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Synthesis of novel β-dialkylamino-α,β-unsaturated trifluoromethylketones containing cyclobutene fragment and their reactions with organolithium and Grignard reagents

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ABSTRACT

The highly reactive trifluoromethylenaminoketones, with a strained cyclobutene and norbornadiene moieties were firstly prepared from the corresponding β-halogeno-α,β-unsaturated trifluoromethylketones in almost quantitative yields. The ambident properties of these compounds in the reactions with organolithiums were discovered. The simple methods to control the selectivity of 1,2- or 1,4-addition of lithiated nucleophiles have been investigated.

1. Introduction

The construction of novel fluorine building blocks appropriate for subsequent synthetic elaboration is a reason of the extensive investigation of α,β-unsaturated trifluoromethylketones, especially containing leaving group in β-position. Such ketones have been used as the starting compounds in a variety of heterocyclic synthesis[1–3] and have also been viewed as a target objects because of their possible biological activity.[4,5] Of particular value are β-dialkylamino-α,β-unsaturated trifluoromethylketones since they are not only precursors for heterocyclizations, but, as it was shown recently, are also useful compounds in cross-coupling processes with organolithium and Grignard reagents. This very effective approach was studied only on the examples of the simplest acyclic trifluoroenaminoketones.[6–8] Moreover, β-dialkylamino-α,β-unsaturated trifluoromethylketones incorporating the strained cyclobutene and norbornadiene structures were unknown until now.

Recently we have described the synthesis of halogenated trifluoroacetylacetylenes[9–11] using available bis(trimethylstannyl)-acetylene[12] as a parent compound. It was shown that these highly activated acetylenes possess a unique ability to form [2+2]-cycloadducts **1a–f** (Fig. 1) with simple alkenes under mild conditions in the absence of catalysts and irradiation.[10,11] Due to very simple procedure of separation from isomeric ene adducts, these unsaturated strained ketones can be obtained on large scale with the exception of **1c**, which is less available. Starting acetylenes are also strong dienophiles and react with cyclopentapentadiene and 1,3-cyclohexadiene giving rise to [4+2]-cycloadducts **1g,h** (Fig. 1) in high yields.[9]

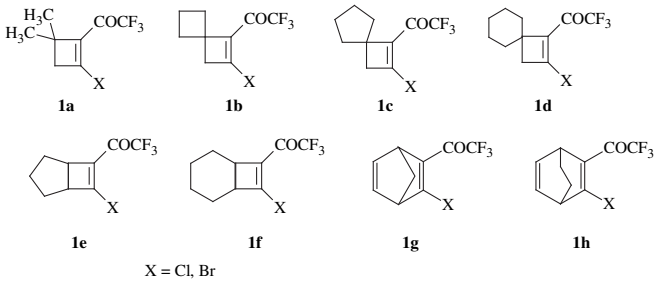

Figure 1.

Herein we describe an effective and simple synthesis of β-dialkylamino-α,β-unsaturated trifluoromethylketones with a strained bicyclic structure. Their ambident properties in the interactions with polar organometallics and how to affect 1,2- or 1,4-additions processes are reported.

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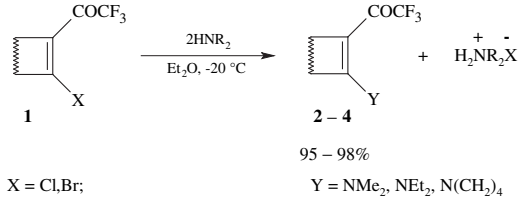
2. Results and discussion

2.1. The synthesis of β-dialkylamino-α,β-unsaturated trifluoromethylketones with cyclobutene and norbornadiene skeletons

We anticipated that owing to the strong mesomeric effect of the trifluoroacetyl group, the halogen atom at the C=C bond should be easily substituted by different nucleophiles. Actually, it was found that the reaction of cycloadducts **1a–h** with 2 equiv of dimethylamine, diethylamine or pyrrolidine in dry ether proceeds very cleanly and rapidly and results in the formation of target enaminoketones **2–4** in excellent yields (Scheme 1).



Scheme 1.

Using this method the following enaminoketones **2–4** were prepared (Fig. 2).

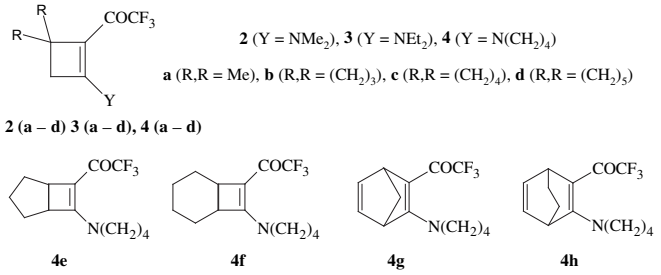
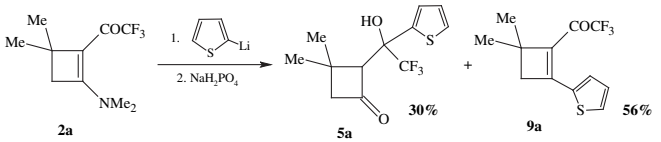


Figure 2.

The isolation of these compounds requires neither distillation nor chromatography and after filtration of the ammonium salts and removing the solvent in vacuum they have sufficient purity not only for preparative purposes, but even for analysis by ^{1}H NMR spectroscopy. Nevertheless, for the analytical purposes it is possible to perform their chromatographic purification, compounds **2a–c** and **3a** can be distilled in vacuum without decomposition and pyrrolidine derivatives **4a–h** can be recrystallized from hexane.

2.2. The reactions of of β-dialkylamino-α,β-unsaturated trifluoromethylketones of cyclobutene and norbornadiene numbers with organometallics

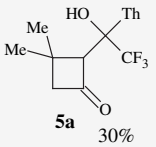
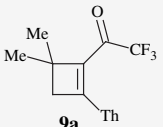
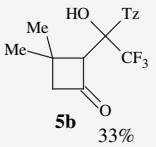
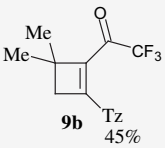
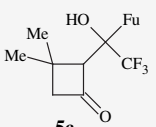
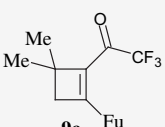
It should be expected that the reactions of enaminoketones **2–4** with organolithiums and Grignard reagents would proceed similarly to simple acyclic analogs, serving as a useful approach for preparation of β-substituted α,β-unsaturated trifluoromethylketones with a variable carbocyclic skeleton. As a first example of such a transformation we have studied the reaction of compound **2a** with 2-thienyllithium. It was found that the addition reaction smoothly proceeds even at −70 °C and after mild acidic hydrolysis of the reaction mixture (saturated solution of NaH_2PO_4) the target thienyl derivative **9a** was isolated in reasonable yield (Scheme 2). However, to our surprise the formation of ketoalkohol **5a** as a sole diastereomer was also observed (minor product). Apparently this compound arouse from 1,2-addition of thienyllithium to the carbonyl group with a subsequent acidic hydrolysis of the enamine moiety. To the best of our knowledge this is the first example of such a reaction sequence as well as 1,2-addition of polar organometallics to β-dialkylamino-α,β-unsaturated trifluoromethylketones. The addition of 2 equiv of acetylenic Grignard reagents to 4-dimethylamino-1,1,1-trifluoro-3-buten-2-one was recently described.[6]



Scheme 2.

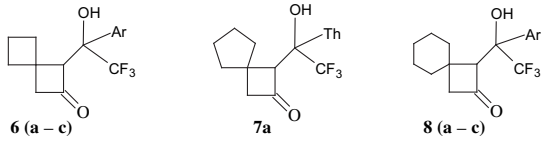
Inspired by the diastereospecific formation of **5a** and successful preparation of **9a** we attempted to increase the regioselectivity of this process and to realize 1,2- or 1,4-addition as a desired route. It was discovered that the type of addition essentially depends on dialkylamino substituent in compounds **2–4**. Apparently, it may be accounted for by not only steric hindrance but also the variation in conjugation, which is valid only for the compounds with a rigid cis-configuration. Initially we investigated the reactions of enaminoketones **2–4** with thienyllithium, thiazolyllithium, and furyllithium. The main relationships of these transformations are conveniently illustrated by the interactions of **2a**, **3a**, and **4a** with these organolithiums (Table 1). Thus, pyrrolidine derivative **4a** exhibited a tendency for conjugated addition (over **2a**), and the corresponding adducts **9** were isolated in good yields. On the other hand the influence of a more bulky diethylamino group in compound **3a** essentially altered the direction of addition and generally resulted in dominant formation of ketoalcohols **5** in preparative yields.

Table 1
The addition of some organolithiums to the enaminoketones **2a**, **3a**, **4a**

Reactants	1,2-Addition product (isolated yield)		1,4-Addition product (isolated yield)		Ratio **5**/**9** in the reaction mixture after acidification
2a, Th–Li					1:2
	5a	30%	**9a**	56%	
3a, Th–Li	**5a**	73%	**9a**	11%	6:1
4a, Th–Li	**5a**	16%	**9a**	65%	1:3
2a, Tz–Li					2:3
	5b	33%	**9b**	45%	
3a, Tz–Li	**5b**	60%	**9b**	8%	5:1
4a, Tz–Li	**5b**	14%	**9b**	56%	2:7
2a, Fu–Li					5:8
	5c	36%	**9c**	44%	
3a, Fu–Li	**5c**	59%	**9c**	14%	5:1
4a, Fu–Li	**5c**	27%	**9c**	60%	1:2

Th=2-thienyl–, Tz=2-thiazolyl–, Fu=2-furyl–.

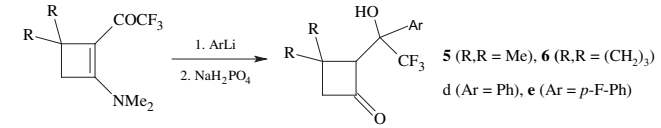
Similar relationships have been also observed in the additions of the same organolithiums to enaminoketones with spirane structures **2b–d**, **3b–d**, and **4b–d**. Therefore, the reactions of diethylamino derivatives **3a–d** with organolithiums possessing relatively low basicity provide a simple and reliable route to ketoalkohols **5–8** in about 60–75% yields (Fig. 3). All these new compounds are crystalline solids, which can be purified by recrystallization from hexane and their separation from 1,4-adducts does not cause any difficulties. But the most striking feature of the ketoalcohol formation is extremely high diastereoselectivity giving a sole diastereomer. It is noteworthy that ketoalkohols **5–8** can be considered as products of an aldol condensation of 3,3-disubstituted cyclobutanones with the corresponding aryltrifluoromethylketones, but our attempts to synthesize some of them in a such way resulted in very low yields of diastereomeric mixtures. Unfortunately till now we have not succeeded in the preparation of crystalline forms of **5–8** suitable for X-ray diffraction analysis.



a (Ar = Th), **b** (Ar = Tz), **c** (Ar = Fu)

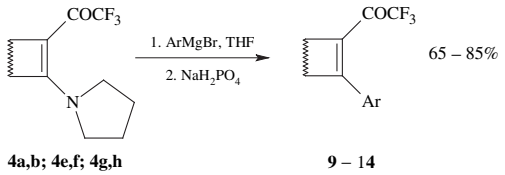
Figure 3.

Further investigation has shown that the yields of ketoalcohols are strongly dependent on the organometallic basicity. Thus, the reaction of diethylamino derivatives **3a–d** with much more basic phenyllithium or 4-fluorophenyllithium afforded only the traces of the target products and large amounts of recovered enaminoketones probably due to enolate formation. An addition of these organometallics to the less bulky **2a**,**b** gave rise to the corresponding ketols **5d**,**e** and **6d**,**e** as a sole diastereomer in each case, albeit in yields in a range of 40–45% (Scheme 3). Interestingly, 1,4-adducts were not detected in these processes.



Scheme 3.

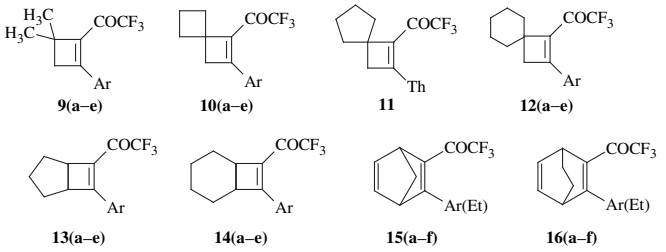
In order to overcome the serious limitation in the synthesis of 1,4-adducts we explored the interactions of enaminoketones **4** with Grignard reagents. In comparison with the reactions of organolithiums reagents, these processes appeared to be more regioselective and less dependent on the nucleophile structure. Thus, pyrrolidine derivatives **4a**,**b** and **4e**,**f** reacted with a variety of organomagnesiums in the temperature range of 0–20 °C regardless of their basicity to afford the corresponding β-substituted derivatives **9–14** in high yields, even better than in the same reactions with organolithiums (Scheme 4). Diels–Alder derivatives **4g**,**h** were also



Scheme 4.

successfully functionalized to afford bicycle compounds **15**,**16**. Satisfactory results were obtained even with ethylmagnesiumbromide and the unstable 2-thiazolylmagnesiumbromide. However, the most important feature of these organolithiums additions is that the 1,2-adducts were not detected even in the trace quantities.

The following compounds were obtained by using this method (Fig. 4).

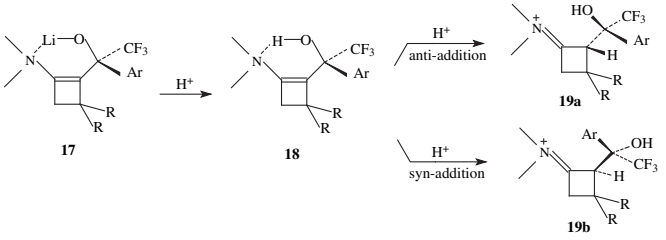


a (Ar = 2-Th), **b** (Ar = 2-Tz), **c** (Ar = 2-Fu), **d** (Ar = Ph), **e** (Ar = 4-F-Ph), **f** (Et)

Figure 4.

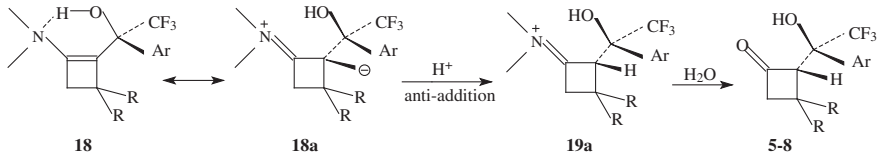
Currently we do not have a convincing explanation accounting for such a difference in the reactivity of organolithium and organomagnesium compounds with enaminoketones **2–4** as well as ambident properties of **2–4**, which have never been described in the reactions of acyclic analogs.[6–8] Probably it can be connected with chelate formation of **2–4** with cationic centers of organometallics possessing different Lewis acidity and geometric parameters. These factors can alter the conjugation in enaminoketones and regioselectivity of addition. The temperature variations did not effect strongly on regioselectivity. Thus, carrying out some reactions of thienyllithium and furyllithium with enaminoketones **2–4** at the same temperature as the reactions with the corresponding organomagnesiums (0–20 °C) we have detected a serious decrease of yields due to the formation of the tarry materials and no significant changes in the ratio of 1,2- and 1,4-products in comparison with the same processes starting at −70 °C.

In order to explain the regiospecific formation of ketoalkohols **5–8** we supposed that intermediate alkoholate **17** exists in a cyclic form owing to intramolecular coordination of lithium ion with dialkylamino group. The corresponding alcohol **18** formed upon the first step of acidification has probably also a cyclic structure stabilized by intramolecular N–H bond (Scheme 5). The protonation of alkohol **18** can proceed as a *syn*- or (and) *anti*- addition relative to trifluoromethyl group affording one of two diastereomeric iminium salts **19a**,**b** or a mixture of them and this is apparently a governing factor for diastereoselectivity.



Scheme 5.

Therefore, the diastereospecific formation of ketoalkohols **5–8** means that the only way of protonation actually takes place. It is well-known that β-carbon atom of C=C– bond in enamine moiety has an intermediate hybridization between sp^2 and sp^3 hybridization state owing to distribution of electron density from nitrogen to β-carbon atom and enamine fragment N–C=C–R is not quite planar.[13] We think that trifluoromethyl group bearing a high negative



Scheme 6.

charge and unshared electron pair in resonance structure **18a** should be oriented in trans-position to each other, thus avoiding strong electrostatic repulsion (Scheme 6). If it so, a proton addition to intermediate **18** occurs from side of unshared electron pair providing iminium salt **19a** as a sole diastereomer, which, in turn, affords diastereomeric pure ketoalcohols **5**–**8** upon the hydrolysis.

Although it might be offered alternative explanations of diastereoselectivity, the given scheme seems reasonable in our point of view. Anyway, in future we will try to prove it experimentally and to continue studying of this interesting reaction.

3. Conclusion

In conclusion, stable β-dialkylamino-α,β-unsaturated trifluoromethylketones with the strained cyclobutene and bicyclic scaffolds have been readily prepared from the corresponding β-halogeno derivatives and secondary amines. The ambident properties of these novel compounds in the reactions with polar organometallics were developed. We found that Grignard reagents form exclusively 1,4-adducts, whereas organolithiums afford both 1,2- and 1,4-products and their ratio depends on the specific nature of dialkylamino group. A variety of trifluoroacylated substituted cyclobutenes and diastereomerically pure α-substituted cyclobutanones are therefore now available.

4. Experimental

4.1. General

Cycloadducts **1** have been prepared according to described procedures.[9–11] Organolithiums and Grignard reagents have been prepared according to the reliable procedures from Brandsma and Verkruijsse.[14] As parent compounds for the synthesis of 1,2-addition products **5**–**8** and 1,4-addition products **9**–**16** we specified the pairs of enaminoketones and organometallics affording maximum yields. Manipulations with organolithiums and Grignard reagents were carried out in argon atmosphere. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker AMX 400 spectrometer at 400 and 100 MHz, respectively, chemical shifts are reported in parts per million relative to 0 for TMS. IR spectra were recorded on Bruker IFS 25 spectrometer and are reported in terms of frequency of absorption (cm^{-1}).

4.2. General procedure for preparation of trifluoromethylenaminoketones 2–4

To a stirred solution of secondary amine (0.011 mol) in dry ether (15 mL) at −25 °C the solution of one of cycloadducts **1a**–**h** (0.005 mol) in ether (5 mL) was added dropwise. After the warming to the ambient temperature the resulting mixture was stirred for 1 h (reaction with **1h** requires 8–10 h), the precipitate of ammonium salt was filtered off and clear solution was concentrated in vacuum. The crude enaminoketones were exposed in vacuum 1 Torr at 20 °C for 1 h and used in the reactions with organometallics without further purification. For the analytical purposes some of the target compounds have been distilled in vacuum, crystallized from hexane or chromatographed on a column (see below).

*4.2.1. 1-[2-(Dimethylamino)-4,4-dimethylcyclobut-1-en-1-yl]-2,2,2-trifluoroethanone (**2a**).* From **1a** and dimethylamine. Pale yellow oil; bp 78–79 °C (0.5 Torr); yield 1.06 g (96%). Found: C, 54.34; H, 6.31; F, 25.73; N, 6.29. $C_{10}H_{14}F_3NO$ requires C, 54.29; H, 6.38; F, 25.76; N, 6.33%. IR (neat) 2964, 1665, 1597, 1151 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.53 (3H, s, CH_3–N), 2.89 (3H, s, CH_3–N), 2.31 (2H, s, CH_2), 1.28 (6H, s, $(CH_3)_2C$); δ_C (100.6 MHz, $CDCl_3$) 168.6 (q, *J* 34 Hz), 164.4, 117.8 (q, *J* 290 Hz), 108.6, 45.3, 42.3, 40.1, 36.7, 27.8.

*4.2.2. 1-[2-(Diethylamino)spiro[3.3]hept-1-en-1-yl]-2,2,2-trifluoroethanone (**3b**).* From **1b** and diethylamine. Almost colorless oil; thorough purification was performed by column chromatography (silica gel, hexane/AcOEt=4:1); yield 1.25 g (96%). Found: C, 59.90; H, 5.85; F, 21.84; N, 5.47. $C_{13}H_{18}F_3NO$ requires: C, 59.76; H, 6.94; F, 21.81; N, 5.36%. R_f=0.6; IR (neat) 2992, 1671, 1592, 1409, 1205, 1173 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.17 (2H, q, *J* 7.3 Hz, –CH_2–N), 3.38 (2H, q, *J* 7.3 Hz, –CH_2–N), 2.62 (2H, s, CH_2–C=C), 2.44 (4H, ddd, *J* 12.4, 9.0, 7.3 Hz, $2CH_2$), 2.10 (2H, m, CH_2), 1.22 (6H, t, *J* 7.3 Hz, $2CH_3$); δ_C (100.6 MHz, $CDCl_3$) 170.0 (q, *J* 34 Hz), 165.4, 119.1 (q, *J* 290 Hz), 109.8, 48.2, 45.7, 46.4, 37.6, 30.4, 29.3, 14.5, 13.7.

*4.2.3. 2,2,2-Trifluoro-1-(7-pyrrolidin-1-ylbicyclo[3.2.0]hept-6-en-6-yl)ethanone (**4e**).* From **1e** and pyrrolidine. Yellowish crystals (from hexane); mp 60–61 °C; yield 1.24 g (96%). Found: C, 60.38; H, 6.20; F, 21.79; N, 5.22. $C_{13}H_{16}F_3NO$ requires: C, 60.22; H, 6.22; F, 21.98; N, 5.40%. IR (mineral oil) 2998, 1670, 1600, 1295, 1202 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.13 (2H, t, *J* 6.6 Hz, –CH_2–N), 3.50 (2H, t, *J* 6.6 Hz, –CH_2–N), 3.31 (1H, dd, *J* 5.9, 3.3 Hz, CH–C=C), 3.09 (1H, dd, *J* 5.9, 3.3 Hz, CH–C=C), 2.06–1.91 (4H, m, –CH_2CH_2– in pyrrolidine), 1.90–1.75 (2H, m, CH_2), 1.66–1.46 (2H, m, CH_2), 1.42–1.30 (2H, m, CH_2); δ_C (100.6 MHz, $CDCl_3$) 172.4 (q, *J* 36 Hz), 163.3, 117.9 (q, *J* 290 Hz), 112.9, 52.6, 47.9, 46.9, 41.5, 26.2, 25.6, 25.0, 23.3, 21.8.

*4.2.4. 2,2,2-Trifluoro-1-(8-pyrrolidin-1-ylbicyclo[4.2.0]oct-7-en-7-yl)ethanone (**4f**).* From **1f** and pyrrolidine. Yellowish crystals (from hexane); mp 75–76 °C; yield 1.33 g (97%). Found: C, 61.70; H, 6.59; F, 20.77; N, 5.93. $C_{14}H_{18}F_3NO$ requires: C, 61.53; H, 6.64; F, 20.86; N, 5.13%. IR (mineral oil) 2996, 1667, 1599, 1304, 1204 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.09 (2H, t, *J* 6.6 Hz, –CH_2–N), 3.56 (2H, t, *J* 6.6 Hz, –CH_2–N), 3.19 (1H, dd, *J* 6.3, 3.5 Hz, CH–C=C), 3.02 (1H, dd, *J* 6.3, 3.5 Hz, CH–C=C), 2.04–1.70 (8H, m, –CH_2CH_2– in pyrrolidine, –CH_2CH_2– in cyclohexane), 1.64–1.40 (4H, m, –CH_2CH_2– in cyclohexane); δ_C (100.6 MHz, $CDCl_3$) 169.7 (q, *J* 37 Hz), 160.8, 117.2 (q, *J* 290 Hz), 109.0, 50.4, 47.4, 46.6, 39.5, 26.2, 25.6, 23.7, 23.1, 21.9, 17.6.

*4.2.5. 2,2,2-Trifluoro-1-(3-pyrrolidin-1-ylbicyclo[2.2.1]hepta-2,5-dien-2-yl)ethanone (**4g**).* From **1g** and pyrrolidine. Yellowish crystals (from hexane); mp 90–91 °C; yield 1.21 g (94%). Found: C, 60.73; H, 5.99; F, 22.13; N, 5.29. $C_{13}H_{14}F_3NO$ requires: C, 60.70; H, 5.94; F, 22.16; N, 5.44%. IR (mineral oil) 3001, 1665, 1620, 1348, 1196, 1150 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.02 (1H, dd, *J* 5.1, 1.3 Hz, –CH=), 6.46 (1H, dd, *J* 5.1, 1.3 Hz, –CH=), 4.09 (2H, t, *J* 6.8 Hz, –CH_2–N), 3.95 (1H, d, *J* 1.3 Hz, C=C–CH–C=C), 3.51 (1H, d, *J* 1.3 Hz, C=C–CH–

C=C), 3.47 (2H, t, *J* 6.8 Hz, –CH_2–N), 2.12 (1H, d, *J* 9.0 Hz, H–C^7), 2.08 (1H, d, *J* 9.0 Hz, H–C^7), 2.03–1.88 (4H, m, –CH_2CH_2– in pyrrolidine); δ_C (100.6 MHz, $CDCl_3$) 181.2, 167.4 (q, *J* 37 Hz), 148.1, 136.0, 119.0 (q, *J* 290 Hz), 106.4, 62.1, 55.2, 53.5, 52.6, 48.1, 25.7, 25.0.

*4.2.6. 2,2,2-Trifluoro-1-(3-pyrrolidin-1-ylbicyclo[2.2.2]octa-2,5-dien-2-yl)ethanone (**4h**).* From **1h** and pyrrolidine. Yellowish crystals (from hexane); mp 65–66 °C; yield 1.29 g (95%). Found: C, 62.15; H, 5.97; F, 20.96; N, 5.06. $C_{14}H_{16}F_3NO$ requires: C, 61.98; H, 5.94; F, 21.01; N, 5.16%. IR (mineral oil) 3008, 2994, 1663, 1638, 1590, 1304, 1210, 1156 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.30 (1H, dd, *J* 5.3, 2.6 Hz, HC=C), 6.16 (1H, dd, *J* 5.3, 2.6 Hz, HC=C), 4.28 (1H, m, H–C^1), 4.03 (1H, m, H–C^4), 4.06 (2H, t, *J* 6.6 Hz, –CH_2–N), 3.49 (2H, t, *J* 6.6 Hz, –CH_2–N), 1.96 (4H, m, –CH_2CH_2– in pyrrolidine), 1.45 (m), 1.19 (m, totally 4H, H_2C^7–H_2C^8); δ_C (100.6 MHz, $CDCl_3$) 176.4, 164.9 (q, *J* 38 Hz), 134.9, 131.5, 117.8 (q, *J* 290 Hz), 111.6, 48.0, 46.3, 45.0, 43.2, 25.2, 24.7, 24.1, 22.7.

4.3. General procedure for preparation 1,2-addition products (5–8) and 1,4-addition products (9–16)

(a) From organolithiums. To the stirred solution or suspension of organolithium (0.007 mol) in THF (7 mL) at −70 °C the solution of one of enaminoketones **2**, **3** (0.006 mol) in THF (2 mL) was added dropwise. The resulting mixture was allowed to warm to 0 °C (30–40 min) and then was quickly poured into vigorously stirred saturated solution of NaH_2PO_4 (15 mL). After the additional 5 min (no more!) of stirring or shaking the organic layer was separated, the aqueous phase was extracted with ether (2×10 mL), dried with Na_2SO_4, and the solvent was removed in vacuum. The residue was diluted with cold hexane (15 mL) and exposed at 10 °C for 1 h. The crystalline 1,2-adducts **5**–**8** were filtered off and crystallized from hexane. Filtrate was concentrated and the residue was chromatographed on a column (silica gel, hexane/AcOEt=20:1) to afford 1,4-adducts **9**–**16**. In the case of thiazolyl derivatives **9**, **10**, **12**–**16** of series (b) the eluent was hexane/AcOEt=2:1.

(b) From Grignard reagents (only for 1,4-addition products **9**–**16**). To the stirred solution of Grignard reagent (0.007 mol) in ether or THF (7 mL) at 20 °C the solution of one of enaminoketones **4** (0.006 mol) in the same solvent was added dropwise (in the case of 2-thiazolylmagnesiumbromide the equimolar amount of enaminoketone was used and the starting temperature was 0 °C and then was gradually increased to 20 °C). After the stirring for 0.5 h at 20 °C the resulting mixture was treated with saturated solution of NaH_2PO_4 (15 mL) and isolation of the target compounds **9**–**16** was performed similarly to the procedure for organolithiums.

*4.3.1. 3,3-Dimethyl-2-[2,2,2-trifluoro-1-hydroxy-1-(2-thienyl)-ethyl]cyclobutanone (**5a**).* From **3a** and 2-thienyllithium. White crystals (from hexane); mp 108–109 °C; yield 1.22 g (73%). Found: C, 51.84; H, 4.74; F, 20.33; S, 11.39. $C_{12}H_{13}F_3O_2S$ requires: C, 51.79; H, 4.71; F, 20.48; S, 11.52%. IR (mineral oil) 3425, 3001, 2990, 1798, 1206, 1157 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39 (1H, d, *J* 5.0 Hz, H–C^5 in thienyl); 7.09 (2H, m, H–C^3 and H–C^4 in thienyl), 4.10 (1H, br s, H–O), 3.92 (1H, s, HC–C=O), 3.03 (1H, d, *J* 16.0 Hz), 2.63 (1H, d, *J* 16.0 Hz, AB-system, CH_2–C=O), 1.40 (3H, s, CH_3), 0.98 (3H, s, CH_3); δ_C (100.6 MHz, $CDCl_3$) 202.6, 137.2, 126.7, 126.2, 125.4, 124.0 (q, *J* 286 Hz), 76.1 (q, *J* 30 Hz), 68.2, 59.0, 31.4, 31.0, 21.9.

*4.3.2. 3,3-Dimethyl-2-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)cyclobutanone (**5d**).* From **2a** and phenyllithium. White crystals (from hexane); mp 133–134 °C; yield 0.69 g (42%). Found: C, 61.92; H, 5.60; F, 21.09. $C_{14}H_{15}F_3O_2$ requires: C, 61.76; H, 5.55; F, 20.93%. IR (mineral oil) 3475, 3019, 2990, 1790, 1206, 1155 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.66 (2H, m, H–Ar), 7.45 (3H, m, H–Ar), 4.03 (1H, s, HC–C=O), 3.90 (1H, br s, H–O), 2.97 (1H, d, *J* 16.0 Hz), 2.70 (1H, d, *J* 16.0 Hz, AB-system, CH_2–C=O), 1.41 (3H, s, CH_3), 1.03 (3H, s, CH_3); δ_C (100.6 MHz, $CDCl_3$) 203.2, 134.3, 129.6, 128.9, 126.8, 124.8 (q, *J* 290 Hz), 77.4 (q, *J* 30 Hz), 68.4, 59.7, 32.5, 31.7, 21.1.

*4.3.3. 1-[2,2,2-Trifluoro-1-hydroxy-1-(1,3-thiazol-2-yl)ethyl]spiro[3.3]-heptan-2-one (**6b**).* From **3b** and 2-thiazolyllithium. White crystals (from hexane); mp 139–140 °C; yield 1.12 g (64%). Found: C, 49.54; H, 4.19; F, 19.43; N, 4.59; S, 11.20. $C_{12}H_{12}F_3NO_2S$ requires: C, 49.48; H, 4.15; F, 19.57; N, 4.81; S, 11.01%. IR (mineral oil) 3559, 3010, 2994, 1790, 1204, 1153 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.89 (1H, d, *J* 1.4 Hz, H–Ar), 7.56 (1H, d, *J* 1.4 Hz, H–Ar), 4.60 (1H, br s, H–O), 4.11 (1H, s, HC–C=O), 2.97 (1H, d, *J* 15.4 Hz), 2.68 (1H, d, *J* 15.4 Hz, AB-system, CH_2–C=O), 2.19 (m), 1.82 (m), 1.15 (m, totally 6H, –$(CH_2)_3$–); δ_C (100.6 MHz, $CDCl_3$) 207.0, 166.8, 142.8, 124.7 (q, *J* 290 Hz), 123.3, 80.2 (q, *J* 30 Hz), 67.9, 59.9, 39.4, 35.8, 32.6, 17.6.

*4.3.4. 1-[2,2,2-Trifluoro-1-(4-fluorophenyl)-1-hydroxyethyl]spiro[3.3]-heptan-2-one (**6e**).* From **2b** and 4-fluorophenyllithium. White crystals (from hexane); mp 155–156 °C; yield 0.77 g (44%). Found: C, 59.83; H, 4.79; F, 25.30. $C_{15}H_{14}F_4O_2$ requires: C, 59.60; H, 4.67; F, 25.14%. IR (mineral oil) 3496, 3006, 2993, 1790, 1201, 1155 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.57 (2H, dd, *J* 8.4, 6.5 Hz, H–Ar), 7.16 (2H, dd, *J* 7.5, 6.5 Hz, H–Ar), 4.40 (1H, br s, H–O), 3.99 (1H, s, HC–C=O), 2.93 (1H, d, *J* 16.0 Hz), 2.70 (1H, d, *J* 16.0 Hz, AB-system, CH_2–C=O), 2.11 (m), 1.72 (m), 1.19 (m, totally 6H, –$(CH_2)_3$–); δ_C (100.6 MHz, $CDCl_3$) 204.7, 159.7 (d, *J* 245 Hz), 133.3(d, *J* 8.2 Hz), 124.4, 123.6 (q, *J* 290 Hz), 121.8 (d, *J* 22.6 Hz), 75.8 (q, *J* 30 Hz), 68.1, 59.1, 36.4, 33.9, 30.5, 17.5.

*4.3.5. 1-[2,2,2-Trifluoro-1-(2-furyl)-1-hydroxyethyl]spiro[3.5]nonan-2-one (**8c**).* From **3d** and 2-furyllithium. White crystals (from hexane); mp 84–85 °C; yield 1.00 g (55%). Found: C, 59.80; H, 5.75; F, 18.69. $C_{15}H_{17}F_3O_3$ requires: C, 59.60; H, 5.67; F, 18.86%. IR (mineral oil) 3495, 3014, 3000, 1793, 1210, 1155 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.53 (1H, d, *J* 2.2 Hz, H–C^5 in furyl), 6.62 (1H, d, *J* 3.4 Hz, H–C^3 in furyl), 6.47 (1H, dd, *J* 3.4, 2.2 Hz, H–C^4 in furyl), 4.09 (1H, br s, H–O), 3.70 (1H, s, HC–C=O), 2.91 (1H, d, *J* 15.5 Hz), 2.62 (1H, d, *J* 15.5 Hz, AB-system, CH_2–C=O), 1.88 (m), 1.65 (m), 1.48 (m), 1.24 (m, totally 10H, –$(CH_2)_5$–); δ_C (100.6 MHz, $CDCl_3$) 201.8, 147.4, 142.2, 124.0 (q, *J* 289 Hz), 109.3, 75.3 (q, *J* 30 Hz), 66.8, 59.9, 35.1, 32.0, 30.4, 24.5, 23.9, 14.5.

*4.3.6. 1-[4,4-Dimethyl-2-(2-thienyl)cyclobut-1-en-1-yl]-2,2,2-trifluoroethanone (**9a**).* From **4a** and 2-thienylmagnesiumbromide. Yellowish crystals; mp 38–39 °C; bp 84–85 °C (1 Torr); yield 1.35 g (87%). Found: C, 55.51; H, 4.23; F, 21.80. $C_{12}H_{11}F_3OS$ requires: C, 55.38; H, 4.26; F, 21.90%. IR (mineral oil) 3010, 2995, 1714, 1608, 1432, 1226, 1169 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.82 (1H, d, *J* 5.0 Hz, H–C^5 in thienyl), 7.72 (1H, d, *J* 3.9 Hz, H–C^3 in thienyl), 7.23 (1H, dd, *J* 5.0, 3,9 Hz, H–C^4 in thienyl), 2.83 (2H, s, CH_2–C=C), 1.52 (6H, s, $(CH_3)_2C$); δ_C (100.6 MHz, $CDCl_3$) 175.4 (q, *J* 38 Hz), 156.0, 137.0, 134.1, 133.4, 133.2, 128.0, 116.2 (q, *J* 289 Hz), 45.1, 42.1, 26.2.

*4.3.7. 2,2,2-Trifluoro-1-[2-(1,3-thiazol-2-yl)spiro[3.3]hept-1-en-1-yl]ethanone (**10b**).* From **4b** and 2-thiazolylmagnesiumbromide prepared from thiazole (0.68 g, 0.008 mol) and EtMgBr (0.006 mol) in THF (10 mL) at 50 °C. Yellowish crystals; mp 45–46 °C; yield 0.98 g (60%). Found: C, 52.80; H, 3.83; F, 20.65; N, 5.01; S, 11.60. $C_{12}H_{10}F_3NOS$ requires: C, 52.74; H, 3.69; F, 20.86; N, 5.13; S, 11.73%. IR (mineral oil) 3014, 3000, 2988, 1708, 1602, 1422, 1225, 1141 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.30 (1H, d, *J* 1.7 Hz, H–Ar), 7.88 (1H, d, *J* 1.7 Hz, H–Ar), 3.17 (2H, s, CH_2–C=C), 2.76 (2H, dd, *J* 12.6, 8.6 Hz, 2C–H in cyclobutane), 2.20 (4H, m, 4C–H in cyclobutane); δ_C (100.6 MHz, $CDCl_3$) 172.9 (q, *J* 38 Hz), 169.0, 159.6, 143.8, 135.8, 132.5, 119.1 (q, *J* 290 Hz), 48.9, 47.9, 33.3, 17.0.

*4.3.8. 2,2,2-Trifluoro-1-[2-(2-furyl)spiro[3.5]non-1-en-1-yl]ethanone (**12c**).* From **4d** and 2-furylmagnesiumbromide. Yellowish oil; yield

1.24 g (73%). Found: C, 61.54; H, 5.50; F, 19.99. $C_{15}H_{15}F_3O_2$ requires: C, 63.37; H, 5.32; F, 20.05%. IR (neat) 3007, 2993, 1702, 1606, 1428, 1230, 1174 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.84 (1H, d, *J* 3.6 Hz, H–C^5 in furyl), 7.70 (1H, d, *J* 1.8 Hz, H–C^3 in furyl), 6.69 (1H, dd, *J* 3.6, 1.8 Hz, H–C^4 in furyl), 2.72 (2H, CH_2–C═C), 1.90 (m), 1.59 (m), 1.45 (m, totally 10H, –$(CH_2)_5$–); δ_C(100.6 MHz, $CDCl_3$) 172.9 (q, *J* 38 Hz), 151.7, 150.4, 146.4, 134.8, 120.5, 117.1 (q, *J* 288 Hz), 114.7, 54.0, 50.3, 35.3, 25.8, 24.4.

*4.3.9. 2,2,2-Trifluoro-1-(7-phenylbicyclo[3.2.0]hept-6-en-6-yl)ethanone (**13d**).* From **4e** and phenylmagnesiumbromide. Yellowish oil; yield 1.26 g (79%). Found: C, 67.82; H, 4.95; F, 21.28. $C_{15}H_{13}F_3O$ requires: C, 67.66; H, 4.92; F, 21.41%. IR (neat) 3010, 2997, 1702, 1597, 1422, 1232, 1170 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.92 (2H, dd, *J* 7.7, 1.9 Hz, H–Ar), 7.55 (3H, m, H–Ar), 3.70 (1H, dd, *J* 7.9, 3.4 Hz, HC–C═C), 3.55 (1H, dd, *J* 7.9, 3.4 Hz, HC–C═C), 1.71 (m), 1.58 (m), 1.40 (m, totally 6H, –$(CH_2)_3$–); δ_C (100.6 MHz, $CDCl_3$) 173.3 (q, *J* 38 Hz), 152.8, 139.5, 133.7, 131.7, 129.2, 128.2, 118.3 (q, *J* 288 Hz), 52.7, 49.0, 25.0, 24.8, 22.6.

*4.3.10. 2,2,2-Trifluoro-1-[8-(4-fluorophenyl)bicyclo[4.2.0]oct-7-en-7-yl]ethanone (**14e**).* From **4f** and 4-fluorophenylmagnesiumbromide. Yellowish crystals; mp 33–34 °C; yield 1.14 g (64%). Found: C, 64.59; H, 4.79; F, 25.58. $C_{16}H_{14}F_4O$ requires: C, 64.43; H, 4.73; F, 25.48%. IR (mineral oil) 3010, 2995, 1704, 1602, 1424, 1229, 1171 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.88 (2H, dd, *J* 8.8, 6.5 Hz, H–Ar), 7.32 (2H, dd, *J* 8.8, 8.0 Hz, H–Ar), 3.49 (1H, dd, *J* 10.0, 4.9 Hz, HC–C═C), 3.28 (1H, dd, *J* 10.0, 4.9 Hz, HC–C═C), 1.76 (m), 1.49 (m, totally 8H, –$(CH_2)_4$–); δ_C (100.6 MHz, $CDCl_3$) 174.0 (q, *J* 37 Hz), 163.1 (d, *J* 251 Hz), 162.1, 137.3, 132.3 (d, *J* 22 Hz), 128.6, 117.6 (q, *J* 290 Hz), 48.1, 41.9, 24.5, 22.5, 18.8, 17.4.

*4.3.11. 2,2,2-Trifluoro-1-[3-(2-thienyl)bicyclo[2.2.1]hepta-2,5-dien-2-yl]ethanone (**15a**).* From **4g** and 2-thienylmagnesiumbromide. Yellowish crystals; mp 62–63 °C; yield 1.49 g (92%). Found: C, 57.91; H, 3.32; F, 20.95; S, 11.65. $C_{13}H_9F_3OS$ requires: C, 57.77; H, 3.36; F, 21.09; S, 11.86%. IR (mineral oil) 3004, 1700, 1665, 1602, 1221, 1171 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.16 (1H, d, *J* 5.0 Hz, H–C^5 in thienyl), 7.70 (1H, d, *J* 3.4 Hz, H–C^3 in thienyl), 7.33 (1H, dd, *J* 5.0, 3,4 Hz, H–C^4 in thienyl), 7.01 (1H, dd, *J* 5.2, 2,7 Hz, H–C═C), 6.88 (1H, dd, *J* 5.2, 2,7 Hz, H–C═C), 4.36 (1H, d, *J* 1.7 Hz, H–C^1), 4.24 (1H, d, *J* 1.7 Hz, H–C^4), 2.32 (1H, d, *J* 7.4 Hz, –CH_2–), 2.20 (1H, d, *J* 7.4 Hz, –CH_2–); δ_C (100.6 MHz, $CDCl_3$) 175.5 (q, *J* 40 Hz), 169.8, 144.4, 138.8, 137.8, 134.7, 133.7, 133.3, 128.3, 117.2 (q, *J* 288 Hz), 67.8, 58.2, 51.2.

*4.3.12. 1-(3-Ethylbicyclo[2.2.1]hepta-2,5-dien-2-yl)-2,2,2-trifluoroethanone (**15f**).* From **4g** and ethylmagnesiumbromide. Colorless oil; bp 39–40 °C (1 Torr); yield 0.75 g (58%). Found: C, 61.20; H, 5.19; F, 26.33. $C_{11}H_{11}F_3O$ requires: C, 61.11; H, 5.13; F, 26.36%. IR (neat) 3014, 1708, 1670, 1600, 1229, 1175 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.80 (1H, dd, *J* 4.9, 3.0 Hz, H–C═C), 6.73 (1H, dd, *J* 4.9, 3.0 Hz, H–C═C), 3.96 (1H, d, *J* 3.0 Hz, H–C^1), 3.59 (1H, d, *J* 3.0 Hz, H–C^4), 2.35 (1H, d, *J* 7.3 Hz, –CH_2–), 2.26 (1H, d, *J* 7.3 Hz, –CH_2–), 1.96 (1H, m, –CH_2–C═C), 1.90 (1H, m, –CH_2–C═C), 1.21 (3H, t, *J* 6.8 Hz, CH_3–); δ_C (100.6 MHz, $CDCl_3$) 179.8 (q, *J* 38 Hz), 164.7, 143.4, 141.4, 139.6, 116.9 (q, *J* 289 Hz), 63.3, 54.8, 47.8, 39.5, 23.0.

*4.3.13. 2,2,2-Trifluoro-1-[3-(2-furyl)bicyclo[2.2.2]octa-2,5-dien-2-yl]ethanone (**16c**).* From **4h** and 2-furylmagnesiumbromide. Yellowish oil; bp 95–96 °C(1 Torr); yield 1.05 g (65%). Found: C, 62.72; H, 4.15; F, 21.16. $C_{14}H_{11}F_3O_2$ requires: C, 62.69; H, 4.13; F, 21.25%. IR (neat) 3008, 1705, 1628, 1600, 1233, 1174 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.78 (1H, d, *J* 3.8 Hz, H–C^5 in furyl), 7. 52 (1H, d, *J* 1.8 Hz, H–C^3 in furyl), 6.70 (1H, dd, *J* 3.8, 1.8 Hz, H–C^3 in furyl), 6.35 (1H, t, *J* 6.3 Hz, H–C═C), 6.20 (1H, t, *J* 6.3 Hz, H–C═C), 4.30 (1H, m, H–C^1), 4.09 (1H, m, H–C^4), 1.58 (2H, m, –CH_2–), 1.43 (2H, m, –CH_2–); δ_C (100.6 MHz, $CDCl_3$) 174.8 (q, *J* 39 Hz), 156.4, 152.0, 149.5, 134.5, 131.6, 129.6 124.8, 118.7 (q, *J* 288 Hz), 115.7, 44.0, 37.2, 26.2, 24.5.

*4.3.14. 1-(3-Ethylbicyclo[2.2.2]octa-2,5-dien-2-yl)-2,2,2-trifluoroethanone (**16f**).* From **4h** and ethylmagnesiumbromide. Colorless oil; bp 46–47 °C (1 Torr), yield 0.86 g (62%). Found: C, 62.72; H, 5.73; F, 24.69. $C_{12}H_{13}F_3O$ requires: C, 62.60; H, 5.69; F, 24.76%. IR (neat) 3009, 1706, 1630, 1600, 1230, 1172 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.44 (1H, t, *J* 6.1 Hz, H–C═C), 6.25 (1H, t, *J* 6.1 Hz, H–C═C), 4.28 (2H, m, H–C^1, H–C^4), 1.90 (1H, m, –CH_2C═C), 1.85 (1H, m, –CH_2C═C), 1.53 (m), 1.30 (m, totally 4H, –CH_2CH_2–), 1.20 (3H, t, *J* 7.0 Hz, CH_3–); δ_C (100.6 MHz, $CDCl_3$) 177.8 (q, *J* 38 Hz), 165.4, 147.9, 133.9, 132.3, 117.3 (q, *J* 288 Hz), 45.0, 37.8, 26.0, 23.8.

Supplementary data

Physical and all the spectroscopic data for compounds **2b–d**, **3a**, **3c**, **3d**, **4a–d**, **5b**, **5c**, **5e**, **6a**, **6c**, **6d**, **7a**, **8a**, **8b**, **9b–e**, **10a**, **10c–e**, **11**, **12a**, **12b**, **12d**, **12e**, **13a–c**, **13e**, **14a–d**, **15b–e**, **16a**, **16b**, **16d**, **16e** are provided. Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2010.03.026.

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