GREEN ONE-POT MULTICOMPONENT SYNTHESIS OF 4-ARYL-6-CARBAMOYLMETHYLTHIO-5-CYANO-2-METHYL-1,4-DIHYDROPYRIDINE-3-CARBOXYLIC ACID METHYL ESTERS

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Abstract: 4-Aryl-6-carbamoylmethylthio-5-cyano-2-methyl-1,4-dihydropyridine-3-carboxylic acid methyl esters 7 were obtained by an one-pot condensation of 2-(3-chloro- or 2,4-dichlorobenzylidene)-3-oxobutyric acid methyl esters and 2-cyanothioacetamide in the presence of stoichiometric amount of piperidine or ammonium hydroxide with subsequent alkylation with iodoacetamide or chloroacetamide. Application of ammonium hydroxide instead of piperidine and much cheaper chloroacetamide instead of iodoacetamide does not influence significantly the yield of reactions, but makes this method greener: gives rise to environmentally friendly waste product – ammonium chloride and 22-23 % atom economy.

Introduction

1,4-Dihydropyridines (DHPs) are known as effective calcium antagonists and many cardiovascular drugs on their basis are now used in the clinics or still are in different stages of development [1-4]. 6-Alkylthio-1,4-DHPs display cardiovascular [5,6], hepatoprotective [7], antioxidant (AOA) [8], and antiradical (ARA) [9] activity, however, these compounds are still insufficiently studied pharmacologically.

Green chemistry is based on a number of principles that ensure that both processes and end products are clean and safe. It aims to conserve both energy and raw materials and make chemical processes cheaper than by applying conventional methods. A lot of chemical reactions are revised today. The use of green chemistry is growing because it is environmentally friendly, and also because of legislation and international agreements that aim to reduce pollution. One of the basic ideas of green chemistry is to prevent the production of hazardous and polluting materials rather than producing them and then cleaning up. Another key idea of green chemistry is atom economy. This considers how much of the reactants in a chemical reaction end up in the final useful products. The atom economy (also called atom utilisation) of a reaction is a measure of the percentage of the starting materials that actually ends up in the useful products.

Results and discussion

In continuation of searching biologically active compounds in the series of 6-alkylthio-1,4-DHPs [6] we have synthesized 4-aryl-6-carbamoylmethylthio-5-cyano-2-methyl-1,4-dihydropyridine-3-carboxylic acid methyl esters (7) with increased lipophilicity (one or two Cl atoms are introduced in the molecule) by making use of the conventional method (stepwise synthesis) [10, 11] and recently demonstrated convenient one-pot multi-component synthesis [6, 12]. To make them more competitive in the drug design market we have further revised this method to make it "greener".

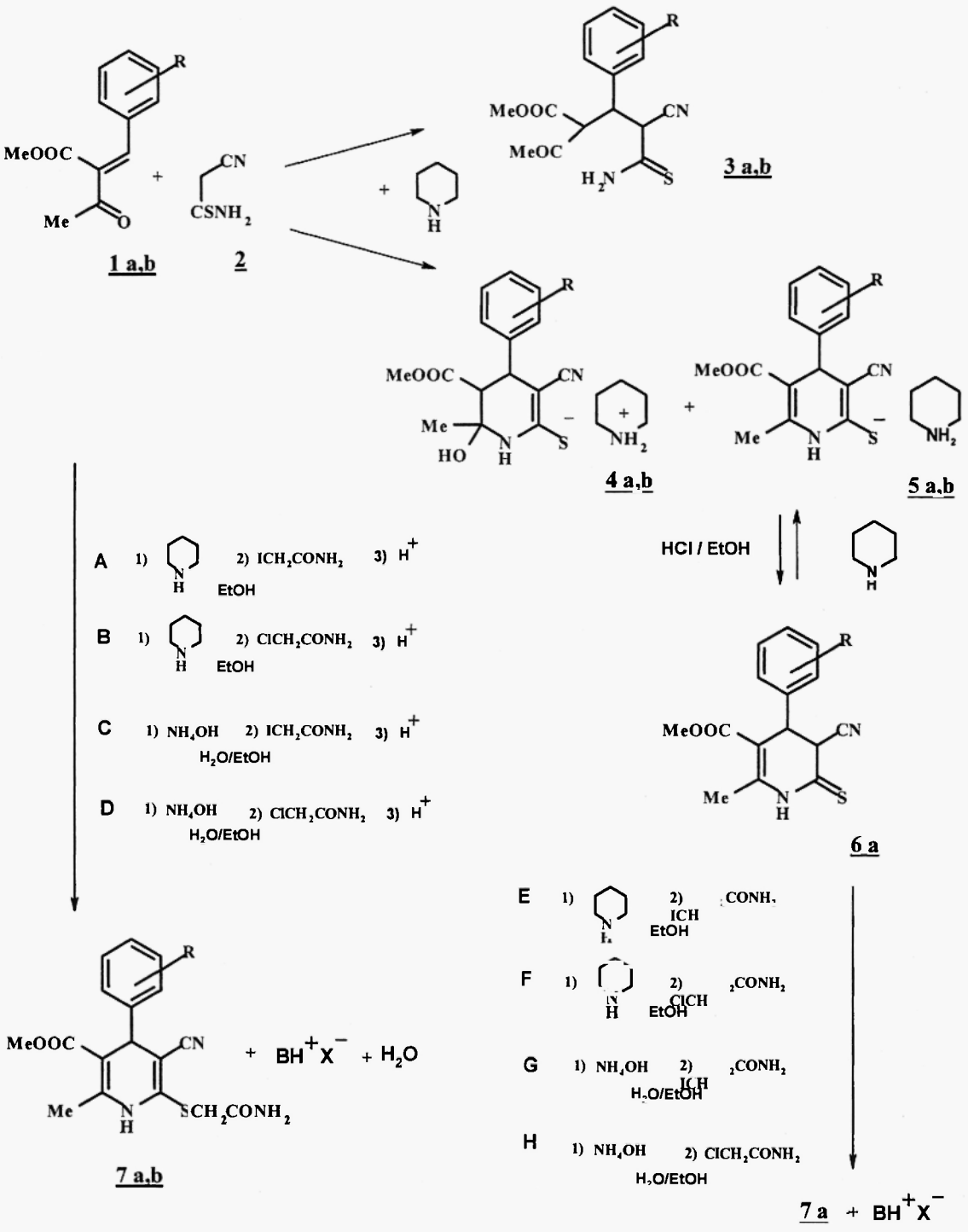
The Michael reaction of 2-(3-chloro- or 2,4-dichlorobenzylidene)-3-oxobutyric acid methyl esters 1 with 2-cyanothioacetamide 2 in the presence of catalytic amount of piperidine at room temperature gives rise to the mixture of unstable products. We did not succeed in isolation of 2-acetyl-4-cyano-4-thiocarbamoylbutyric acid methyl esters 3 - the primary adducts of the Michael reaction. Application of stoichiometric amount of piperidine gave rise to the mixture of piperidinium 2-hydroxy-1,2,3,4-tetrahydropyridine-6-thiolates 4 and 1,4-dihydropyridine-6-thiolates 5. Tetrahydropyridine-6-thiolate 4b (IR, $\nu_{C=O}$ at 1727 cm^{-1} and confirming elemental analysis) dominates in crystalline aggregation in case of mixture of compounds 4b and 5b, but in $CDCl_3$ solution already after 10 min the ratio of 4b to 5b is 1 : 2

and after 1 h only signals of 1,4-dihydropyridine-6-thiolates 5b are observed. Pure 1,4-dihydropyridine-6-thiolates 5a were obtained by brief heating of compounds 1a, 2 and piperidine (63 %), but acidification of thiolate 5a gave rise to 97 % yield of thione 6a. Alkylation of both thione 6a (in the presence of stoichiometric amount of base) and thiolates 5 proceeded formation of target 4-aryl-6-carbamoylmethylthio-5-cyano-2-methyl-1,4-dihydropyridine-3-carboxylic acid methyl esters (7) in high yield. The calculated total yields for such stepwise synthesis were moderate (48-54 %).

It is worth to mention, that 6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylic acid methyl esters 6 are unstable in diluted solution [8,9] and due to increased lipophilicity we did not succeed to isolate 4-(2,4-dichlorophenyl)-substituted thiolate 5b and thione 6b. The target 6-carbamoylmethylthio-1,4-dihydropyridine-3-carboxylic acid methyl ester 7b was obtained by making use of one-pot multi-component method [6,12], which was less labour-, also energy- and solvent-consuming. Carrying out condensations of 2-(3-chloro- or 2,4-dichlorobenzylidene)-3-oxobutyric acid ethyl esters 1 with 2-cyanothioacetamide 2 in the presence of stoichiometric amount of piperidine with subsequent alkylation with iodoacetamide and acidification of the formed reaction mixture (to reach complete dehydration), the yields of 1,4-dihydropyridine-3-carboxylic acid methyl esters 7 were 63 % and 84 %. Application of ammonium hydroxide instead of piperidine and much cheaper chloroacetamide instead of iodoacetamide did not influence significantly the yields of reactions, but gave rise to environmentally friendly waste product – ammonium chloride. Comparing the reaction waste products: piperidinium iodide, piperidinium chloride, ammonium iodide and ammonium chloride (molecular masses 213.05, 121.61, 144.94 and 53.49, correspondingly) demonstrated that in case of preparation of 6-carbamoylmethylthio-1,4-dihydropyridine 7a (methods A-D) the atom economy was increased from 62.1 % in case of applying piperidine and iodoacetamide (73.0 % - piperidine and chloroacetamide; 69.9 % - ammonium hydroxide and iodoacetamide) to 84.1 % in case of ammonium hydroxide and chloroacetamide (by alkylation of thione 6a from 63.9 to 87.6 %), but in case of 6-carbamoylmethylthio-1,4-dihydropyridine 7b (methods A-D) from 64.1 to 85.2 %.

The structures of synthesized compounds were proved by spectroscopic methods. In the IR spectra of hydrogenated 5-cyanopyridine-6-thiolates **4b** and **5a**, 5-cyano-6-thioxo-1,4,5,6-tetrahydropyridine 6a and 5-cyano-1,4-dihydropyridines **7a,b** characteristic absorption bands of C≡N group at 2160-2180, 2254 and 2198-2220 cm^{-1}, correspondingly, are observed, which are in agreement with the type of conjugation of cyano group [13,14]. Absorption bands of $\nu_{C=O}$ in the spectra of compounds **4-7** are in agreement with the type of conjugation of C=O groups, too. In the ^1H NMR spectra of 2-hydroxy-1,2,3,4-tetrahydropyridine-6-thiolate **4b** the characteristic 3-H and 4-H proton signals at 2.68 and 4.50 ppm with $^3J_{3\,4}$ = 12 Hz appear, but in case of compounds **5** and **7** the characteristic 4-H proton signals at 4.56 – 5.10 ppm are observed. In case of 5-cyano-6-thioxo-1,4,5,6-tetrahydropyridine **6a** two doublets with $J_{4\,5}$ = 6.4 Hz and 2.4 Hz are observed which means that this compound is formed as a mixture of cis- and trans-isomers (ratio ~ 1:1).

In conclusion, a convenient method of one-pot synthesis of 4-aryl-6-carbamoylmethylthio-5-cyano-2-methyl-1,4-dihydropyridine-3-carboxylic acid methyl esters 7 has been elaborated by one-pot condensation of 2-(3-chloro- or 2,4-dichlorobenzylidene)-3-oxobutyric acid methyl esters, 2-cyanothioacetamide, ammonium hydroxide and chloroacetamide in ethanol-water media. Application of ammonium hydroxide instead of piperidine and chloroacetamide instead of iodoacetamide makes the synthesis cheaper, allows to reach 22 – 23 % atom economy and gives rise to environmentally friendly waste product – ammonium chloride.



a) R = 3-Cl, b) R = 2,4-Cl_2; BH^+ = piperidinium, ammonium; X = Cl, I

Table-1: Yield and atom economy of the synthesized compounds **7**

Compound	Method	Yield, %	Yield calculated on comp. **2**, %	Atom economy, %
7a	**A**	63	63	62.1
	B	55	55	73.0
	C	63	63	69.9
	D	65	65	**84.1**
	E	79	48*	63.9
	F	78	48	75.7
	G	89	54	72.3
	H	88	54	**87.6**
7b	**A**	84	84	64.1
	D	73	73	**85.2**

* 0.63 x 0.97 x 79 = 48 %

Experimental

Melting points were determined on a Boetius apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 580 B spectrometer (in nujol) and peak positions ν_{max} were expressed in cm^{-1}. ^1H NMR spectra were recorded on a Varian Mercury-200 (200 MHz) spectrometer. Chemical shifts are expressed in δ (p.p.m. downfield from TMS) and coupling constants (*J*) in Hz. The course of the reactions and the individuality of substances were monitored by TLC on Kieselgel 60 F Merck plates with dichloromethane – hexane – methanol (5 : 5 : 1) as eluent. Compounds were recrystallized from ethanol.

Piperidinium 5-cyano-4-(2,4-dichlorophenyl)-3-methoxycarbonyl-2-methyl-1,4,5,6-tetrahydropyridi-ne-6-thiolate 5b. A mixture of 2-(2,4-dichlorobenzylidene)-3-oxobutyric acid methyl ester 1b (1.37 g, 5 mmol), 2-cyanothioacetamide 2 (0.5 g, 5 mmol) and piperidine (0.55 ml, 5.5 mmol) in 15 ml of ethanol was stirred for 30 min at ambient temperature, then cooled to – 5° C. The precipitate was filtered and washed with 5 ml of cold ethanol to give 1.31 g (57 %) of thiolate 4b as colourless powder; ~ 120 °C (dehydration), mp 135 – 137 °C. IR (v/cm): 1727 (C=O); 2160 (C≡N); 3224 (NH); ^1H NMR (DMSO-d_6, δ, ppm): 1.36 (3H, s, 2-Me); 1.60 and 3.00 (10H, m and m, $C_5H_{10}N$); 2.68 and 4.50 (2H, d and d, J = 12 Hz); 3.60 (3H, s, OMe); 7.10 – 7.60 (3H, m, C_6H_3); 8.14 (1H, s, NH). Calcd. for $C_{20}H_{25}Cl_2N_3O_2S$: C 52.40, H 5.50, N 9.17, S 6.99. Found C 52.44, H 5.49, N 9.14, S 7.00.

Piperidinium 5-cyano-4-(2,4-dichlorophenyl)- 3-methoxycarbonyl-2-methyl-1,4-dihydropyridine-6-thiolate 5b. ^1H NMR (DMSO-d_6, δ, ppm): 1.60 and 3.00 (10H, m and m, $C_5H_{10}N$); 2.20 (3H, s, 2-Me); 3.40 (3H, s, OMe); 4.82 (1H, s, 4-H); 7.14 – 7.42 (3H, m, C_6H_3); 8.32 (1H, s, NH).

Piperidinium 4-(3-Chlorophenyl)-5-cyano-3-methoxycarbonyl-2-methyl-1,4-dihydropyridine-6-thiolate 5a. A mixture of 2-(3-chlorobenzylidene)-3-oxobutyric acid ethyl ester 1a (1.19 g, 5 mmol), 2-cyanothioacetamide 2 (0.5 g, 5 mmol) and piperidine (0.55 ml, 5.5 mmol) in 20 ml of ethanol was shortly heated until dissolution, stirred for 30 min at ambient temperature, then chilled to – 5° C. The precipitate was filtered and washed with 5 ml of cold ethanol to give 1.28 g (63 %) of thiolate 5a as colourless powder; mp 151 – 153 °C. IR (v/cm): 1698 (C=O); 2180 (C≡N); 3240 (NH); ^1H NMR (DMSO-d_6, δ, ppm): 1.60 and 3.00 (10H, m and m, $C_5H_{10}N$); 2.23 (3H, s, 2-Me); 3.46 (3H, s, OMe); 4.28 (1H, s, 4-H); 7.04 – 7.42 (4H, m, C_6H_4); 8.32 (1H, s, NH). Calcd. for $C_{20}H_{24}ClN_3O_2S$: C 59.18, H 5.96, N 10.35, S 7.90. Found C 59.17, H 6.11, N 10.26, S 7.90.

4-(3-Chlorophenyl)-5-cyano-2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylic acid methyl ester 6a.

A mixture of thiolate 5a (0.41 g, 1 mmol) in 3 ml of 0.5 M HCl ethanol solution was shortly heated until dissolution and stirred for 30 min at ambient temperature. The precipitate was filtered and washed with 2 ml of ethanol and 5 ml of water to give 0.31 g (97 %) of thione 6a as yellow crystals; mp 137 – 139 °C. IR (ν/cm): 1665 (C=O); 2254 (C≡N); 3284 (NH); ^{1}H NMR ($CDCl_3$, δ, ppm): 2.52 and 2.58 [3H, s and s, cis- and trans-(2-Me)]; 3.68 and 3.72 (3H, s and s, cis- and trans-OMe); 4.18 and 4.46, 4.24 and 4.40 [2H, d and d, J = 2.4 Hz, trans-(5-H) and (4-H), d and d, J = 7.2 Hz, cis-(5-H) and (4-H)]; 6.94 – 7.32 (4H, m, cis- and trans-C_6H_4); 8.68 (1H, br.s, NH). Calcd. for $C_{15}H_{13}ClN_2O_2S$: C 56.16, H 4.08, N 8.73, S 10.00. Found C 55.87, H 3.88, N 8.73, S 9.98.

6-Carbamoylmethylthio-4-(3-chlorophenyl)-5-cyano-2-methyl-1,4-dihydropyridine-3-carboxylic acid methyl ester 7a.

A. A mixture of 2-(3-chlorobenzylidene)-3-oxobutyric acid methyl ester 1a (0.24 g, 1 mmol) and 2-cyanothioacetamide 2 (0.10 g, 1 mmol) and piperidine (0.1 ml, 1 mmol) in 10 ml of ethanol was stirred for 10 min at ambient temperature. Then to the reaction mixture iodoacetamide (0.19 g, 1.05 mmol) was added, shortly heated and stirred for 10 min at ambient temperature. Finally 1M HCl in ethanol was added (0.3 ml), heated to reflux and stirred for 30 min at ambient temperature. The precipitate was filtered and washed with 5 ml of ethanol and 10 ml of water to give 0.23 g (63 %) of DHP 7a as colourless crystals; mp 178 – 180 °C. IR (ν/cm): 1679, 1699 (C=O); 2198 (C=N); 3214, 3270, 3346, 3410 (NH, NH_2); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.30 (3H, s, 2-Me); 3.50 (3H, s, OMe); 3.62 and 3.78 (2H, d and d, J = 15 Hz, SCH_2); 4.56 (1H, s, 4-H); 7.05 – 7.55 (4H, m, C_6H_4); 7.62 and 7.93 (2H, br. s and br. s, $CONH_2$), 10.54 (1H, s, NH). Calcd.for $C_{17}H_{16}ClN_3O_3S$: C 54.04, H 4.27, N 11.12, S 8.49. Found C 53.90, H 4.19, N 11.11, S 8.51.

In a similar manner [2-(2,4-dichlorobenzylidene)-3-oxobutyric acid methyl ester was used instead of 2-(3-chlorobenzylidene)-3-oxobutyric acid methyl ester)] **6-carbamoylmethylthio-4-(2,4-dichlorophenyl)-5-cyano-2-methyl-1,4-dihydropyridine-3-carboxylic acid methyl ester 7b** was obtained (84 %) as colourless crystals; mp 210 – 212 °C. IR (ν/cm): 1670, 1709 (C=O); 2200 (C=N); 3178, 3342, 3444 (NH, NH_2); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.32 (3H, s, 2-Me); 3.47 (3H, s, OMe); 3.60 and 3.74 (2H, d and d, J = 14 Hz, SCH_2); 5.10 (1H, s, 4-H); 7.34, 7.38 and 7.55 (3H, s, d and d, J = 2 Hz, C_6H_3); 7.62 and 7.92 (2H, br. s and br. s, $CONH_2$), 10.48 (1H, s, NH). Calcd.for $C_{17}H_{15}Cl_2N_3O_3S$: C 49.52, H 3.67, N 10.19, S 7.78. Found C 49.29, H 3.52, N 10.10, S 7.71.

B. In a similar manner (chloroacetamide was used instead of iodoacetamide) ester 7a was obtained.
C. In a similar manner (ammonium hydroxide was used instead of piperidine) ester 7a was obtained.
D. In a similar manner (chloroacetamide was used instead of iodoacetamide and ammonium hydroxide instead of piperidine) esters 7a and 7b were obtained.

E. A mixture of thione 6a (0.64 g, 2 mmol) and piperidine (0.20 ml, 2 mmol) in 10 ml of ethanol was shortly heated until dissolution and stirred for 10 min at ambient temperature. Then iodoacetamide (0.37 g, 2 mmol) was added to the reaction mixture, shortly heated and stirred for 15 min at the ambient temperature. The precipitate was filtered and washed with 5 ml of ethanol and 10 ml of water to give 0.60 g (79 %) of ester 7a as colourless crystals; mp 178 – 180 °C.

F. In a similar manner (chloroacetamide was used instead of iodoacetamide) ester 7a was obtained.
G. In a similar manner (ammonium hydroxide was used instead of piperidine) ester 7a was obtained.
H. In a similar manner (chloroacetamide was used instead of iodoacetamide and ammonium hydroxide instead of piperidine) ester 7a was obtained.

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