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Preparation of New Trifluoromethyl Substituted Tri- and Tetracyclic Heterocycles with Peganin Skeleton from a Methyl 3,3,3-Trifluoropyruvate / 2-Aminobenzylamine Adduct

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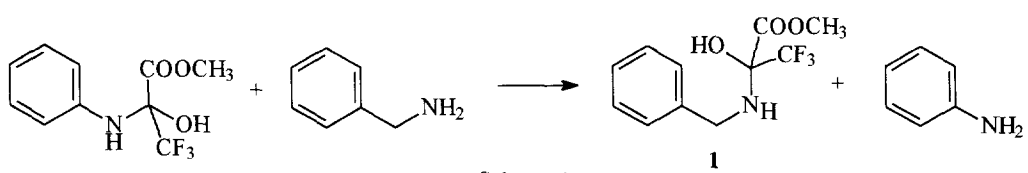
Abstract: Addition of 2-aminobenzylamine to methyl trifluoropyruvate afforded methyl 2-((2-aminobenzyl)amino)-3,3,3-trifluoro-2-hydroxypropionate, which reacted with various ketones to give new fluorinated tricyclic and tetracyclic heterocycles with the skeleton of the alkaloid Peganin. Copyright © 1996 Elsevier Science Ltd

The trifluoromethyl group has been often introduced into organic molecules with the aim to modify biological activity[1]. Along with direct trifluoromethylation or fluorination of a one-carbon substituent, the use of fluorinated synthons has become the tactics of choice especially in the syntheses of trifluoromethylated heterocycles[2]. Methyl 3,3,3-trifluoropyruvate has been extensively employed in the preparation of fluorinated five- and six-membered heterocycles[3,4]. Synthetic applications of polyfunctional compounds arising from mono-addition of nucleophiles to the keto group of methyl 3,3,3-trifluoropyruvate are much less known[5]. We wish to report here the synthesis of new fluorinated tricyclic and tetracyclic heterocycles with the skeleton of the alkaloid peganin (**2**) by the reaction of methyl-2-((2-aminobenzyl)amino)-3,3,3-trifluoro-2-hydroxy-propionate (**3**) with ketones.

Methyl 3,3,3-trifluoropyruvate furnished the (arylmethyl)amine adduct (e.g., **1**) exclusively in competitive experiments with one equivalent of (arylmethyl)amine (e.g., benzylamine or (diphenylmethyl)amine) and one equivalent of arylamine (e.g., aniline or 2-methylamine). The reason for the chemoselectivity is probably more thermodynamic than kinetic, as the mixture of the aniline adduct, methyl 2-anilino-3,3,3-trifluoro-2-hydroxypropionate, and benzylamine yielded quantitatively the corresponding benzylamine adduct, methyl 2-(benzylamino)-3,3,3-trifluoro-2-hydroxypropionate (**1**) (Scheme 1).

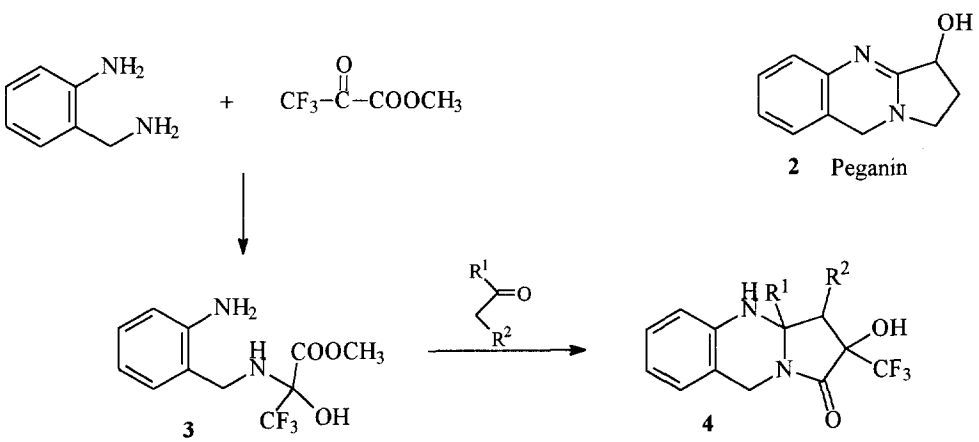


1

Scheme 1

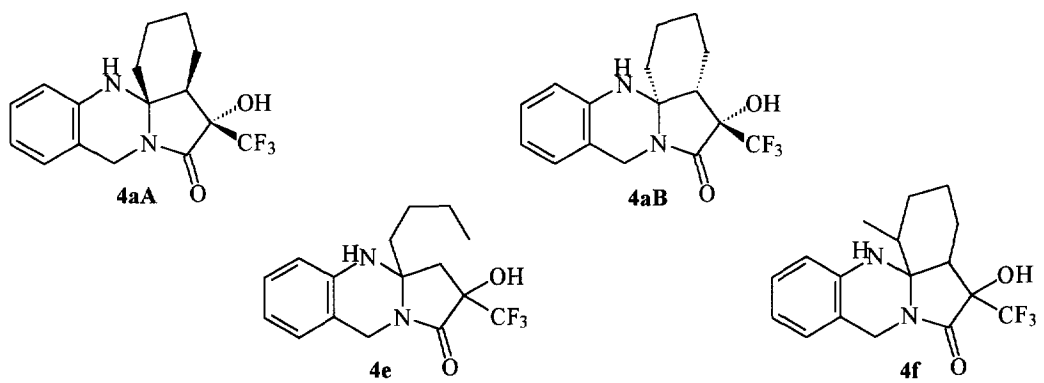
Consequently, the addition of 2-aminobenzylamine to methyl 3,3,3-trifluoropyruvate afforded the corresponding mono-adduct, methyl 2-((2-aminobenzyl)amino)-3,3,3-trifluoro-2-hydroxypropionate (**3**), in almost quantitative yield (see Scheme 2).

The adduct **3** on reaction with ketones $R^1COCH_2R^2$ furnished heterocyclic system **4**, 3,3a-dialkyl-2-hydroxy-2-(trifluoromethyl)-3,3a,4,9-tetrahydropyrrolo[2,1-b]quinazolin-1(2H)-one (Scheme 2). The skeleton of heterocycle **4** is identical to that of alkaloid Peganin (**2**).



Scheme 2

The heterocycle **4** contains three asymmetric centres and its structure was determined by X-ray crystallography of the two isolated major diastereoisomers **4aA**,**4aB** of the cyclohexanone derived product **4a** (Scheme 3).



Scheme 3

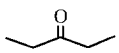
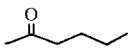
The analysis revealed a cis-annelation of the cyclohexane ring with both relative configurations on the trifluoromethylated ring carbon. The relative configuration on the C2 and C3 atoms of the heterocyclic

skeleton can easily be assigned by means of ^{19}F NMR spectroscopy. The chemical shifts of the trifluoromethyl group in the cis position to the alkyl group R^2 (e.g., **4aA)** lies in the range of -72 to -76 ppm, whereas the corresponding trans trifluoromethyl group (e.g., **4aB)** shift can be found between -78 and -81 ppm[6].

Various ketones can be employed in this new cyclization reaction (Table 1) and pilot experiments revealed that even the reaction with aldehydes was feasible. In the case of unsymmetrical ketones, 2-hexanone and 2-methylcyclohexanone, the respective products **4e, 4f** of the reaction with less hindered kinetic enamines were obtained (see Scheme 3).

The reactions of symmetrical ketones were performed at room temperature in diethyl ether. In the case of unsymmetrical ketones, low concentration of the kinetic enamine **6** (see Scheme 4) in the reaction mixture resulted in a very sluggish reaction and hence higher temperature (100°C) and ether solvent of a proper boiling point (dioxane) were employed. Reaction conditions, product ratios and yields are listed in Table 1.

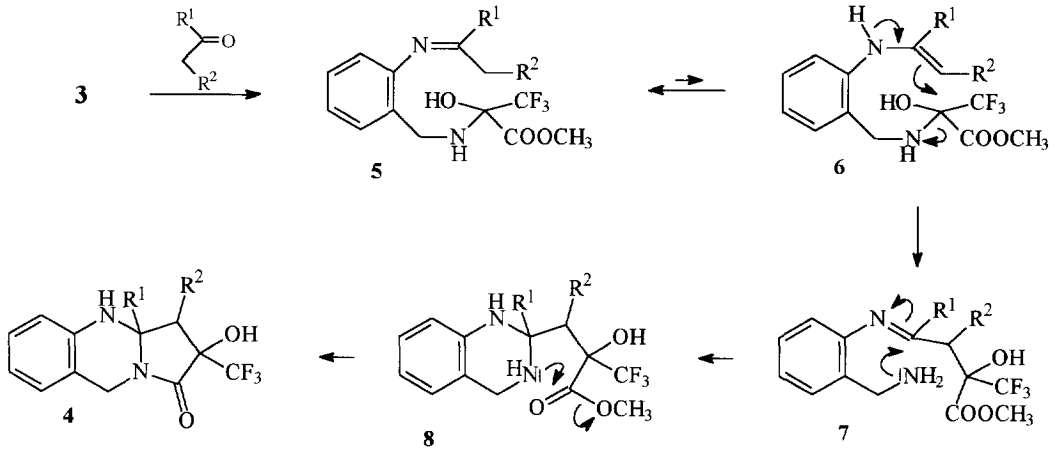
Table 1. The results of the reaction of the adduct **3** with ketones.

Starting ketone	Product code	Reaction temperature	Reaction time (h)	Yields		
				cis (**A**)	trans (**B**)	Σ (**A** +**B**)
	**4a**	20°C	200	38.2	28.3	66.5
	**4a**	100°C	1.25	17.6	69.3	86.9
	**4b**	20°C	70	30.4	43.8	74.2
	**4c**	20°C	100	25.8[a]	13.4[a]	39.2
	**4d**	20°C	240	32.3[b]	15.3[b]	47.6
	**4e**	100°C	70	51.7[a]	27.2[a]	78.9
	**4f**	100°C	30	4.9	54.9	59.8

[a] We were unable to assign the relative configuration on the C2 and C3a atoms in diastereoisomers formed
[b] Mixtures of two diastereoisomers with both relative configurations on the 2 and 3a carbons

Methyl 3,3,3-trifluoropyruvate has been C-alkylated by aromatic enamines[7] with subsequent cyclic amide formation. In our cyclization mechanism proposal (see Scheme 4), we suppose that the methyl 3,3,3-trifluoropyruvate - 2-aminobenzylamine adduct **3** reacts with the ketone to furnish the Schiff base **5**. Enamine **6**, which is in equilibrium with imine **5**, rearranges to imine **7** with further reversible steps resulting in the

formation of the most thermodynamically stable heterocycle **4**. Our attempts to trace the potential reaction intermediates **5 - 8** in the course of the reaction by the ^{1}H and/or ^{19}F NMR spectroscopy were unsuccessful, probably because of their low concentration in the complex reaction mixture.



Scheme 4

Structures of all compounds synthesized were confirmed by elemental analyses, ^{1}H, ^{13}C, ^{19}F NMR and IR spectroscopy.

The reported new cyclization reaction of methyl trifluoropyruvate - 2-aminobenzylamine adduct **3** extended the scope of use of fluorinated synthons in the synthesis of new heterocycles.

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6. ^{19}F NMR of **6a**: **6aA** - $\delta(CF_3)$ = -73.5 ppm; **6aB** - $\delta(CF_3)$ = -79.5 ppm.
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