Conference paper

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Competitive ways for three-component cyclization of polyfluoroalkyl-3-oxo esters, methyl ketones and amino alcohols

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Abstract: The competitive routes were found for three-component cyclization of polyfluoroalkyl-3-oxo esters, methyl ketones with 3-amino alcohols. It was shown that the reactions with 3-aminopropanol in 1,4-dioxane predominantly lead to hexahydropyrido[2,1-*b*][1,3]oxazin-6-ones, and in ethanol to 3-hydroxypropylaminocyclohexenones. In contrast, cyclizations with 2-aminoethanol and its analogues, regardless of the reaction conditions, yield hexahydrooxazolo[3,2-*a*]pyridin-5-ones as the main products. The *trans*- and *cis*-diastereomeric structure of heterocycles was established using X-ray and ^{1}H, ^{19}F, ^{13}C NMR spectroscopy, 2D ^{1}H-^{13}C HSQC and HMBC experiments. The mechanism is proposed for competitive transformations of polyfluoroalkyl-3-oxo esters, methyl ketones with 3-amino alcohols.

Keywords: amino alcohols; diastereomers; cyclohex-2-en-1-ones; hexahydrooxazolo[3,2-*a*]pyridin-5-ones; hexahydropyrido[2,1-*b*][1,3]oxazin-6-ones; Mendeleev-21; methyl ketones; polyfluoroalkyl-3-oxo esters; three-component cyclization.

Introduction

Multicomponent reactions (MCR) play an important role in generating a variety of compounds whose structure is formed from three or more reagents in one step. MCR are extremely efficient, atom-economical, and technically feasible processes [1–4]. In the literature there are many examples illustrating the use of trifluoroacetoacetic ester in MCR to obtain different heterocyclic products [5–12].

Generally speaking, trifluoroacetoacetic ester belongs to the universally acknowledged building blocks of organic synthesis for obtaining a variety of open-chain, carbo- and hetero-cyclic molecules [13–15], including practically important compounds. Synthesis of trifluoromethyl-substituted heterocycles is especially promising for pharmaceutical chemistry, because the heterocycles have unique physical and biological properties due to the presence of the trifluoromethyl group [16–18]. It is an established fact that the replacement of methyl group by trifluoromethyl moiety leads to an increase in metabolic stability and lipophilicity of organic molecules, which can contribute to improving the pharmacokinetic characteristics of bioactive compounds [19–21]. A great

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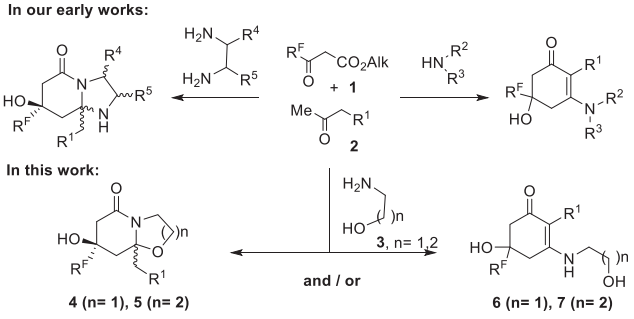
achievement in this field is the trifluoroacetoacetic ester-based production of the medicinal drug celecoxib as a selective COX-2 inhibitor [22, 23].

Our research team [24–34] and other researchers [35–38] have found numerous examples illustrating the synthesis of various heterocyclic systems from polyfluoroalkyl-containing 3-oxo esters and their derivatives in a way which is uncharacteristic of the non-fluorinated analogues.

Recently, we discovered a new three-component reaction of polyfluoroalkyl-3-oxo esters, methyl ketones with 1,2-di- and monoamines. It was found that the use of 1,2-ethanediamines in such reactions leads to chemo-, regio- and stereo-selective formation of hexahydroimidazo[1,2-*a*]pyridine-5-ones [39], which under dehydration conditions are transformed into 1-(2-aminoethyl)-6-alkyl-4-polyfluoroalkylpyridinones, including tuberculostatic active ones [40]. The introduction of di- and monoalkyl amines into this three-component reaction changed the direction of cyclization, which allowed cyclohex-2-en-1-ones to be obtained [41]. Thus, varying the amine component in the new three-component reaction can result in both heterocyclic and carbocyclic compounds (Scheme 1).



Scheme 1: The routes of the reactions polyfluoroalkyl 3-oxo esters **1** with methyl ketones **2** and amines **3**.

In this work, the three-component reactions of polyfluoroalkyl-3-oxo esters **1** and methyl ketones **2** with 1,2- and 1,3-amino alcohols **3** were investigated. Amino alcohols are commercially available reagents that contain two nonequivalent reaction centres, whereby they can react as *N*,*O*-dinucleophiles generating a bicyclic backbone of hexahydrooxazolo(azino)pyridines **4**, **5**, and/or as *N*-mononucleophiles giving a cyclohexenone core **6, 7** (Scheme 1).

Oxazolo(azino)piperidine moiety is present in some natural products and drug-like molecules [42–46]. In addition, these compounds are used as intermediate products for the synthesis of bioactive alkaloids, for example, (R)-(–)-coniine, (–)-anabasine, (–)-solenopsin A, (±)-adalinine, etc. [47–49], as well as of a wide range of other optically pure carbo- and hetero-cycles [50, 51]; therefore, it shows promise to develop new approaches to the synthesis of these heterocycles derivatives.

The main method used for preparing hexahydrooxazolo[3,2-*a*]pyridinones and hexahydropyrido[2,1-*b*] oxazinones involves two-component cyclizations of 1,2- and 1,3-amino alcohols with acids having a ketone [52–57] or aldehyde [58–60] group at the C5 position [61]. Glutaric anhydride can be used instead of acids in condensation with amino alcohols, but in this case it is necessary to carry out subsequent reduction [62, 63]. The formation of the hexahydrooxazolo(azino)pyridine backbone is described as a result of four-component cyclization of butenoic acid, a 1,2- or 1,3-amino alcohol and gaseous CO and H_2 [64, 65]. Oxazolopiperidones were also prepared by condensation of Ser-OMe and 3-(5-oxo-1,3-oxazolidin-4-yl)propanal [66] or by cyclization of 2,4-dimethyl-4-(3-oxo-1-phenylbutyl)-1,3-oxazol-5(4*H*)-one with alanine [67]. The only example found in literature, which illustrates the synthesis of 3-phenyl-8a-(trifluoromethyl)hexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridin-5-one, is by the reaction of 6,6,6-trifluoro-5-oxohexanoic acid with (*S*)-(+)-phenylglycinol [68].

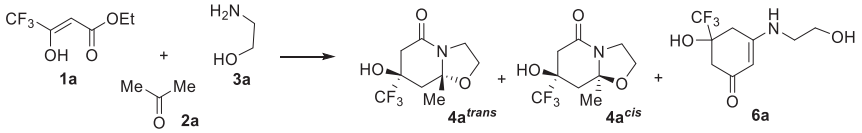
Previously, we have reported on the value of synthesis of new cyclohexenone structures [41].

Results and discussion

In the present work, possible alternative ways were studied for the recently discovered three-component cyclization of polyfluoroalkyl-3-oxo esters **1** and methyl ketones **2** with 1,2- and 1,3-amino alcohols **3** as amine component into bicyclic heterocycles (hexahydrooxazolo[3,2-*a*]pyridin-5-ones **4** and hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazin-6-ones **5**) or cyclohex-2-en-1-ones **6, 7**. The probable formation of diastereomeric bicycles cannot be overlooked, because the cyclization of polyfluoroalkyl-3-oxo esters **1** and methyl ketones **2** with 1,2-ethanediamines resulted in 7-hydroxy-7-(polyfluoroalkyl)hexahydroimidazo[1,2-*a*]pyridin-5(1*H*)-ones in *trans*- and/or *cis*-forms depending on their structure and the reaction conditions [39].

Indeed, when we examined the ^{1}H, ^{19}F NMR spectra of the reaction mixture of trifluoroacetoacetic ester **1a**, acetone **2a** and 2-aminoethanol **3a** in acetonitrile after three-day ageing, we detected the formation of two hexahydrooxazolo[3,2-*a*]pyridin-5-ones **4a**^{cis} and **4a**^{trans} as well as cyclohex-2-en-1-ones **6a** as a minor product. Although the reaction in acetonitrile runs with the high total yield, the diastereoselectivity was low in these transformations (Table 1, entry 1), so we decided to optimize the reaction conditions. To control their course, we used the ^{19}F NMR spectroscopy, since all three products bearing CF_3-group had singlet signals with determined chemical shifts (**4a**^{trans} at δ 79.73 ppm, **4a**^{cis} at δ 80.79 ppm and **6a** at δ 80.38 ppm). It turned out that in aprotic low-polar solvents (THF, 1,4-dioxane) a high conversion of the initial reagents was achieved (Table 1, entries 2, 3), but in 1,4-dioxane the reaction took place with high diastereoselectivity to give predominantly one bicycle **4a**^{trans} (Table 1, entry 3). Under all these conditions, the formation of cyclohexenone **6a** was observed only in trace amounts. Previously, for the effective formation of cyclohexenones in similar three-component synthesis, it was proposed to carry out the reaction in absolute ethanol with zeolites [41]. However, even under these conditions, we could not obtain product **6a** with an acceptable yield (table 1, entries 4, 5). According to ^{19}F NMR spectrum, its formation was recorded only with the yield at 8% (entry 5). Attempts to isolate cyclohexenone **6a** as an individual compound were unsuccessful. Instead, it turned out that the proportion of *cis*-isomer **4a**^{cis} in ethanol increases significantly. It should be noted that three-component cyclization of ester **1a**, acetone **2a** with aminoethanol **3a** were sensitive to heating, because under these conditions there was a strong tarring of the reaction mass in contrast to similar reactions with 1,2-ethanediamines [39].

Table 1: Optimization of the reaction conditions for the 2-aminoethanol **3a**.

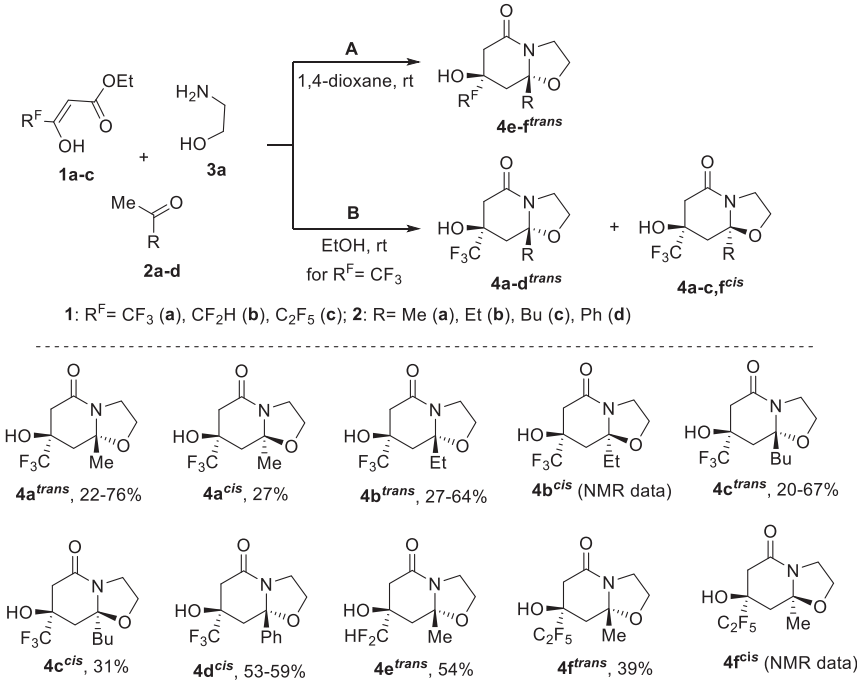


Entry	Conditions[a]	Time, days	Products, yield [%][b]			Total yield [%][b]
			4a^{trans}	**4a**^{cis}	**6a**	
1	CH_3CN, HPLC	3	55	35	3	93
2	THF, 99+%	3	61	25	2	88
3	1,4-dioxane, 99+%	3	80	9	Trace	89
4	EtOH (abs)	3	42	33	7	82
5	EtOH (abs), zeolites	3	33	25	8	66

[a]Conditions: Reactions performed with **1a** (1 mmol), **2a** (1 mmol) and **3a** (1 mmol) in 5 mL of the solvent at room temperature.
[b]Determined by ^{19}F NMR analysis of the mixture.

Thus, in order to obtain the *trans*-isomers of hexahydrooxazolo[3,2-*a*]pyridin-5-ones **4**^{trans} regioselectively, we carried out the reactions of esters **1** with methyl ketones **2** and aminoethanol **3a** in 1,4-dioxane at room temperature, whereas *cis*-isomers **4**^{cis} were isolated from reactions in absolute ethanol.

As expected, in the three-component reaction of trifluoroacetoacetic ester **1a** with 2-aminoethanol **3a** in 1,4-dioxane, varying the methyl ketone component **2** by using 2-butanone **2b** and 2-hexanone **2c** instead of acetone **2a** led to the formation of bicycles *trans*-diastereomers **4b**^{trans}, **4c**^{trans} (Scheme 2). *Cis*-isomers **4b**^{cis}, **4c**^{cis} were isolated from a mixture of isomers that formed in approximately equal ratios in ethanol. The isomers were separated by fractional crystallization or column chromatography. However, we failed to find conditions for the isolation of **4b**^{cis} as an individual compound.

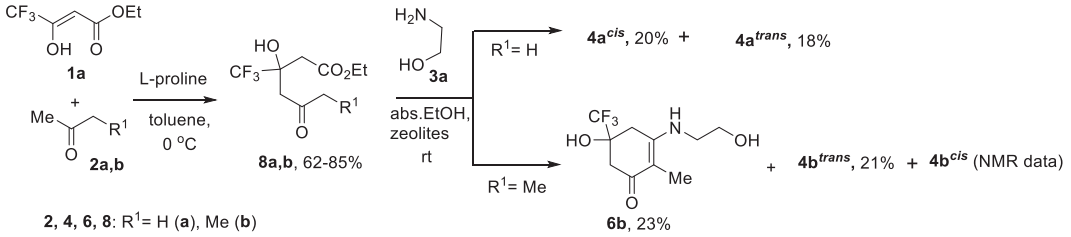


Scheme 2: Three-component reaction of polyfluoroalkyl-3-oxo esters **1**, methyl ketones **2** and 2-aminoethanol **3a.**

Unlike alkyl methyl ketones **2a–c**, the three-component reaction of acetophenone **2d** with ester **1a** and 2-aminoethanol **3a** even in ethanol resulted in one *cis*-diastereomer of hexahydrooxazolo[3,2-*a*]pyridin-5-ones **4d**^{cis}. The change and increase in stereoselectivity of this reaction may be due to the presence of a bulk phenyl substituent, which plays the role of a conformational anchor.

Further, it was found that the replacement of trifluoroacetoacetic ester **1a** by difluoromethyl- and pentafluoroethyl-containing 3-oxo esters **1b** and **1c** in reaction with acetone **2a** and aminoethanol **3a** in 1,4-dioxane gives *trans*-diastereomers of bicycles **4e**^{trans} and **4f**^{trans}. At the same time, their yields are reduced compared to the trifluoromethyl analogue. Carrying out these reactions in ethanol led to a significant tarring of the reaction mass. We were able to isolate only the *cis*-isomer **4f**^{cis} in the mixture of 3 : 5 with the *trans*-isomer **4f**^{trans} from the reaction of pentafluoroethyl ester **1c**.

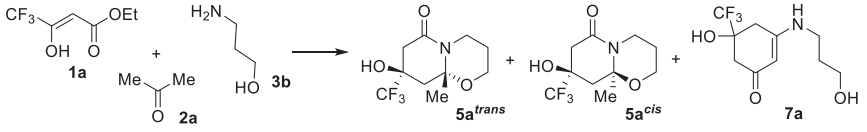
We failed to isolate cyclohexenone **6a** as an individual substance from the three-component reaction of trifluoroacetoacetic ester **1a** with methyl ketone **2a** and aminoethanol **3a**, so we tried to realize its synthesis in ethanol via a two-component reaction of aminoethanol **3a** and aldol **8a** obtained from ester **1a** with methyl ketone **2a** according to the method [41]. However, under these conditions, cyclohexenone **6a** was formed as a byproduct along with heterocycle **4a**^{trans} (Scheme 3). Nevertheless, a similar reaction of ethyl-substituted aldol **8b** with aminoethanol **3a** allowed cyclohexenone **6b** to be isolated from a mixture with bicycle **4b**^{trans}. Note that the heterocycles **4a**^{trans}, **4b**^{trans} were obtained from aldol **8a,b** in 1,4-dioxane, albeit with lower yields compared to the three-component synthesis.



Scheme 3: Two-component synthesis of cyclohexenones **6** and hexahydrooxazolo[3,2-*a*]pyridin-5-ones **4.**

In contrast to the reactions with aminoethanol **3a**, three-component cyclization of ester **1a** and acetone **2a** with 3-amino-1-propanol **3b** in aprotic solvents proceeded stereoselectively to form one diastereomer of hexahydropyrido[2,1-*b*][1,3]oxazin-6-one **5a**^{trans}, whereas the isomer **5a**^{cis} was either formed in trace amounts or not at all (Table 2, entries 1–4). The highest yields of bicycle **5a**^{trans} were achieved in THF and 1,4-dioxane (Table 2, entries 2–4), but in 1,4-dioxane the selectivity of the reaction was higher. Another feature of the transformations with aminopropanol **3b** was the obtaining of cyclohexenone **7a** when ethanol was used as a solvent (Table 2, entries 5, 6). It should also be noted that cyclizations with amino alcohol **3b** took more time (7–10 days), and they occurred with moderate yields with incomplete conversion of the starting ester **1a**. The attempts to increase the reaction rate and yields by adding triethylamine as a catalyst did not lead to the desired result (Table 2, entries 4, 6).

Table 2: Optimization of the reaction conditions for the 3-amino-1-propanol **3b**.

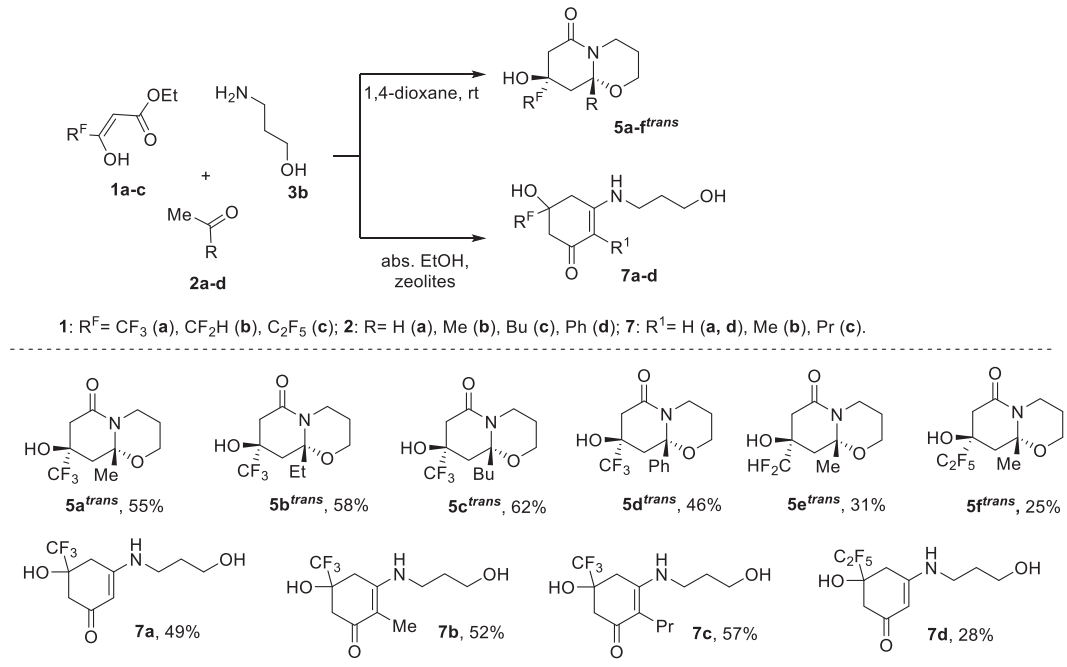


Entry	Conditions[a]	Time, days	Products, yield [%][b]			Yield total
			5a^{trans}	5a^{cis}	7a	
1	CH_3CN, HPLC	10	27	8	6	41
2	THF, 99+%	10	60	trace	7	67
3	1.4-dioxane, 99+%	10	58	trace	trace	58
4	1.4-dioxane, 99+%, NEt_3	7	50	-	3	53
5	EtOH (abs), zeolites	10	8	4	53	61
6	EtOH (abs), NEt_3, zeolites	7	9	-	51	60

[a]Conditions: Reactions performed with **1a** (1 mmol), **2a** (1 mmol) and **3b** (1 mmol) in 5 mL of the solvent at room temperature.
[b]Determined by ^{19}F NMR analysis of the mixture.

The reactions were monitored using ^{19}F NMR spectra, in which all three products can be identified by singlet signals of their CF_3 groups (**5a**^{trans} at δ 79.76 ppm, **5a**^{cis} at δ 80.21 ppm and **7a** at δ 80.38 ppm).

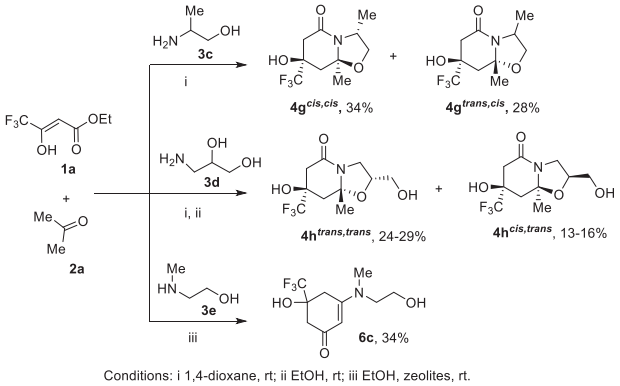
Realization of three-component reactions of trifluoroacetoacetic ester **1a** with methyl ketones **2a–d** and 3-amino-1-propanol **3b** in 1,4-dioxane allowed hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazin-6-ones **5a–d** to be obtained as a single *trans*-diastereomer (Scheme 4). Introduction of 3-oxoesters **1b** ($R^F = CF_2H$) or **1c** ($R^F = C_2F_5$) instead of ester **1a** in the reaction with acetone **2a** and 3-amino-1-propanol **3b** also led to the formation of hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazin-6-ones **5e**^{trans} and **5f**^{trans}, albeit with a small yield.



Scheme 4: Three-component reaction of polyfluoroalkyl-3-oxo esters **1**, methyl ketones **2** and 3-amino-1-propanol **3b.**

The use of abs. ethanol with zeolites as a condition for the three-component reaction of trifluoroacetoacetic ester **1a** with methyl ketones **2a–c** and 3-amino-1-propanol **3b** resulted in cyclohexenones **7a–c** (Scheme 4). A similar product **7d** was obtained in the reaction of pentafluoroethyl substituted ester **1c** with acetone **2a** and amino propanol **3b** under the same conditions.

In the studied three-component reactions, we also introduced amino alcohols **3c–e** having various substituents that can affect the result of these transformations. It was found that the use of (+/–)-2-amino-1-propanol **3c** in the reaction with ester **1a** and acetone **2a** in 1,4-dioxane led to *cis,cis*- and *trans,cis*-diastereomers of heterocycle **4g** (Scheme 5). Obviously, the methyl substituent in the aminoethanol **3a** affects the conformation of the resulting bicycle **4g**.



Scheme 5: Variation of amino alcohols **3** in the reaction with ester **1a** and acetone **2a.**

(+/–)-3-Amino-1,2-propanediol **3d** can react with ester **1a** and acetone **2a** as aminoethanol to form hexahydrooxazolo[3,2-*a*]pyridin-5-one **4h** and/or as 3-amino-2-propanol give hexahydropyrido[2,1-*b*][1,3]oxazin-6-one **5h.** However, regardless of the reaction conditions, two *trans,trans*- and *cis,trans*-diastereomers of

hexahydrooxazolo[3,2-*a*]pyridin-5-one **4h** were obtained. Such reaction course may be preferable because of the thermodynamic benefit of the formation of a five-membered cycle over the formation of a six-membered one.

When 2-(methylamino)ethanol **3e** was used as an amino alcohol component in the reaction with ester **1a** and acetone **2a**, only cyclohexenone **6c** could be formed (Scheme 5), because in this case the nitrogen atom cannot act as a bridge centre in the bicycle **4**.

The structures of all synthesized compounds were confirmed by IR, ^{1}H, ^{19}F, ^{13}C NMR spectroscopy and high-resolution mass spectrometry. Based on 2D ^{1}H-^{13}C HSQC and HMBC experiments, full correlation of signals in ^{1}H and ^{13}C NMR spectra was carried out. The relative configuration of substituents at stereocenters was determined by homonuclear 2D ^{1}H-^{1}H NOESY experiments. The structures of diastereomers **4** and **5** are shown in schemes 2–4. The relative configurations are given with respect to a hydroxyl group. Diastereomers **4** and **5** are racemates.

A direct confirmation of the *trans*-position of hydroxyl oxygen and oxazole or oxazine cycle oxygen is the cross-peak in the NOESY spectra between the OH-group proton and the substituent protons at the nodal carbon atom observed for all *trans*-isomers of type **4** and **5** structures. The spectra of *cis*-isomers show no cross-peak (OH, R); and the relative configuration is established on the basis of a set of other NOE correlations (see Supplementary).

Some diagnostic features of *cis*- and *trans*-configuration were established using the ^{1}H, ^{19}F NMR spectra analysis of hexahydrooxazolo[3,2-*a*]pyridine-5-ones **4** isomers. In the ^{1}H spectra, the most striking differences are related to the value of the nonequivalence (Δ_{6AB}) of diastereotope protons at C-6 and to the value of the geminal constant between them ($^{2}J_{6AB}$). *Cis*-isomers **4**^{cis} is characterized with a significant value Δ_{6AB} = 0.33 – 0.48 ppm, whereas in *trans*-isomers the value Δ_{6AB} < 0.07 ppm up to the degeneration of AB-system to spin system A_2 (Δ_{6AB} = 0). Besides, the constant $^{2}J_{6AB}$ in the transition from *cis*- to *trans*-isomers increases in absolute value from 15 to 17.8 Hz.

The presence of long-range spin-spin interaction between the protons of the methylene groups of the pyridinone cycle in compounds **4** and **5** with a characteristic value of the constant $^{4}J_{H,H}$ = 1.3 – 3.5 Hz indicates a pseudo-equatorial position of the interacting protons. The identification of axial and equatorial protons was used in the analysis of 2D NOESY spectra and for determining the relative configuration.

In the ^{19}F NMR spectra of compounds **4**, **5** having a trifluoromethyl substituent, the ^{19}F signals of *trans*- diastereomers are observed in a stronger field of δ ~ 79.8 ppm as compared to *cis*-diastereomers with δ ~ 80.4 – 80.8 ppm.

The structures of compounds **4a**^{trans}, **4a**^{cis}, **4c**^{cis}, **4h**^{trans,trans}, **5a**^{trans}, **7c** were confirmed by X-ray diffraction analysis data (Fig. 1 and Fig. 2).

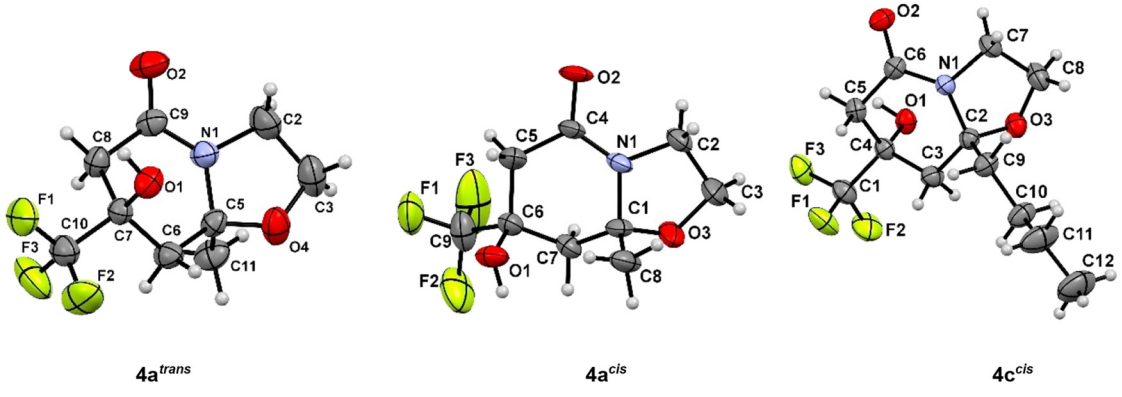


Fig. 1: ORTEP diagrams of compounds **4a**^{trans}, **4a**^{cis}, **4c**^{cis}.

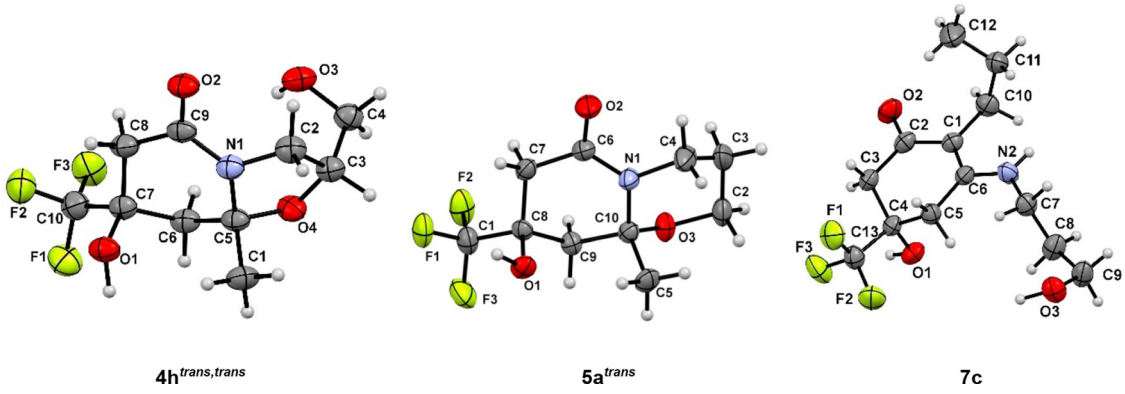
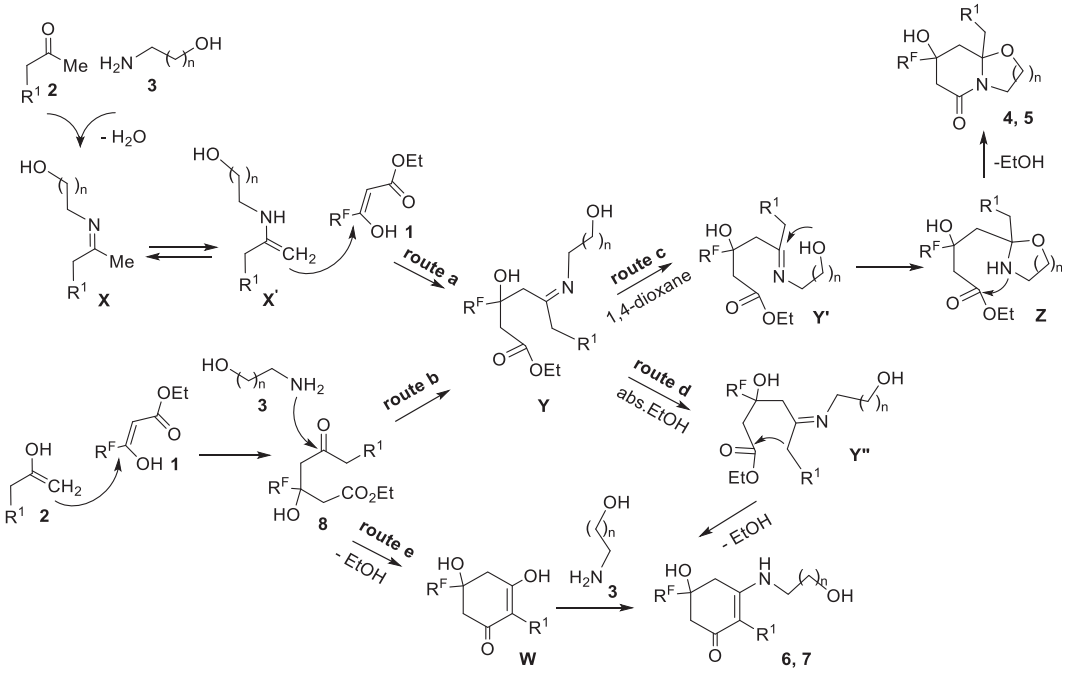


Fig. 2: ORTEP diagrams of compounds **4h**^{trans,trans}, **5a**^{trans}, **7c**.

For the reactions under consideration, it can be assumed that both bicycles **4, 5** and cyclohexenones **6, 7** are obtained via the enaminoester **Y** as a key intermediate. We can offer two ways to generate **Y:** (1) through enamine **X** formed from ketone **1** and amine **3** (pathway **a**) by the known enamine mechanism [69] or (2) through aldol **8** (pathway **b**) (Scheme 6). In the aprotic medium we observed the predominant formation of bicycles **4, 5**. Probably, these heterocycles are obtained as a result of intramolecular cyclization of the intermediate **Y′** due to nucleophilic addition of the hydroxyl group to the C=N bond (route **c**) to form the cycle **Z**, which further underwent intramolecular amidation of the ester fragment to give a bicyclic backbone **4, 5**. In ethanol, the reaction can proceed through the alternative pathway **d**, which becomes the main pathway for 3-aminopropanol **3b**. Most likely, in this case hydroxyl reaction centre of the intermediate **Y″** is blocked due to its solvation by solvent molecules (ethanol), resulting in intramolecular cyclization of enaminoketone **Y″** coming along the path **d** with the formation of aminocyclohexanones **6, 7** via the condensation ethoxycarbonyl fragment with an activated methylene group. For a spatially distant hydroxypropyl group, more efficient solvation is possible, which is the reason for the preferred formation of cyclohexenones **7**. Preparation of



Scheme 6: The proposed mechanism for the formation of bicycles **4, 5** and cyclohexenones **6, 7**.

hexahydrooxazolopyridinones **4** from aldol **8** in abs. ethanol can be explained by the possible intermediate formation of dihydroxycyclohexenone **W** (the pathway **e**) followed by its interaction with aminoethanol **3a**. All processes are autocatalysed, because amino alcohols **3a, b** act not only as reagents but also as base catalysts.

Conclusions

In summary, based on the three-component reaction of commercially available reagents, such as polyfluoroalkyl-3-oxo esters, methyl ketones and amino alcohols, the approaches are offered to obtaining hexahydrooxazolo[3,2-*a*]pyridin-5-ones, hexahydropyrido[2,1-*b*][1,3]oxazin-6-ones and cyclohexenones functionalized with amino alcohol fragment. It was found that the cyclization of 3-oxo ester and methyl ketone reagents with 3-aminopropanol in ethanol leads mainly to 3-hydroxypropylaminocyclohex-2-enones, whereas in 1,4-dioxane the main products are hexahydropyrido[2,1-*b*][1,3]oxazine-6-ones in the form of *trans*-diastereomers. In contrast to that, similar cyclization with aminoethanol and its analogues, regardless of the reaction conditions, yields hexahydrooxazolo[3,2-*a*]pyridine-5-ones mainly. In this case, the reaction with alkyl methyl ketones in 1,4-dioxane proceeds stereoselectively to form *trans*-diastereomers, while a mixture of *cis*-and *trans*-diastereomers is generated in ethanol, which allows the *cis*-isomer to be isolated. In the case that acetophenone is introduced in the cyclization with both amino alcohols, *cis*-diastereomer heterocycles are the predominant products. The synthesis of 3-hydroxyethylaminocyclohex-2-enones is possible in rare cases only.

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