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1-Bromo-2-trifluoroacetylcyclobutenes as novel building blocks for the construction of trifluoromethyl substituted heterocycles. Part 3: Synthesis of trifluoromethylsubstituted pyridines, condensed with cyclobutene moieties

Andrey B. Koldobskii *, Ekaterina V. Solodova, Ivan A. Godovikov, Pavel V. Verteletskii, Valery N. Kalinin

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov Str. 28, 119991 Moscow, Russian Federation

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ABSTRACT

This paper describes a general synthetic approach to 3-cyano-4-trifluoromethylpyridines fused with cyclobutene rings with variable spiro conjunctions. The reaction of various 1-bromo-2-trifluoroacetylcyclobutenes with ammonia results in the substitution of bromine with an NH_2 group leading to corresponding enaminoketones in high yields, which, in turn, form the target pyridines by treatment with diethyl ethoxymethylencyanophosphonate in the presence of sodium hydride.

1. Introduction

Pyridine and related derivatives constitute an important class of heterocyclic compounds. This ring system is found in a variety of natural products exhibiting diverse biological activities [1]. Moreover, the pyridine ring is a comprising part of effective drugs with a wide range of activity [2,3]. The introduction of a trifluoromethyl group into an organic molecule often induces significant changes in its chemical and physiological properties. Although the trifluoromethylated pyridines represent relatively new compounds, many of them exhibit very useful and interesting properties in many fields of medicine and agriculture [4,5]. Owing to these reasons an elaboration of new construction methods for these heterocycles is an important synthetic challenge and during the last two decades numerous witty and effective approaches to trifluoromethylated pyridine have been developed [6].

It should be specially stressed that cyclobutarenes represent a relatively new and very perspective class of strained bicyclic structures [7]. In spite of vigorous growth of the number of publications dealing with these compounds, there are only few examples of trifluoromethylated cyclobutarenes [8,9] and to the best of our knowledge there are no examples of cyclobutarenes, containing trifluoromethylated heterocyclic moieties. Recently we have developed unusual [2 + 2]-cycloaddition reactions of 1-trifluoroacetyl-2-halogenoacetylenes with simple alkenes to afford substituted 1-halogeno-2-trifluoroacetylcyclobutenes **1a–e** [10,11] and Diels–Alder reaction giving norbornene **1f** [12,13] (Fig. 1).

In our two recent articles of this series we have also shown that compounds **1a–f** are versatile reagents for different heterocyclizations [14,15]. Herein, we report a direct amination of cycloadducts **1a–f** with ammonia and the utility of the resulting new β-amino-α,β-unsaturated trifluoromethylketones with a strained cyclobutene and norbornadiene structures for the synthesis of corresponding trifluoromethylated pyridines.

2. Results and discussion

2.1. Synthesis of β-amino-α,β-unsaturated trifluoromethylketones with cyclobutene and norbornadiene skeletons

We anticipated that owing to the strong mesomeric effect of the trifluoroacetyl group, the compounds **1a–f** should easily react with ammonia. Testing various reaction conditions and solvents showed that the best results were obtained using a saturated solution of ammonia in isopropanol at ambient temperature. In case of **1a–e**, the amination was completed within 8–10 h. The

* Corresponding author. Tel.: +7 499 135 9251; fax: +7 499 135 6549.
E-mail address: andikineos@rambler.ru (A.B. Koldobskii).

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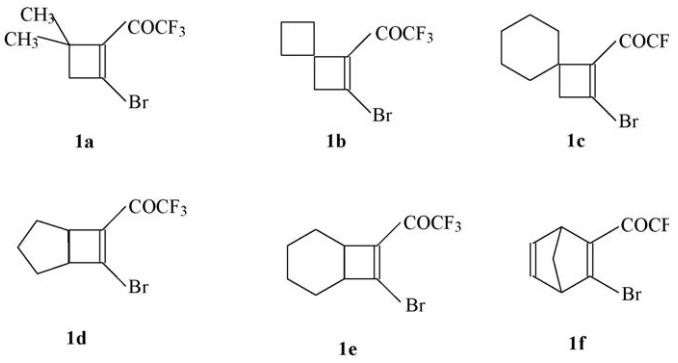
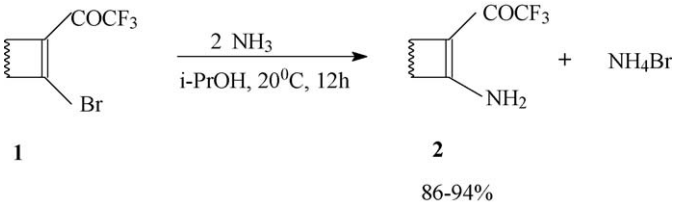


Fig. 1. The starting [2 + 2]-cycloadducts.



Scheme 1.

norbornene **1f** reacted much more faster. The process was very easy to perform and the yields of earlier unknown enaminoketones **2** were in the range of 85–95% (Scheme 1).

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

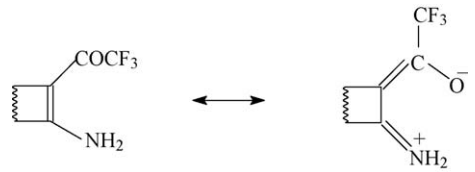


Fig. 3. The azadiene resonance form of enaminoketones.

The enaminoketones **2a–f** proved to be stable crystalline solids which can be purified by crystallization from hexane. It is interesting to note that the signals of the NH_2 protons in the ^1H NMR spectra in $CDCl_3$ appear as two broad singlets with chemical shifts in the ranges of 6.00–6.50 and 7.00–7.50 ppm (with exception of the **2f** spectrum having the corresponding signals in much lower field) slightly depending on concentration. The signals of the two carbon atoms of the C=C bond have a large difference of chemical shifts in ^{13}C NMR spectra and appear between 104.0–106.0 and 168.0–172.0 ppm. These data apparently prove the redistribution of electron pair from the NH_2 group to the carbonyl function and a significant impact of resonance form with N=C and C=C conjugated bonds (Fig. 3).

2.2. Synthesis of trifluoromethylated pyridines condensed with substituted cyclobutenes

To the best of our knowledge there are only two examples of pyridine ring construction via primary trifluoromethylenaminoketones. In both cases only the simplest representative was used (Scheme 2). Thus, its reaction with various 1,3-dicarbonyl compounds in the presence of trifluoroacetic acid afforded the

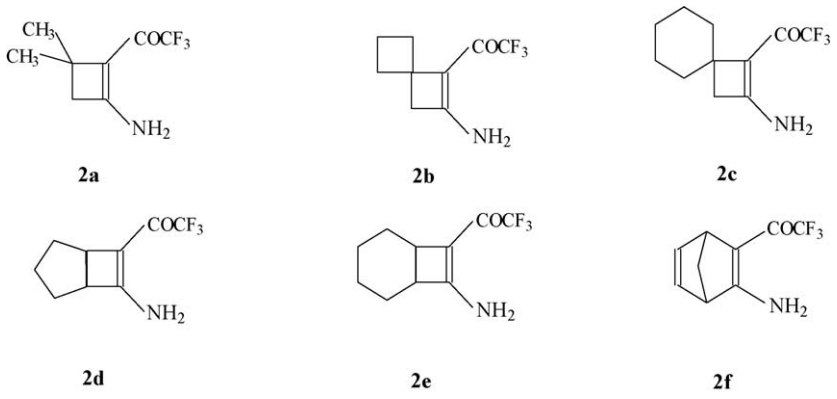
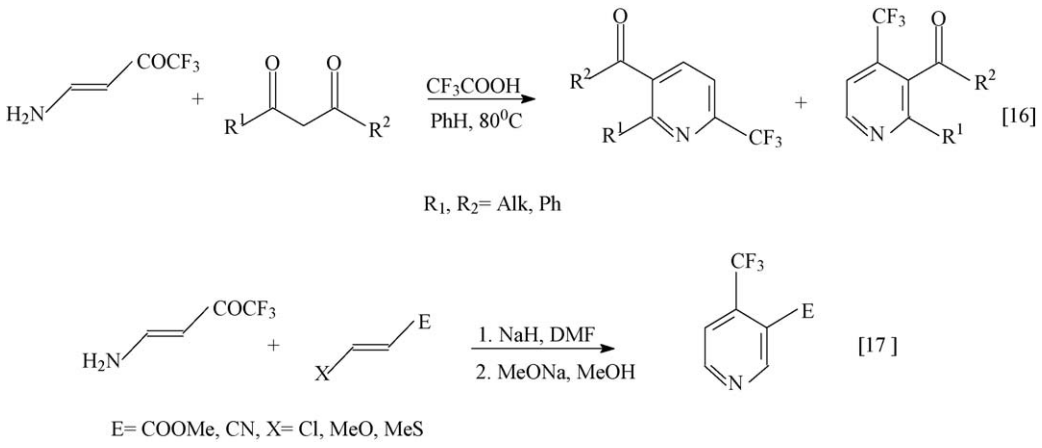
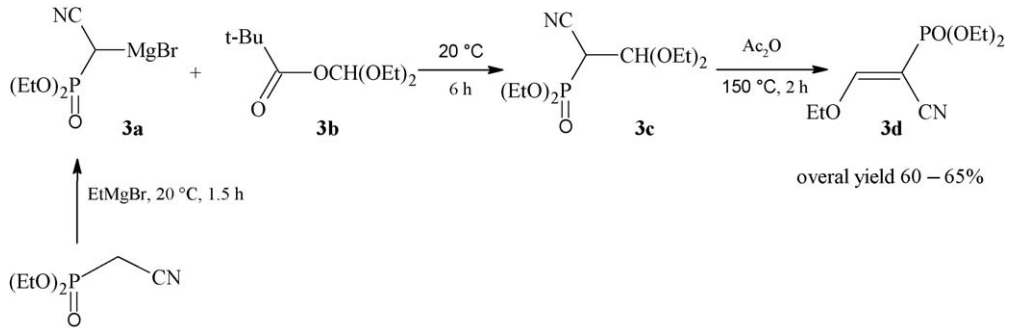


Fig. 2. The target enaminoketones.



Scheme 2.



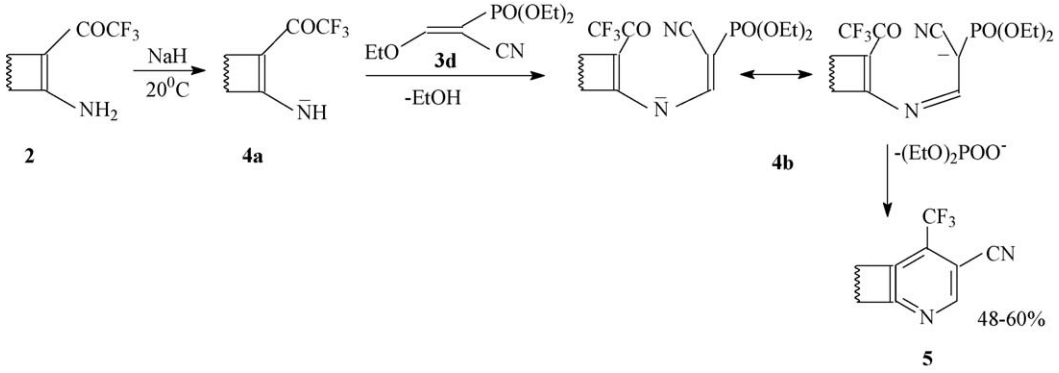
Scheme 3.

2- or the 4-trifluoromethylated substituted pyridine or a mixture of them [16]. According to patented data, in the presence of sodium hydride the trifluoromethylenaminoketones condensed with acrylates and acrylonitriles containing the leaving groups in β-position, leading to substituted 4-trifluoromethylpyridines [17] (Scheme 2).

Initially we anticipated that the methods outlined in Scheme 2 should also be applicable in pyridine synthesis starting from enaminoketones **2a**–**f**. However, despite numerous affords we were unable to obtain reasonable yields of corresponding pyridines using this protocol. Thus, refluxing of **2a**,**d** and acetylacetone in benzene in the presence of acid afforded tarry materials, whereas their reaction with β-chloroacrylonitrile induced by sodium hydride resulted in the formation of complex mixtures, containing very small amounts of the target pyridines. Probably these failures are due to the strained cyclobutene structures of **2a**–**f** and also to the fixed *cis*-configuration of the trifluoroacetyl and the amino group. While analyzing alternative approaches for pyridine construction, we have paid attention on diethyl ethoxymethylencyanophosphonate **3d**, which potentially should be a useful reagent in different cyclizations. To our surprise there are only two papers of the same authors describing the synthesis of **3d** in very low yield and subsequent reaction with alkali [18,19]. Our attempts to improve the described procedure and to prepare the phosphonate **3d** by interaction of triethyl ortoformate with diethyl cyanomethylphosphonate in acetic anhydride gave approximately the same low yields as in original work. In order to increase the yield of **3d** we decided to elaborate an "anionic" version of this condensation including the generation of magnesium derivative of diethyl cyanomethylphosphonate **3a** and its subsequent reaction with some ortoformates, having a good leaving group. The stable diethoxymethyl pivalate **3b**, described long time ago [20] seemed to be the best candidate for this transformation. Actually, it was found that the organomagnesium compound **3a** exothermically substitutes the pivaloyloxy group in diethoxymethylpivalate **3b** to afford the crude diethoxy derivative **3c**. Without purification **3c** was subsequently treated with acetic anhydride to furnish phosphonate **3d** as a single stereoisomer in reasonable yield (Scheme 3). It should be noted that in the ^{1}H NMR spectra of vinylphosphonates *cis*-vicinal coupling constants $^3J_{HP}$ are in the range of 7–15 Hz, whereas *trans*-vicinal constants are much bigger and usually comprise 30–40 Hz [19]. Since the corresponding value observed by us for **3d** is equal to 8.8 Hz, it indicates that hydrogen and the phosphonate substituent at the C=C– bond of **3d** are *cis*-oriented to each other.

We have already mentioned that the phosphonate **3d** has never been used before in cyclization reactions. It might be expected that the ethoxy group in **3d** should be easily displaced by various nucleophiles as well as in the cases of closely related ethoxymethylene derivatives of malonodinitrile, malonic and cyanoacetic esters, which are versatile and frequently used reagents in a variety of cyclizations [21]. However, the potential specific feature of **3d** in base catalyzed reactions with conjugated enaminoketones having an NH_2 group implies the possibility of subsequent Wittig–Horner–Emmons reaction leading to substituted pyridines. The Wittig–Horner–Emmons reactions usually proceed under relatively mild conditions and this circumstance seemed to us very important before beginning an employment of enaminoketones **2a**–**f**.

Since the amino group in compounds **2a**–**f** is a very weak nucleophilic center, N-deprotonation using a base was necessary to effect its addition to phosphonate **3d**. Testing various bases, we have found that sodium hydride in a mixture of DMF: THF = 1:1 ensures satisfactory yields of pyridines **5**. It might be proposed that the addition of the nitrogen-centered-anion **4a** to the β-carbon atom of **3d** causes ethanol elimination to produce the delocalized anion **4b** followed by intramolecular Wittig–Horner–Emmons reaction (Scheme 4). An alternative mechanism of pyridine formation may include the cascade of Michael addition–intramolecular Wittig–Horner–Emmons reaction–ethanol elimination.



Scheme 4.

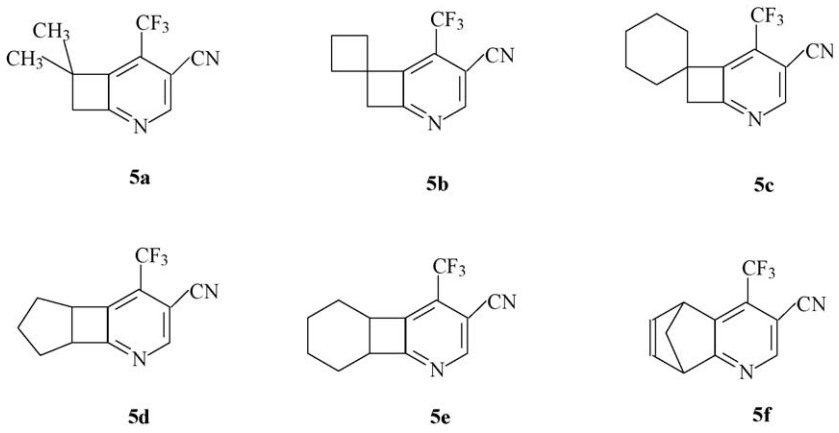


Fig. 4. The target condensed pyridines.

However, this way seems less probable because of strongly reduced positive charge of the carbonyl group in the intermediate formed after Michael addition.

Using this method the following condensed pyridines **5a–f** have been obtained (Fig. 4).

The pyridines **5a–f** thus obtained proved to be relatively stable compounds and were purified by column chromatography.

Since the halogenated trifluoroacetylacetylenes easily form [2 + 2]-cycloadducts with various alkenes and cyclic vinyl ethers as well as Diels–Alder adducts with conjugated (including heterocyclic) dienes, it should be expected, that this approach will appear rather useful and general for the preparation of trifluoromethylated pyridines fused with different strained rings with variable bicyclic conjunctions. Apparently such structures are of interest for biochemical researches and as useful intermediates for further diverse transformations.

3. Conclusion

In summary we have elaborated a new general method for the construction of cyclobutarenes, containing trifluoromethylated pyridines, fused with strained cyclobutene rings with variable spiro conjunctions. This approach includes the direct amination of the available [2 + 2]-cycloadducts **1**. The resulting enaminoketones **2a–f** undergo deprotonation by sodium hydride followed by a reaction sequence with the participation of diethyl ethoxymethylenecyanophosphonate **3d** to afford the corresponding pyridines **5**.

4. Experimental

4.1. General

Cycloadducts **1a–f** have been prepared according to described procedures [10–13], diethoxymethyl pivalate **3b** has been synthesized in two simple steps from triethyl ortoformate [20]. Manipulations with 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 ppm 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 the preparation of enaminoketones 2a–f

To a stirred solution of ammonia (0.34 g, 0.02 mol) in *i*-PrOH (5 mL) at 20 °C the solution one of the cycloadducts **1a–f** (0.008 mol) in *i*-PrOH (2 mL) was added dropwise. The resulting mixture was stirred for 12 h at ambient temperature (in the case of norbornadiene **1f** the amination proceeded much faster and was complete within 1 h) after which an ammonium salt was filtered off and most of the solvent was evaporated in vacuum. The residue was diluted with CH_2Cl_2 (5 mL), the ammonium salt was filtered off, the solvent was removed in vacuum and the residue was crystallized from hexane.

4.2.1. 1-(2-Amino-4,4-dimethylcyclobut-1-en-1-yl)-2,2,2-trifluoroethanone (2a)

Obtained from **1a**. White crystals (from hexane); mp 86 °C; yield 1.34 g (87%). IR (mineral oil): ν 3330, 3315, 2970, 1662, 1595, 1370, 1290, 1175 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (6H, s, $(CH_3)_2C$), 2.45 (2H, s, CH_2), 6.17 (1H, br. s, H–N), 7.33 (1H, br. s, H–N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.2 ($2CH_3$), 40.2 ($\underline{C}H_2$–C=C), 44.9 ($\underline{C}$–C=C), 106.6 ($\underline{C}$=C–N), 115.4 (q, J_{CF} = 290 Hz, CF_3), 167.6 (C=$\underline{C}$–N), 170.6 (q, J_{CF} = 35 Hz, C=O); Anal. Calcd. for $C_8H_{10}F_3NO$: C, 49.7; H, 5.2; F, 29.5; N, 7.3. Found: C, 49.7; H, 5.1; F, 29.4; N, 7.3.

4.2.2. 1-(2-Aminospiro[3.3]hept-1-en-1-yl)-2,2,2-trifluoroethanone (2b)

Obtained from **1b**. White crystals (from hexane); mp 89–90 °C; yield 1.41 g (86%). IR (mineral oil): ν 3415, 3345, 2998, 1670, 1590, 1374, 1273, 1175 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87 m (totally 6H, $(CH_2)_3$), 2.02 m, 2.48 m, 2.77 (2H, s, CH_2–C=C), 6.22 (1H, br. s, H–N), 7.37 (1H, br. s, H–N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.4, 29.6 (–$(CH_2)_3$–), 42.1 ($\underline{C}H_2$–C=C), 46.0 ($\underline{C}$–C=C), 105.2 ($\underline{C}$=C–N), 115.6 (q, J_{CF} = 287 Hz, CF_3), 169.0 (C=$\underline{C}$–N), 172.7 (q, J_{CF} = 33 Hz, C=O); Anal. Calcd. for $C_9H_{10}F_3NO$: C, 52.7; H, 4.9; F, 27.8; N, 6.8. Found: C, 52.8; H, 4.9; F, 27.8; N, 6.7.

4.2.3. 1-(2-Aminospiro[3.5]non-1-en-1-yl)-2,2,2-trifluoroethanone (2c)

Obtained from **1c**. White crystals (from hexane); mp 101–102 °C; yield 1.68 g (90%). IR (mineral oil): ν 3438, 3333, 3000, 1668, 1590, 1370, 1290, 1161 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.18 m (totally 10 H, $(CH_2)_5$), 1.53 m, 1.68 m, 2.39 (2H, s, CH_2–C=C), 6.13 (1H, br. s, H–N), 7.43 (1H, br. s, H–N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 25.3, 35.9 (–$(CH_2)_5$), 41.6 ($\underline{C}H_2$–C=C), 45.3 ($\underline{C}$–C=C), 104.2 ($\underline{C}$=C–N), 115.4 (q, J_{CF} = 287 Hz, CF_3), 169.4 (C=$\underline{C}$–N), 172.5 (q, J_{CF} = 33 Hz, C=O); Anal. Calcd. for $C_{11}H_{14}F_3NO$: C, 56.6; H, 6.1; F, 24.5; N, 6.0. Found: C, 56.8; H, 6.1; F, 24.4; N, 5.9.

4.2.4. 1-(7-Aminobicyclo[3.2.0]hept-6-en-6-yl)-2,2,2-trifluoroethanone (2d)

Obtained from **1d**. White crystals (from hexane); mp 95–96 °C; yield 1.51 g (92%). IR (mineral oil): ν 3440, 3335, 2998, 1662, 1600,

1365, 1270, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.37 m (totally 6H, $(CH_2)_3$), 1.79 m, 3.24 (1H, dd, J = 6.0, 3.5 Hz, CH–C=C), 3.42 (1H, dd, J = 6.0, 3.5 Hz, CH–C=C), 6.39 (1H, br. s, H–N), 7.12 (1H, br. s, H–N); ^{13}C NMR (100 MHz, $CDCl_3$): 23.5, 26.6, 28.8 (–$(CH_2)_3$–), 42.0 (CH–C=C), 47.5 (CH–C=C), 104.0 (C=C–N), 115.7 (q, J_{CF} = 287 Hz, CF_3), 171.3 (C=C–N), 172.1 (q, J_{CF} = 34 Hz, C=O). Anal. Calcd. for $C_9H_{10}F_3NO$: C, 52.7; H, 4.9; F, 27.8; N, 6.8. Found: C, 52.8; H, 5.1; F, 27.6 N, 6.8.

4.2.5. 1-(8-Aminobicyclo[4.2.0]oct-7-en-7-yl)-2,2,2-trifluoroethanone (2e)

Obtained from **1e**. White crystals (from hexane); mp 92–93 °C; yield 1.58 g (90%). IR (mineral oil): ν 3412, 3346, 3000, 1669, 1590, 1363, 1270, 1185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.53 m (totally 8H, $(CH_2)_4$), 1.72 m, 3.00 (1H, dd, J = 6.4, 3.5 Hz, CH–C=C), 3.14 (1H, dd, J = 6.4, 3.5 Hz, CH–C=C), 6.20 (1H, br. s, H–N), 7.25 (1H, br. s, H–N); ^{13}C NMR (100 MHz, $CDCl_3$): 17.7, 18.1, 21.8, 23.8 (–$(CH_2)_4$–), 35.2 (CH–C=C), 40.9 (CH–C=C), 105.5 (C=C–N), 115.2 (q, J_{CF} = 287 Hz, CF_3), 168.4 (C=C–N), 172.7 (q, J_{CF} = 34 Hz, C=O). Anal. Calcd. for $C_{10}H_{12}F_3NO$: C, 54.8; H, 5.5; F, 26.0; N, 6.4. Found: C, 54.9; H, 5.7; F, 25.9; N, 6.3.

4.2.6. 1-(3-Aminobicyclo[2.2.1]hepta-2,5-dien-2-yl)-2,2,2-trifluoroethanone (2f)

Obtained from **1f**. White crystals (from hexane); mp 111–112 °C; yield 1.53 g (94%). IR (mineral oil): ν 3453, 3319, 1660, 1615, 1595, 1264, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.07 (1H, d, J = 9.4 Hz, H–C^7), 2.17 (1H, d, J = 9.4 Hz, H–C^7), 3.50 (1H, d, J = 1.3 Hz, H–C^1), 3.93 (1H, d, J = 1.3 Hz, H–C^4), 6.41 (1H, dd, J = 5.0, 1.3 Hz, H–C=C), 6.88 (1H, dd, J = 5.0, 1.3 Hz, H–C=C), 8.54 (1H, br. s, H–N), 9.24 (1H, br. s, H–N); ^{13}C NMR (100 MHz, $CDCl_3$): 45.9 (CH_2), 52.9, 63.0 (C^1, C^4), 107.8 (C=C–N), 115.3 (q, J_{CF} = 287 Hz, CF_3), 135.5, 147.1 (CH=CH), 171.5 (C=C–N), 173.0 (q, J_{CF} = 33 Hz, C=O); Anal. Calcd. for $C_9H_8F_3NO$: C, 53.2; H, 4.0; F, 28.1; N, 6.9. Found: C, 53.2; H, 4.0; F, 28.2; N, 6.8.

4.3. Preparation of diethyl ethoxymethylencyanophosphonate (3d)

To a stirred solution of EtMgBr (0.1 mol) in THF (100 mL) at 20 °C a solution of diethyl cyanomethylphosphonate (18.60 g, 0.105 mol) in THF (50 mL) was added dropwise and stirring was continued at ambient temperature until ethane evolution ceased (approximately 0.5 h) and then additionally for 1 h. The resulting mixture with an insoluble material was in several portions poured to a stirred solution of diethoxymethylpivalate **3b** (24.48 g, 0.12 mol) in THF (100 mL). The latter solution was occasionally cooled with ice water keeping the internal temperature below 35–40 °C. When the addition of the magnesium derivative **3a** to the solution of **3b** was completed, the resulting mixture was stirred for additional 6 h at ambient temperature and then was poured into a saturated solution of NaH_2PO_4 (200 mL). The organic phase was separated and the aqueous solution was extracted with diethyl ether (2× 50 mL). The combined organic phase was dried with Na_2SO_4 followed by evaporation of the solvent in vacuum and heating the residue at 100 °C in vacuum 1 Torr for 1 h. The residue was dissolved in acetic anhydride (17.16 g, 0.13 mol) containing freshly dried $ZnCl_2$ (0.2 g) and the resulting solution was heated at 140–150 °C, until AcOEt was completely distilled over a short Vigreux column. The reaction mixture was diluted with $CHCl_3$ (50 mL), washed with 20% aqueous solution of NaCl (20 mL), dried over Na_2SO_4 and after evaporation of solvent the residue was distilled in vacuum to afford the phosphonate **3d** (14.45 g, 62%) as a colorless liquid, bp 160–162 °C (0.4 Torr) (lit. [19] 160–162 °C (0.1 Torr)). IR (film): ν 2991, 2922, 2217, 1610, 1457, 1395, 1237 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.10–1.42 (9H, m, $3CH_3O$), 3.86–4.09 (4H, m, $(CH_2O)_2P$), 4.16 (2H, q, J = 6.9 Hz, CH_2O), 7.43 (1H, d, J = 8.8 Hz, H–C=); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.0 (CH_3), 15.9 (CH_3), 62.8 (CH_2O), 73.3 (CH_2O), 78.4 (d, J_{CP} = 210 Hz, C=C–PO), 112.6 (d, J_{CP} = 7.5 Hz, CN), 173.5 (d, J_{CP} = 20.5 Hz, C=C–PO). Anal. Calcd. for $C_9H_{16}O_4PN$: C, 46.4; H, 6.9; P, 13.3. Found: C, 46.5; H, 6.9; P, 13.1.

4.4. General procedure for the preparation of pyridines 5a–f

To a stirred suspension of NaH (0.12 g, 0.005 mol) in a mixture of DMF (10 mL) and THF (5 mL) a solution of one of the enaminoketones **2a–f** (0.005 mol) and phosphonate **3d** (1.40 g, 0.006 mol) in THF (5 mL) was added dropwise while cooling with ice water. The reaction mixture was stirred at 20 °C for 1 h and additionally at 60 °C for 1.5 h. Approximately two thirds of the solvent volume were evaporated in vacuum and some drops of AcOH were added. The concentrate was diluted with $CHCl_3$ (50 mL), washed with 5% solution of $NaHCO_3$ (20 mL) and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (silica gel, CH_2Cl_2) to afford pyridines **5a–f**.

4.4.1. 7,7-Dimethyl-5-(trifluoromethyl)-2-azabicyclo[4.2.0]octa-1,3,5-triene-4-carbonitrile (5a)

Obtained from **2a**. Colorless oil, yield 0.59 g (52%). IR (film): ν 3038, 2990, 2220, 1477, 1380, 1274, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (6H, s, $(CH_3)_2C$), 2.77 (2H, s, CH_2), 8.76 (1H, s, H–C=N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7 ($2CH_3$), 45.2 (C$(CH_3)_2$), 53.0 (CH_2), 113.4 (C–CN), 115.8 (CN), 121.1 (q, J_{CF} = 274 Hz, CF_3), 142.5 (q, J_{CF} = 34.0 Hz, C–CF_3), 144.6 (C=C–CF_3), 152.3 (CH=N), 168.0 (C=N); Anal. Calcd. for $C_{11}H_9F_3N_2$: C, 58.4; H, 4.0; F, 25.2, N, 12.4. Found: C, 58.6, H, 4.1, F, 25.1, N, 12.2.

4.4.2. 5-(Trifluoromethyl)-2-azaspiro[bicyclo[4.2.0]octane-7,1′-cyclobutane]-1,3,5-triene-4-carbonitrile (5b)

Obtained from **2b**. Colorless crystals, yield 0.57 g (48%), mp 44–45 °C. IR (mineral oil): ν 3050, 2998, 2218, 1471, 1380, 1275, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.19–2.29 (2H, m, 2C–H in cyclobutane), 2.54–2.70 (4H, m, 4C–H in cyclobutane), 3.25 (2H, s, CH_2–Ar), 8.83 (1H, s, H–C=N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.7, 32.1 (–$(CH_2)_3$–), 47.3 (C$(CH_2)_3$), 53.8 (CH_2–Ar), 113.8 (C–CN), 116.2 (CN), 121.9 (q, J_{CF} = 274 Hz, CF_3), 142.7 (q, J_{CF} = 34.0 Hz, C–CF_3), 146.1 (C=C–CF_3), 152.5 (CH=N), 169.4 (C=N); Anal. Calcd. for $C_{12}H_9F_3N_2$: C, 60.5; H, 3.8; F, 23.9, N, 11.8. Found: C, 60.7; H, 3.9; F, 23.8; N, 11.7.

4.4.3. 5-(Trifluoromethyl)-2-azaspiro[bicyclo[4.2.0]octane-7,1′-cyclohexane]-1,3,5-triene-4-carbonitrile (5c)

Obtained from **2c**. Colorless crystals, yield 0.72 g (54%), mp 56–57 °C. IR (mineral oil): ν 3045, 3010, 2220, 1466, 1364, 1282, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.22–1.35 (m), 1.56–1.68 (m), 1.86–2.19 (m) (totally 10H, $(CH_2)_5$), 2.90 (2H, s, CH_2–Ar), 8.74 (1H, s, H–C=N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 25.7, 33.7 (–$(CH_2)_5$–), 46.0 (C$(CH_2)_5$), 46.8 (CH_2–Ar), 112.6 (C–CN), 115.5 (CN), 120.9 (q, J_{CF} = 274 Hz, CF_3), 142.3 (q, J_{CF} = 34.0 Hz, C–CF_3), 143.7 (C=C–CF_3), 151.8 (CH=N), 167.7 (C=N); Anal. Calcd. for $C_{14}H_{13}F_3N_2$: C, 63.1 H, 4.9; F, 21.4; N, 10.5. Found: C, 63.3; H, 4.8; F, 21.4; N, 10.5.

4.4.4. 4-(Trifluoromethyl)-5,6,7,7a-tetrahydro-4bH-cyclopenta[3,4]cyclobuta[1,2-b]pyridine-3-carbonitrile (5d)

Obtained from **2d**. Colorless crystals, yield 0.67 g (56%), mp 39–40 °C. IR (mineral oil): ν 3040, 3000, 2224, 1458, 1355, 1270, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.38–1.50 (m), 1.55–1.64 (m), 1.82–2.03 (m) (totally 6H, $(CH_2)_3$), 3.73 (1H, dd, J = 6.2, 3.5 Hz, –CH–CH–), 3.90 (1H, dd, J = 6.2, 3.5 Hz, –CH–CH–), 8.81 (1H, s, H–C=N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.3, 26.4, 27.7 (–$(CH_2)_3$–),

51.2, 59.5 (–CH–CH–), 112.2 (C–CN), 116.3 (CN), 122.0 (q, J_{CF} = 75 Hz, CF_3), 141.8 (q, J_{CF} = 34.0 Hz, C–CF_3), 142.9 (C=C–CF_3), 153.3 (CH=N), 170.5 (C=N); Anal. Calcd. for $C_{12}H_9F_3N_2$: C, 60.5; H, 3.8; F, 23.9; N, 11.8. Found: C, 60.4; H, 3.9; F, 23.8; N, 11.7.

*4.4.5. 4-(Trifluoromethyl)-4b,5,6,7,8,8a-hexahydrobenzo[3,4]cyclobuta[1,2-b]pyridine-3-carbonitrile (**5e**)*

Obtained from **2e**. Colorless oil, yield 0.73 g (58%). IR (film): ν 3044, 3005, 2990, 2224, 1460, 1373, 1268, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.34–1.55 (m), 1.58–2.03 (m) (totally 8H, –$(CH_2)_4$–), 3.41 (1H, dd, J = 6.5, 4.2 Hz, –CH–CH–), 3.60 (1H, dd, J = 6.5, 4.2 Hz, –CH–CH–), 8.80 (1H, s, H–C=N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 15.7, 19.0, 21.1 (–$(CH_2)_4$–), 42.8, 48.6 (–CH–CH–), 111.7 (C–CN), 116.6 (CN), 121.1 (q, J_{CF} = 274 Hz, CF_3), 141.2 (q, J_{CF} = 35.0 Hz, C–CF_3), 142.0 (C=C–CF_3), 151.9 (CH=N), 168.8 (C=N); Anal. Calcd. for $C_{13}H_{11}F_3N_2$: C, 61.9; H, 4.4; F, 22.6, N, 11.1. Found: C, 62.1; H, 4.4; F, 22.5; N, 11.0.

*4.4.6. 4-(Trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methanoquinoline-3-carbonitrile (**5f**)*

Obtained from **2f**. Yellowish crystals, yield 0.70 g (59%), mp 72–73 °C. IR (mineral oil): ν 3025, 3000, 2220, 1690, 1445, 1370, 1280, 1185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.39 (1H, d, J = 7.5 Hz, CH_2), 2.52 (1H, d, J = 7.5 Hz, CH_2), 4.17 (1H, d, J = 1.3 Hz, H–C^1), 4.32 (1H, d, J = 1.3 Hz, H–C^4), 6.90 (1H, dd, J = 4.9, 1.3 Hz, H–C=), 7.01 (1H, dd, J = 4.9, 1.3 Hz, H–C=), 8.95 (1H, s, H–C=N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.8 (CH_2), 59.6, 68.0 (C^1, C^4), 114.2 (C–CN), 118.3 (CN), 123.9 (q, J_{CF} = 274 Hz, CF_3), 144.6 (q, J_{CF} = 33.0 Hz, C–CF_3), 146.5, 150.2 (CH=CH), 152.0 (C=C–CF_3), 155.7 (CH=N), 170.9 (C=N); Anal. Calcd. for $C_{12}H_7F_3N_2$: C, 61.0; H, 3.0; F, 24.1; N, 11.9. Found: C, 61.2; H, 3.0; F, 24.1; N, 11.8.

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