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New Example of Acyl Cleavage of Benzoyl-1,1,1-trifluoroacetone in a Three-Component Synthesis of 4-Aryl-2-thioxo-6-phenyl-1,2-dihydropyridine-3-carbonitriles

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Abstract—A three-component condensation of aromatic aldehydes, cyanothioacetamide, and benzoyl-1,1,1-trifluoroacetone, involving the acyl cleavage of the latter, results in 4-aryl-2-thioxo-6-phenyl-1,2-dihydropyridine-3-carbonitriles. Their alkylation was studied.

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Previously, we found that arylmethylene cyanothioacetamides react with benzoyl-1,1,1-trifluoroacetone under the Michael reaction conditions to form 4-aryl-2-thioxo-6-phenyl-1,2-dihydropyridine-3-carbonitriles rather than the expected substituted 5-trifluoroacetylpyridine-2(1*H*)-thiones. This is due to the acyl cleavage of benzoyl-1,1,1-trifluoracetone during the reaction [1].

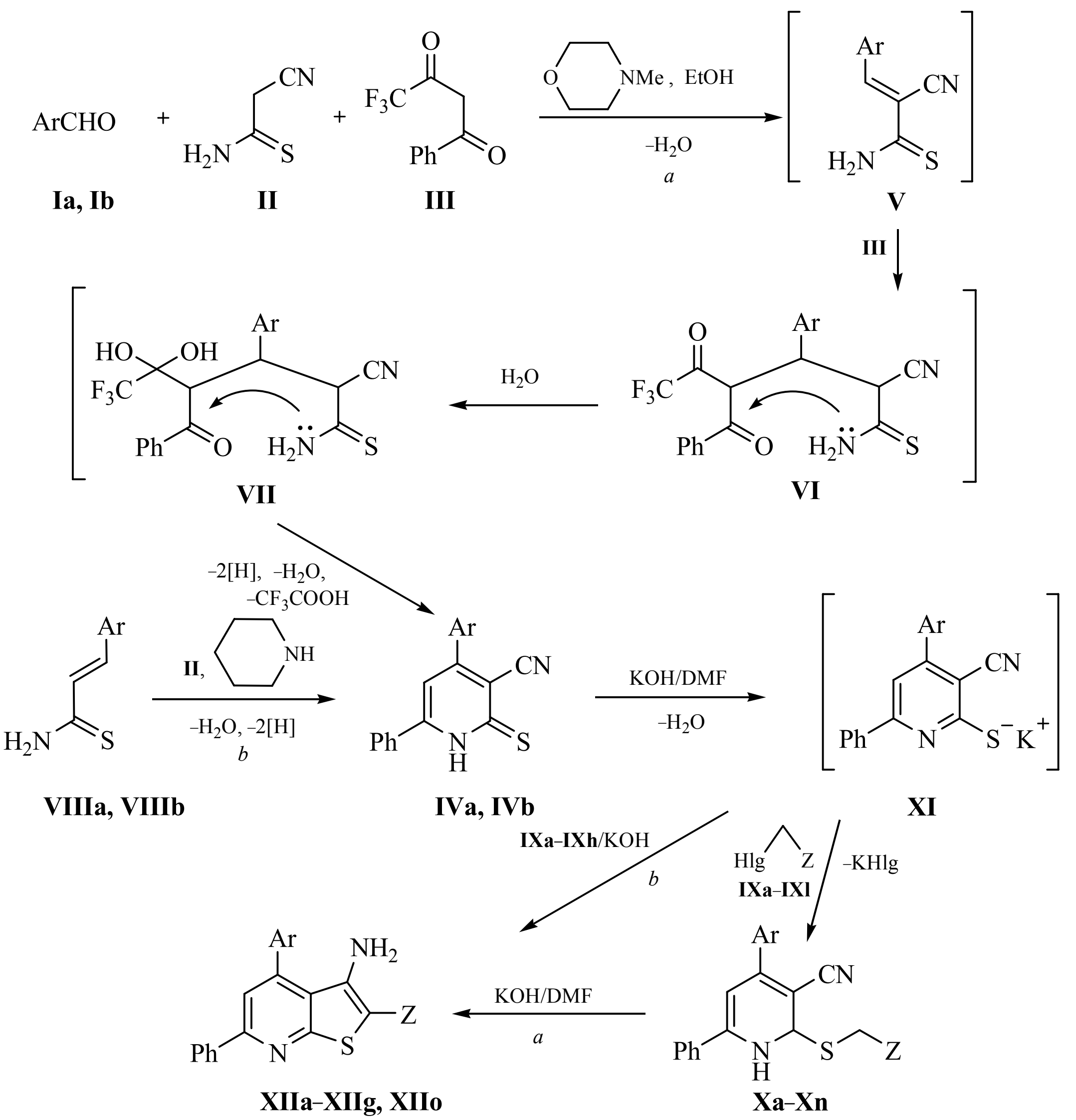
In the present work we show that the three-component condensation of aromatic aldehydes **I** with cyanothioacetamide **II** and benzoyl-1,1,1-trifluoracetone **III** occurs in ethanol at 20°C in the presence of two-fold excess of *N*-methylmorpholine to give 4-aryl-2-thioxo-6-phenyl-1,2-dihydropyridine-3-carbonitriles **IV** (method *a*). The reaction proceeds apparently through the Knoevenagel condensation to form the products **V** followed by the Michael addition of CH-acid **III**. The corresponding obtained adducts **VI** undergo the acyl cleavage [2] through intermediates **VII** formation followed by the intramolecular cyclization to yield the substituted pyridine-2(1*H*)-thiones **IV** by eliminating water and trifluoroacetic acid.

The structure of compounds **IV** was confirmed by the spectroscopic studies, authentic synthesis from chalcone **VIII** and cyanothioacetamide **II** in the presence of piperidine (method *b*) [3], as well as by the chemical transformations.

Thus, the treating of compounds **IVa** and **IVb** with alkali in a DMF solution followed by reacting with alkyl halides **IXa–IXl** gives rise to thioethers **Xa–Xn**. The reaction occurs probably via the formation of salts **XI** and their regioselective alkylation involving the sulfur atom, which is typical for such systems [4]. Further treating of thioethers **Xa–Xn** with alkali in DMF affords substituted thieno[2,3-*b*]pyridines **XIIa–XIIg** (method *a*), which can be obtained also by the one-pot reaction of pyridine thiones **IVa** and **IVb** with alkylating agents **IXa–IXh** in an alkaline medium (method *b*). Thus, the thiophene ring closure in this reaction indicates the vicinal location of cyano and alkylsulfanyl groups. Compounds **XII** are promising for designing products with antienzymatic [5, 6], antidepressant [7], neurotropic [8], and antitumor [9, 10] actions. The yields, elemental analysis data, and melting points of the synthesized compounds **X, XII** are given in Table 1.

The IR spectra of the obtained compounds **X** contain the characteristic absorption bands of the stretching vibrations of the conjugated cyano group in the range of 2220–2230 cm^{-1}. In the spectra of thienopyridines **XII** these signals are absent, and there are absorption bands of the stretching and bending vibrations of amino group at ν 3211–3348 and 1640–1649 cm^{-1}, respectively.

In the ^{1}H NMR spectra of compounds **X** there are the signals of aromatic protons, C^{5}H pyridine ring proton, the protons of *Z* fragment with the corresponding chemical shifts δ (Table 2), and the SCH$_2$ proton signals at δ 3.28–5.07 ppm. The ^{1}H NMR spectra of compounds **XII** contain a broad singlet of the NH$_2$ protons at δ 5.41–6.83 ppm instead of SCH$_2$ protons, which is typical for such systems [11].



I, IV, VIII, Ar = 2-$MeOC_6H_4$ (**a**), 4-BrC_6H_4 (**b**); IX, Hlg = Br, Z = PhCO (**a**); Cl, COOMe (**b**); Br, 4-$MeOC_6H_4CO$ (**c**); Br, 4-ClC_6H_4CO (**d**); Br, 4-PhC_6H_4CO (**e**); Cl, 4-BrC_6H_4NHCO (**f**); Cl, $COOCH_2Ph$ (**g**); Cl, CN (**h**); Br, 2-MeC_6H_4 (**i**); I, Me $(CH_2)_4$ (**j**); I, Me (**k**); Cl, Ph (**l**); **X, XII**, Ar = 4-BrC_6H_4, Z = $COOCH_2Ph$ (**a**); 2-$MeOC_6H_4$, PhCO (**b**); 2-$MeOC_6H_4$, COOMe (**c**); 2-$MeOC_6H_4$, 4-$MeOC_6H_4CO$ (**d**); 2-$MeOC_6H_4$, 4-ClC_6H_4CO (**e**); 2-$MeOC_6H_4$, 4-PhC_6H_4CO (**f**); 2-$MeOC_6H_4$, 4-BrC_6H_4NHCO (**g**); 2-$MeOC_6H_4$, $COOCH_2Ph$ (**h**); 2-$MeOC_6H_4$, CN (**i**); 2-$MeOC_6H_4$, 2-MeC_6H_4 (**j**); 2-$MeOC_6H_4$, $Me(CH_2)_4$ (**k**); 2-$MeOC_6H_4$, Me (**l**), 4-BrC_6H_4, Ph (**m**); 4-BrC_6H_4, 4-BrC_6H_4NHCO (**n**); 4-BrC_6H_4, CN (**o**).

EXPERIMENTAL

The IR spectra were recorded on an IKS-40 instrument (mulls in mineral oil). The ^1H NMR spectra were registered on a Bruker WP-100SY instrument (100 MHz) in DMSO-d_6 relative to internal TMS. The mass spectra were taken on a Crommas GC/MS-Hewlett-Packard 5890/5972 spectrometer, column HP-5 MS (70 eV) in a CH_2Cl_2 solution. The melting points were determined on a Koeffler block. The reaction progress and purity of the obtained compounds were monitored by TLC on Silufol UV 254 plates eluting with an acetone–hexane mixture (3:5) and detecting with iodine vapor and UV irradiation.

4-(2-Methoxyphenyl)-2-thioxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (IVa). *a*. A mixture of 1.21 ml (10 mmol) of *o*-anisaldehyde **Ia**, 1.0 g (10 mmol) of cyanothioacetamide **II**, and 1 drop of *N*-methylmorpholine in 20 ml of ethanol was stirred at 20°C for 15 min, after which was added 1.54 ml (10 mmol) of benzoyl-1,1,1-trifluoroacetone **III** and 2.2 ml (20 mmol)

Table 1. Yields, melting points, and elemental analysis data of 4-aryl-2-*Z*-methylsulfanyl-6-phenylpyridine-3-carbonitriles **Xa–Xn** and 3-amino-4-aeyl-6-phenyl-2-*Z*-thieno[2,3-*b*]pyridines **XIIa–XIIg, XIIo**

Comp. no.	Yield, % (*a*/*b*)	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
Xa	74	181–182 (AcOH)	62.88	3.65	5.33	$C_{27}H_{19}BrN_2O_2S$	62.92	3.72	5.44
Xb	66	141–143 (BuOH)	74.13	4.50	6.33	$C_{27}H_{20}N_2O_2S$	74.29	4.62	6.42
Xc	70	135–137 (MeCN)	67.58	4.49	7.02	$C_{22}H_{18}N_2O_3S$	67.68	4.65	7.17
Xd	73	205–207 (BuOH)	74.52	4.81	6.13	$C_{28}H_{22}N_2O_2S$	74.64	4.92	6.22
Xe	78	140–142 (BuOH)	68.70	3.95	5.84	$C_{27}H_{19}ClN_2O_2S$	68.86	4.07	5.95
Xf	74	210–212 (BuOH)	77.14	4.68	5.31	$C_{33}H_{24}N_2O_2S$	77.32	4.72	5.46
Xg	78	211–213 (AcOH)	60.98	3.72	7.78	$C_{27}H_{20}BrN_3O_2S$	61.14	3.80	7.92
Xh	82	165–166 (BuOH)	71.95	4.68	5.81	$C_{28}H_{22}N_2O_3S$	72.08	4.75	6.00
Xi	68	157–159 (AcOH)	70.40	4.15	11.69	$C_{21}H_{15}N_3OS$	70.57	4.23	11.76
Xj	75	103–105 (BuOH)	76.62	5.19	6.47	$C_{27}H_{22}N_2OS$	76.75	5.25	6.63
Xk	69	63–64 (MeOH)	74.48	6.37	6.85	$C_{25}H_{26}N_2OS$	74.59	6.51	6.96
Xl	73	81–83 (EtOH)	72.71	5.13	7.94	$C_{21}H_{18}N_2OS$	72.81	5.24	8.09
Xm	70	180–181 (AcOH)	65.49	3.67	5.95	$C_{25}H_{17}BrN_2S$	65.65	3.75	6.12
Xn	78	227–229 (DMF)	53.85	2.81	7.14	$C_{26}H_{17}Br_2N_3OS$	53.91	2.96	7.25
XIIa	75/69	183–185 (AcOH)	62.80	3.61	5.32	$C_{27}H_{19}BrN_2O_2S$	62.92	3.72	5.44
XIIb	81/78	220–222 (AcOH)	74.03	4.58	6.34	$C_{27}H_{20}N_2O_2S$	74.29	4.62	6.42
XIIc	74/80	198–200 (AcOH)	67.61	4.48	6.99	$C_{22}H_{18}N_2O_3S$	67.68	4.65	7.17
XIId	69/75	182–184 (AcOH)	74.54	4.88	6.18	$C_{28}H_{22}N_2O_2S$	74.64	4.92	6.22
XIIe	72/81	181–183 (AcOH)	68.77	3.96	5.79	$C_{27}H_{19}ClN_2O_2S$	68.86	4.07	5.95
XIIf	66/78	229–231 (DMF)	77.25	4.60	5.33	$C_{33}H_{24}N_2O_2S$	77.32	4.72	5.46
XIIh	84/77	195–196 (BuOH)	61.02	3.71	7.84	$C_{27}H_{20}BrN_3O_2S$	61.14	3.80	7.92
XIIo	–/70	245–247^a (AcOH)	59.01	2.85	10.22	$C_{20}H_{12}BrN_3S$	59.12	2.98	10.34

[a] At 210°C sublimation occurs.

of *N*-methylmorpholine. The mixture was stirred for 4 h and left standing for 48 h. Then the reaction mixture was diluted with 10% hydrochloric acid to pH 5 and kept for 1 day. The precipitate formed was filtered off, washed with water, ethanol and hexane. Yield 2.2 g (69%), yellow powder, mp 138–140°C (AcOH). IR spectrum, ν, cm^{-1}: 3380 (NH), 2228 (C≡N). ^{1}H NMR spectrum, δ, ppm: 3.84 s (3H, Me), 7.08 s (1H, C^{5}N, pyridine), 7.12 t (1H, H$_{Ar}$, *J* 8.1 Hz), 7.23 d (1H, H$_{Ar}$, *J* 8.7 Hz), 7.39–7.63 m (5H, H$_{Ar}$), 7.84 d (1H, H$_{Ar}$, *J* 8.1 Hz), 8.03 m (1H, H$_{Ar}$), 14.23 br. s (1H, NH). Found, %: C 71.52; H 4.29; N 8.71. $C_{19}H_{14}N_2OS$. Calculated, %: C 71.68; H 4.43; N 8.80.

4-(4-Bromophenyl)-2-thioxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (IVb) was prepared similarly to compound **IVa** using 1.85 g (10 mmol) of 4-bromobenzaldehyde **Ib**. Yield 2.64 g (72%), mp 219–221°C (AcOH) (216–218°C [3]).

The method *b* used was described in [3]. The yield of compound **IVa** was 75%, of **IVb**, 77%.

2-Alkylsulfanyl-4-aryl-6-phenylpyridine-3-carbonitriles Xa–Xn were prepared by the method of [12].

GC–MS spectrum of compound **Xh**, *m*/*z* (I_{rel}, %): 467 (100) $[M+1]^+$.

3-Amino-4-aryl-6-phenyl-2-Z-thieno[2,3-*b*]pyridines (XIIa–XIIg, XIIo). *a*. To a solution of 10 mmol of thioether **X** in 15 ml of DMF was added with stirring 5.6 ml (10 mmol) of 10% aqueous solution of KOH. The reaction mixture was stirred for 6 h, and then diluted with an equal volume of water. The resulting precipitate was filtered off, washed with water, ethanol, and hexane.

GC–MS spectrum of compound **XIIh**, *m*/*z* (I_{rel}, %): 467 (100) $[M+1]^+$.

b. To a stirred solution of 10 mmol of pyridinethione **IV** in 20 ml of DMF was sequentially added 5.6 ml (10 mmol) of 10% aqueous solution of KOH and 10 mmol of the alkylating agent **IX**. The mixture was stirred for 4 h, and then the same amount

Table 2. The IR and ^{1}H NMR spectral data of 4-aryl-2-Z-methylsulfanyl-6-phenylpyridine-3-carbonitriles **Xa–Xn** and 3-amino-4-aeyl-6-phenyl-2-Z-thieno[2,3-*b*]pyridines **XIIa–XIIg, XIIo**

Comp. no.	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm (^3J, Hz)	
	C≡N or NH$_2$	C=O, δ NH$_2$	SCH$_2$ (s) or NH$_2$ (br.s)	other signals
Xa	2226	1710	4.36	5.14 s (2H, OCH$_2$), 7.28 s (5H, Ph), 7.49 m (3H, Ph), 7.62 d and 7.84 d (4H, C$_6$H$_4$, *J* 7.52), 7.92 s (1H, C^{5}H$_{Py}$), 8.20 m (2H, Ph)
Xb	2224	1714	5.06	3.82 s (3H, Me), 7.11–7.92 m (13H, H$_{Ar}$), 8.15 d (2H, H$_{Ar}$, *J* 8.84)
Xc	2225	1702	4.27	3.67 s (3H, COOMe), 3.82 s (3H, Me), 7.11–7.37 m (2H, H$_{Ar}$), 7.42–7.73 m (5H, Ph), 7.88 s (1H, C^{5}H$_{Py}$), 8.19 m (2H, H$_{Ar}$)
Xd	2230	1715	5.01	2.44 s (3H, Me), 3.82 s (3H, MeO), 7.02–7.61 m (9H, H$_{Ar}$), 7.72 s (1H, C^{5}H$_{Py}$), 7.85 d (2H, H$_{Ar}$, *J* 7.72), 8.05 d (2H, H$_{Ar}$, *J* 8.85)
Xe	2228	1718	5.04	3.83 s (3H, Me), 7.02–7.55 m (7H, H$_{Ar}$), 7.64 d and 8.16 d (4H, 4-ClC$_6$H$_4$, *J* 8.58), 7.79 s (1H, C^{5}H$_{Py}$), 7.88 d (2H, H$_{Ar}$, *J* 8.75)
Xf	2222	1703	5.07	3.84 s (3H, Me), 7.02–7.61 m (12H, H$_{Ar}$), 7.72 s (1H, C^{5}H$_{Py}$), 7.87–7.99 m (4H, H$_{Ar}$), 8.21 d (2H, H$_{Ar}$, *J* 8.14)
Xg	2220 3211	1667	4.31	3.82 s (3H, Me), 7.09–7.49 m (7H, H$_{Ar}$), 7.61 d (4H, H$_{Ar}$, *J* 7.52), 7.81 s (1H, C^{5}H$_{Py}$), 8.15 d (2H, H$_{Ar}$, *J* 8.79), 10.62 br. s (1H, NH)
Xh	2225	1717	4.37	3.81 s (3H, Me), 5.14 s (2H, OCH$_2$), 7.13 t (2H, H$_{Ar}$, *J* 7.02), 7.26 s (5H, Ph), 7.31–7.62 m (5H, H$_{Ar}$), 7.84 s (1H, C^{5}H$_{Py}$), 8.17 d (2H, H$_{Ar}$, *J* 8.66)
Xi	2227 2248	–	4.53	3.83 s (3H, Me), 7.26 t (2H, H$_{Ar}$, *J* 7.11), 7.39–7.68 m (5H, H$_{Ar}$), 7.98 s (1H, H$_{Ar}$), 8.34 m (2H, H$_{Ar}$)
Xj	2221	–	4.73	2.42 s (3H, Me), 3.81 s (3H, MeO), 7.02–7.29 m (5H, H$_{Ar}$), 7.34–7.65 m (6H, H$_{Ar}$), 7.84 s (1H, C^{5}H$_{Py}$), 8.27 m (2H, H$_{Ar}$)
Xk	2228	–	3.28 t (*J* 7.11)	0.85 t (3H, Me, *J* 7.19), 1.12–1.56 m (6H, 3CH$_2$), 1.69–1.87 m (2H, CH$_2$), 3.83 s (3H, MeO), 7.04–7.65 m (6H, H$_{Ar}$), 7.81 s, 8.23 m (2H, H$_{Ar}$)
Xl	2226	–	3.47 q (*J* 7.23)	1.42 t (3H, Me, *J* 7.23), 3.81 s (3H, MeO), 7.01–7.32 m (3H, H$_{Ar}$), 7.44–7.69 m (4H, H$_{Ar}$), 7.81 s (1H, C^{5}H$_{Py}$), 8.22 m (2H, H$_{Ar}$)
Xm	2227	–	4.71	7.16–7.39 m (2H, H$_{Ar}$), 7.41–7.65 m (6H, H$_{Ar}$), 7.70–7.81 m (4H, H$_{Ar}$) 7.92 s (1H, C^{5}H$_{Py}$), 8.28 m (2H, H$_{Ar}$)
Xn	2229	1677	4.31	7.22–7.81 m (11H, H$_{Ar}$), 7.92 s (1H, C^{5}H$_{Py}$), 8.18 d (2H, H$_{Ar}$, *J* 8.59), 10.62 br. s (1H, NH)
XIIa	3190 3342	1702 1646	5.41	5.31 s (2H, CH$_2$), 7.31–7.62 m (10H, H$_{Ar}$), 7.71 s (1H, C^{5}H$_{Py}$), 7.74–7.91 m (2H, H$_{Ar}$), 8.19 m (2H, H$_{Ar}$)
XIIb	3214 3348	1714 1647	6.83	3.77 s (3H, Me), 7.11–7.85 m (13H, H$_{Ar}$), 8.23 m (2H, H$_{Ar}$)
XIIc	3228 3332	1710 1640	5.71	3.79 br. s (6H, 2MeO), 7.12–7.83 m (8H, H$_{Ar}$), 8.19 m (2H, H$_{Ar}$)
XIId	3197 3324	1715 1646	6.79	2.41 s (3H, Me), 3.76 s (3H, MeO), 7.12–7.62 m (9H, H$_{Ar}$), 7.75 d (2H, H$_{Ar}$, *J* 7.71), 7.81 s (1H, C^{5}H$_{Py}$), 8.21 m (2H, H$_{Ar}$)
XIIe	3211 3330	1718 1648	6.77	3.78 s (3H, Me), 7.13–7.65 m (9H, H$_{Ar}$), 7.74 d (2H, H$_{Ar}$, *J* 8.56), 7.89 s (1H, C^{5}H$_{Py}$), 8.18 m (2H, H$_{Ar}$)
XIIf	3225 3319	1717 1647	6.80	3.80 s (3H, Me), 7.19–7.98 m (17H, H$_{Ar}$), 8.20 m (2H, H$_{Ar}$)
XIIh	3244 3335	1670	5.97	3.76 s (3H, Me), 7.12–7.83 m (12H, H$_{Ar}$), 8.23 m (2H, H$_{Ar}$), 9.66 br. s (1H, NH)
XIIo	2208 3212 3345	1649	5.68	7.23–7.68 m (6H, H$_{Ar}$), 7.79 d (2H, H$_{Ar}$, *J* 7.51), 8.22 m (2H, H$_{Ar}$)

of alkali was added. The reaction mixture was stirred again for 4 h and diluted with an equal volume of water. The resulting precipitate was filtered off, washed with water, ethanol, and hexane. The melting points and chromatographic characteristics of compounds **XIIa–XIIg, XIIo** are similar to those obtained by the method *a* (Tables 1 and 2).

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