite some time, we have been interested in a biomimetic approach to reductive amination of carbonyl-compounds based on an intramolecular reduction-oxidation process via a base-catalyzed 1,3-proton shift in the aza-allylic system of azamethines (imines) (Scheme 1).[4] We demonstrated the synthetic potential of this conventional reducing reagent-free biomimetic transamination process, referred to as a base-catalyzed 1,3-proton shift reaction (PSR), for the efficient preparation of fluorine-containing amino compounds of a wide range of potential synthetic and biological applications. Previously, we reported a number of practical approaches for biomimetic transamination, via PSR, of perfluoroalkylcarboxylic acids,[5] fluorine-containing aldehydes and ketones,[6] α- and β-keto carboxylic acids[7] to the corresponding fluorinated amines and amino acids.

As an extension of our PSR methodology for preparing polyfunctional molecules, we studied the reactions between 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (**1**) and various derivatives of benzylamine with the aim of reductive amination of one of the carbonyl groups in **1**. Of particular interest were the reactions of picolylamines **2a–c** with diketone **1** as we previously showed that the presence of pyridine moiety substantially facilitated the desired 1,3-proton transfer.[6b,8] Surprisingly, all three reactions of diketone **1** with picolylamines **2a–c**, conducted under the same conditions,[9] gave very different reaction outcomes. Thus, the reaction of *m*-

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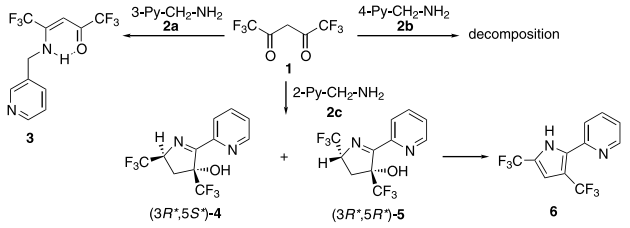
picolylamine (**2a**) with **1** furnished the expected enamine **3** (Scheme 2), while the reaction of *p*-picolylamine (**2b**) resulted in a mixture of at least 10 unidentified compounds.[10] By contrast, the reaction between *o*-picolylamine (**2c**) and diketone **1** proceeded cleanly giving rise to a mixture of two diastereomeric compounds **4** and **5** in 71% yield and in a ratio of 63:37, respectively (Table 1, entry 1). Structure and relative configuration of the products were unequivocally deduced from their NMR spectra. In particular, signals of trifluoromethyl groups of compound **4** appear in ^{19}F NMR as doublet of quartets (−74.4 ppm, $J=8.0$, 4.5 Hz) and quartet (ppm, $J=4.5$ Hz) indicating that the trifluoromethyl groups in **4** are located in close proximity (*cis*) to each other.[11] Since the reaction outcome, the formation of products **4** and **5**, was really unexpected, we decided first to investigate the catalytic role of *p*-toluenesulfonic acid. Therefore, we conducted reaction between diketone **1** and free amine **2c**. Interestingly, the reaction proceeded with a similar reaction rate, giving rise to a mixture of products **4** and **5** with a noticeable increase in a ratio of the major product **4** (entry 2). However, the yield of products **4** and **5** was relatively low, presumably due to substantial haloform-type decomposition of highly electrophilic diketone **1**.[6b]



Scheme 2.

Table 1. Reactions between diketone **1** and picolylamine **2c**[a]

Entry	Acid	Ratio[b] **4**/**5**	Yield[c] (%)
1	*p*-Toluenesulfonic acid[d]	63/37	71
2	None	70/30	53[e]
3	*p*-Toluenesulfonic acid	47/53	47[f]
4	Acetic acid	85/15	71
5	Trifluoroacetic acid	44/56	76
6	Benzoic acid	92/8	71
7	None	83/17	–[g]
8	None	61/39	–[h]

[a] All reactions were conducted at reflux for 1 h in toluene in a sealed tube. Ratio of the starting diketone **1** and picolylamine **2c**, or is salt, was 1:1.1.

[b] Determined by ^{19}F NMR (300 MHz) analysis of the crude reaction mixtures.

[c] Combined (isolated) yield of products **4** and **5**.

[d] Reaction was conducted in the presence of 5 mol% of *p*-toluenesulfonic acid.

[e] Apart from compounds **4** and **5**, the corresponding amide of trifluoroacetic acid was isolated in 25% yield. See text.

[f] Conversion of the starting products was less than 60%.

[g] The reaction time was 30 min.

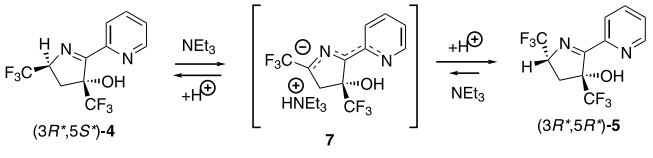
[h] The reaction time was 3 h.

By contrast, the reaction of **1** with toluenesulfonate of picolylamine **2** proceeded at low rate and resulted in a decreased diastereoselectivity (entry 3). To improve further the diastereoselectivity and yield of products **4** and **5**, we conducted a series of reactions using various salts of **2c**. Some representative examples are summarized in Table 1. Thus, the highest chemical yield was obtained with the trifluoroacetic acid salt of **2c** (76%, entry 5) while the best diastereoselectivity (92/8) was observed in the reaction using the benzoic acid salt of **2c** (entry 6). The reaction between **1** and benzoate of **2c** was conducted on a 2.8 g scale and major product **4** was isolated in diastereomerically pure form by column chromatography.[12]

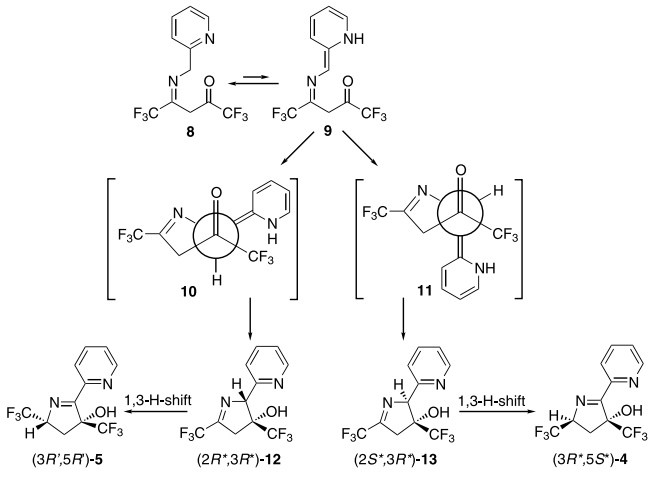
It is necessary to note that a prolonged heating of the reaction mixtures (more than 1 h) generally resulted in lower diastereoselectivity and formation of pyrrole **6**. Compound **6** could be obtained as a major product after 24 h reaction in the presence of *p*-toluenesulfonic acid or under the conditions described previously for general preparation of substituted-2-pyridylpyrroles from 1,3-diones and *o*-picolylamine.[13]

Taking into account that in the major (3*R**,5*S**)-diastereomer **4** the trifluoromethyl groups are in a close proximity to each other, we assumed that this diastereomer might be thermodynamically unstable due to significant unfavorable steric repulsive interactions. Indeed, treatment of (3*R**,5*S**)-**4** with triethylamine in an acetonitrile solution at 75°C resulted in a complete epimerization of (3*R**,5*S**)-**4** to thermodynamically more stable (3*R**,5*R**)-diastereomer **5** isolated in high chemical yield (95%) (Scheme 3).[14] The equilibrium ratio of 95/5 was obtained starting from each diastereomerically pure **4** and **5** as well as from their 1:1 mixture. The epimerization was monitored by ^{19}F NMR on the crude reaction mixture and the ratio of the diastereomers (95/5) did not change upon the work-up and chromatographic isolation of diastereomerically pure product (3*R**,5*R**)-**5**. We can assume that epimerization of **4** to **5** was possible due to high C–H acidity of the proton in α-position to the trifluoromethyl group in **4** which could be easily abstracted by the base to form the intermediate anion **7**. Protonation of anion **7** to a new covalent state gave rise to less sterically constrained and thus thermodynamically favorable diastereomer **5**.

To account for the observed chemical and stereochemical outcome in the reactions of diketone **1** with free amine **2c**, as well as with its salts, we can propose the reaction sequence presented in Scheme 4. The reaction appears to proceed through the formation of the imine **8** which can tautomerize to give enamine structure **9**.[13]



Scheme 3.



Scheme 4.

Further cyclization of **9**, by nucleophilic attack on the carbonyl carbon by the carbon of the (2-pyridyl)methyl moiety, is thought to occur via transition states (TSs) **10** and/or **11**.[15] Taking into account highly organized structures of TSs **10** and **11**, we can expect that the cyclization step should be highly diastereoselective leading to the formation of the intermediate (2*R**,3*R**)-**12** and (2*S**,3*R**)-**13**, respectively. Considering steric and electronic features of the TSs **10** and **11**, we can assume that TS **11** might be thermodynamically favored over TS **10** providing predominant formation of compound (2*S**,3*R**)-**13** containing the hydroxy group and the hydrogen (in α-position to the imine group) in *cis*-disposition to each other. Based on the results of our previous studies of kinetics and mechanism of 1,3-PSR,[16] as well as the data obtained in the series of asymmetric 1,3-PSR[4,6c,7c] transformations, we can expect that the compound (2*S**,3*R**)-**13** might undergo, thermal or base-catalyzed, suprafacial 1,3-PSR giving rise to the final product (3*R**,5*S**)-**4**. Similarly, the intermediate (2*R**,3*R**)-**12**, once formed, will afford the corresponding (3*R**,5*R**)-**5** in highly diastereoselective manner. The discussed above mechanistic rational could be applicable for the reactions conducted with free-amine **2c** or with the salts of **2c** derived from acetic and benzoic acids (entries 2, 4 and 6). On the other hand, the mechanism and mode of the stereochemical preferences could be different in the reactions conducted with an equimolar amounts of strong acids (entries 3 and 5). In this case the strong acid, such as *p*-toluenesulfonic (entry 3) or trifluoroacetic acid (entry 5) might be capable of protonating all three nucleophilic centers in imine **8** and enamine **9** resulting in non-diastereoselective formation of the intermediates (2*S**,3*R**)-**13** and (2*R**,3*R**)-**12**. Furthermore, to account for the different diastereoselectivity observed in the reactions conducted with free-amine **2c** and with the salts of **2c** derived from acetic and benzoic acids (entries 2 versus 4 and 6) we assumed that under the acid-free conditions the major product (3*R**,5*S**)-**4** can undergo partial epimerization (Scheme 3)[17] to give (3*R**,5*R**)-**5**, while in the presence of the acids this process might be inhibited. To verify this assumption, we conducted the reaction between diketone **1** and amine **2c** to determine the ratio of diastereomers **4** and **5** as a function of the reaction time. As we expected, the excess of the major diastereomer **4** was higher on the earlier reaction stage (30 min) (entry 7) and noticeably lower after heating the reaction mixture for 3 h (entry 8). These results support plausibility of the mechanistic rationale presented in Scheme 4 which involves new, highly diastereoselective and thus potentially useful synthetic transformation (cyclization of **9** to **13**).

In summary, we found that the reaction between 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (**1**) and 2-(aminomethyl)pyridine (**2c**), or its salts with carboxylic acids, unexpectedly produced a mixture of diastereomeric 2-(2-pyridyl)-3-hydroxy-3,5-bis-trifluoromethyl-1-pyrrolines with high (84% de) kinetic (3*R**,5*S**)-diastereoselectivity. The thermodynamic (3*R**,5*R**) diastereomer was prepared as a major product (90% de) by epimerization of the kinetic diastereomer with triethylamine. Each product was easily obtained in a diastereomerically pure form by column chromatography.

Acknowledgements

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9. Standard reaction conditions for preparing imines from carbonyl compounds and primary amines were used: reflux of the starting compounds in toluene in the presence of catalytic amounts of *p*-toluenesulfonic acid and trapping the releasing water with a Dean–Stark device.
10. At least 10 different signals with integral intensity not matching 1:1 were detected (by ^{19}F NMR) in the reaction mixture.
11. *(3R′,5S′)-2-(2′-Pyridinyl)-3-hydroxy-3,5-bis-trifluoromethyl-1-pyrroline* (**4**): R_f=0.40 (hexanes/AcOEt, 3/1, v/v); (65.3%); mp 65–66°C. ^1H NMR δ 2.57 (1H, ddq, J=15.3, 9.0, 0.9 Hz), 2.70 (1H, dd, J=15.6, 5.1 Hz), 5.00 (1H, m), 6.86 (1H, br), 7.48 (1H, ddd, J=7.8, 5.1, 1.2 Hz), 7.87 (1H, td, J=7.8, 1.8 Hz), 8.00 (1H, dm, J=7.8 Hz), 8.56 (1H, dm, J=4.8 Hz). ^{19}F NMR δ −77.3 (CF_3, q, J=4.5 Hz), −74.4 (CF_3, dq, J=8.0, 4.5 Hz). ^{13}C NMR δ 33.3, 71.4 (q, J=30.4 Hz), 88.8 (q, J=30.8 Hz), 123.1, 124.1. (q, J=282.9 Hz), 124.5 (q, J=276.8 Hz), 126.0, 137.5, 147.6, 151.4, 170.2. Anal. calcd for $C_{11}H_8F_6N_2O$: C, 44.31; H, 2.70; F, 38.23; N, 9.39. Found: C, 44.32; H, 2.68; F, 38.24; N, 9.32.
2-(2-Pyridinyl-(3R′,5R′)-ditrifluoromethyl-4,5-dihydro-3H-pyrrol-3-ol) (**5**): R_f=0.49 (hexanes/AcOEt, 3/1, v/v); (5.7%); colorless liquid; ^1H NMR δ 2.41 (1H, ddq, J=14.4, 9.3, 1.5 Hz), 2.70 (1H, dd, J=14.1, 6.9 Hz), 4.59 (1H, m), 7.48 (1H, ddd, J=7.8, 5.1, 1.5 Hz), 7.89 (1H, td, J=7.8, 1.8 Hz), 8.01 (1H, br), 8.17 (1H, dm, J=8.1 Hz), 8.57 (1H, dm, J=5.1 Hz). ^{19}F NMR δ −74.4 (CF_3, s), −75.6 (CF_3, d, J=7.5 Hz). ^{13}C NMR δ 35.2, 69.7 (q, J=30.8 Hz), 88.3 (q, J=30.5 Hz), 123.2, 124.5 (q, J=276.1 Hz), 124.8 (q, J=284.9 Hz), 126.4, 137.7, 147.5, 151.2, 169.1. Anal. calcd for $C_{11}H_8F_6N_2O$: C, 44.31; H, 2.70; F, 38.23; N, 9.39. Found: C, 44.31; H, 2.69; F, 38.24; N, 9.38.
12. General procedure for preparing 3-hydroxyl-3,5-ditrifluoromethyl-myosmine **4** and **5**: To a solution of 2-(aminomethyl)pyridine (2.859 g, 26.435 mmol) in 10 mL of toluene benzoic acid (3.228 g, 26.435 mmol) were added at rt. The resultant suspension was stirred for 5 min followed by an addition of 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (4.996 g, 24.032 mmol) in 10 mL of toluene. The mixture was heated at 140°C for 1 h, cooled down and treated with triethylamine (20 mL) to neutralize the benzoic acid. The mixture was evaporated in vacuum and the products were isolated by column chromatography (hexanes/AcOEt 10/1, v/v).
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14. Epimerization of (3*R**,5*S**)-diastereomer **4** to (3*R**,5*R**) **5**: To a solution of a mixture of diastereomers **4** and **5** (ratio 44/56) (0.2388 g, 0.8 mmol) in CH_3CN (6 mL) was added triethylamine (0.58 mL, 4.00 mmol) and the resultant mixture was kept at 75°C for 24 h. The solvent and triethylamine were removed under reduced pressure and the residue was subjected to column chromatography (hexanes/AcOEt 10/1, v/v) to afford 0.2241 g (94%) of product **5**.
15. TSs **9** and **10** were drawn only for *trans*-conformers of **8** and **9** (relative position of the nitrogens). Similar structures could be drawn for the corresponding *cis*-conformers without influencing the discussed stereochemical outcome.
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17. The pyridine moiety in compounds **4** and **5** is basic enough to assist the epimerization.