

# 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-trifluoroacetone 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-trifluoroacetone **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.

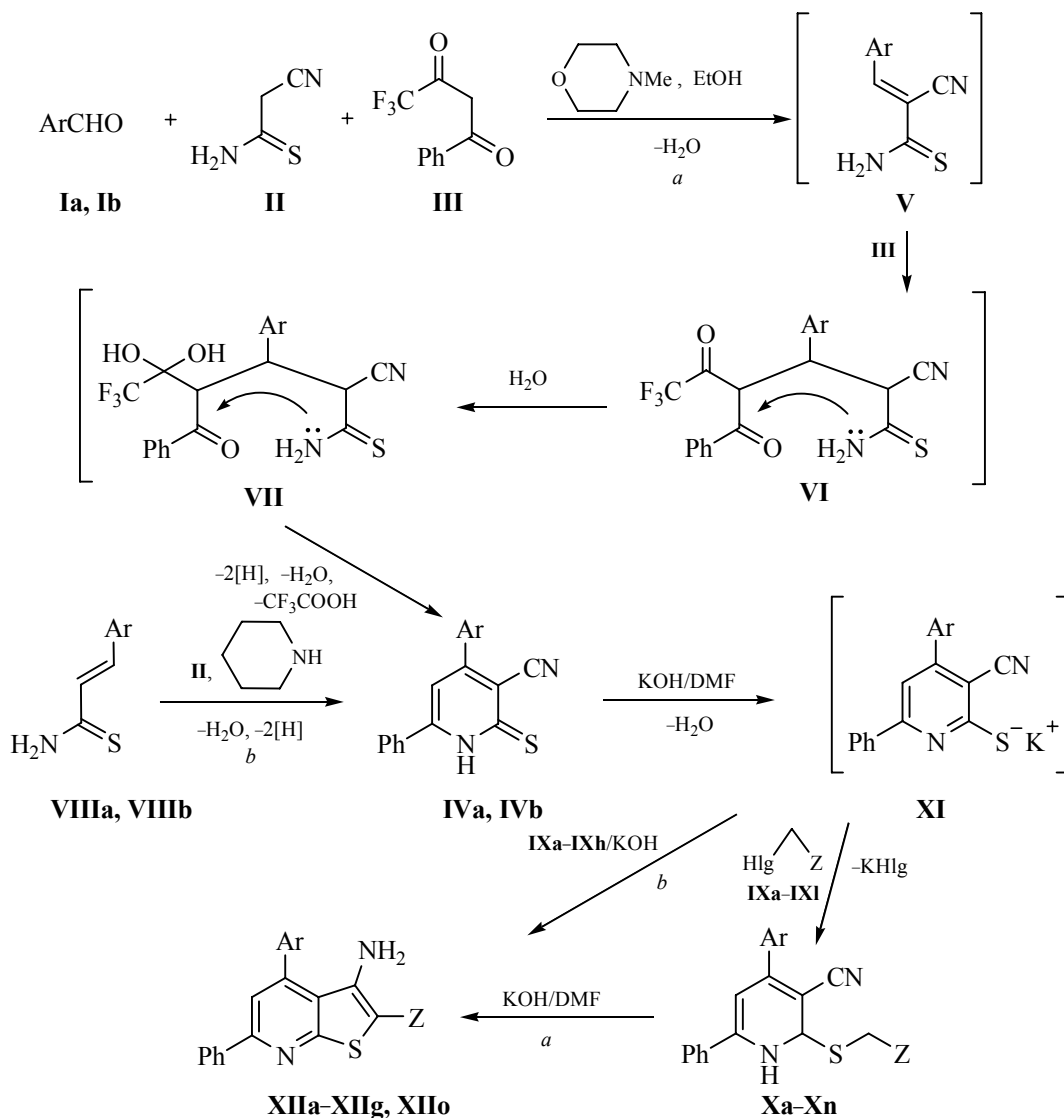
The structure of compounds **IV** was confirmed by the spectroscopic studies, authentic synthesis from chalcone **VIII** and cyanothioacetamide **II** in the presence of piperidine (method *b*) [3], as well as by the chemical transformations.

Thus, the treating of compounds **IVa** and **IVb** with alkali in a DMF solution followed by reacting with alkyl halides **IXa–IXi** 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<sup>-1</sup>. 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  $\nu$  3211–3348 and 1640–1649 cm<sup>-1</sup>, respectively.

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



**I, IV, VIII**, Ar = 2-MeOC<sub>6</sub>H<sub>4</sub> (**a**), 4-BrC<sub>6</sub>H<sub>4</sub> (**b**); **IX**, Hlg = Br, Z = PhCO (**a**); Cl, COOMe (**b**); Br, 4-MeOC<sub>6</sub>H<sub>4</sub>CO (**c**); Br, 4-ClC<sub>6</sub>H<sub>4</sub>CO (**d**); Br, 4-PhC<sub>6</sub>H<sub>4</sub>CO (**e**); Cl, 4-BrC<sub>6</sub>H<sub>4</sub>NHCO (**f**); Cl, COOCH<sub>2</sub>Ph (**g**); Cl, CN (**h**); Br, 2-MeC<sub>6</sub>H<sub>4</sub> (**i**); I, Me (CH<sub>2</sub>)<sub>4</sub> (**j**); I, Me (**k**); Cl, Ph (**l**); **X, XII**, Ar = 4-BrC<sub>6</sub>H<sub>4</sub>, Z = COOCH<sub>2</sub>Ph (**a**); 2-MeOC<sub>6</sub>H<sub>4</sub>, PhCO (**b**); 2-MeOC<sub>6</sub>H<sub>4</sub>, COOMe (**c**); 2-MeOC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>CO (**d**); 2-MeOC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>CO (**e**); 2-MeOC<sub>6</sub>H<sub>4</sub>, 4-PhC<sub>6</sub>H<sub>4</sub>CO (**f**); 2-MeOC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>NHCO (**g**); 2-MeOC<sub>6</sub>H<sub>4</sub>, COOCH<sub>2</sub>Ph (**h**); 2-MeOC<sub>6</sub>H<sub>4</sub>, CN (**i**); 2-MeOC<sub>6</sub>H<sub>4</sub>, 2-MeC<sub>6</sub>H<sub>4</sub> (**j**); 2-MeOC<sub>6</sub>H<sub>4</sub>, Me(CH<sub>2</sub>)<sub>4</sub> (**k**); 2-MeOC<sub>6</sub>H<sub>4</sub>, Me (**l**), 4-BrC<sub>6</sub>H<sub>4</sub>, Ph (**m**); 4-BrC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>NHCO (**n**); 4-BrC<sub>6</sub>H<sub>4</sub>, CN (**o**).

## EXPERIMENTAL

The IR spectra were recorded on an IKS-40 instrument (mulls in mineral oil). The <sup>1</sup>H NMR spectra were registered on a Bruker WP-100SY instrument (100 MHz) in DMSO-*d*<sub>6</sub> 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<sub>2</sub>Cl<sub>2</sub> 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-aryl-6-phenyl-2-Z-thieno[2,3-*b*]pyridines **XIIa–XIIg, XIIo**

Comp. no.	Yield, % ( <i>a/b</i> )	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
<b>Xa</b>	74	181–182 (AcOH)	62.88	3.65	5.33	C <sub>27</sub> H <sub>19</sub> BrN <sub>2</sub> O <sub>2</sub> S	62.92	3.72	5.44
<b>Xb</b>	66	141–143 (BuOH)	74.13	4.50	6.33	C <sub>27</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub> S	74.29	4.62	6.42
<b>Xc</b>	70	135–137 (MeCN)	67.58	4.49	7.02	C <sub>22</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> S	67.68	4.65	7.17
<b>Xd</b>	73	205–207 (BuOH)	74.52	4.81	6.13	C <sub>28</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> S	74.64	4.92	6.22
<b>Xe</b>	78	140–142 (BuOH)	68.70	3.95	5.84	C <sub>27</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>2</sub> S	68.86	4.07	5.95
<b>Xf</b>	74	210–212 (BuOH)	77.14	4.68	5.31	C <sub>33</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> S	77.32	4.72	5.46
<b>Xg</b>	78	211–213 (AcOH)	60.98	3.72	7.78	C <sub>27</sub> H <sub>20</sub> BrN <sub>3</sub> O <sub>2</sub> S	61.14	3.80	7.92
<b>Xh</b>	82	165–166 (BuOH)	71.95	4.68	5.81	C <sub>28</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub> S	72.08	4.75	6.00
<b>Xi</b>	68	157–159 (AcOH)	70.40	4.15	11.69	C <sub>21</sub> H <sub>15</sub> N <sub>3</sub> OS	70.57	4.23	11.76
<b>Xj</b>	75	103–105 (BuOH)	76.62	5.19	6.47	C <sub>27</sub> H <sub>22</sub> N <sub>2</sub> OS	76.75	5.25	6.63
<b>Xk</b>	69	63–64 (MeOH)	74.48	6.37	6.85	C <sub>25</sub> H <sub>26</sub> N <sub>2</sub> OS	74.59	6.51	6.96
<b>Xl</b>	73	81–83 (EtOH)	72.71	5.13	7.94	C <sub>21</sub> H <sub>18</sub> N <sub>2</sub> OS	72.81	5.24	8.09
<b>Xm</b>	70	180–181 (AcOH)	65.49	3.67	5.95	C <sub>25</sub> H <sub>17</sub> BrN <sub>2</sub> S	65.65	3.75	6.12
<b>Xn</b>	78	227–229 (DMF)	53.85	2.81	7.14	C <sub>26</sub> H <sub>17</sub> Br <sub>2</sub> N <sub>3</sub> OS	53.91	2.96	7.25
<b>XIIa</b>	75/69	183–185 (AcOH)	62.80	3.61	5.32	C <sub>27</sub> H <sub>19</sub> BrN <sub>2</sub> O <sub>2</sub> S	62.92	3.72	5.44
<b>XIIb</b>	81/78	220–222 (AcOH)	74.03	4.58	6.34	C <sub>27</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub> S	74.29	4.62	6.42
<b>XIIc</b>	74/80	198–200 (AcOH)	67.61	4.48	6.99	C <sub>22</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> S	67.68	4.65	7.17
<b>XIId</b>	69/75	182–184 (AcOH)	74.54	4.88	6.18	C <sub>28</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> S	74.64	4.92	6.22
<b>XIIe</b>	72/81	181–183 (AcOH)	68.77	3.96	5.79	C <sub>27</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>2</sub> S	68.86	4.07	5.95
<b>XIIIf</b>	66/78	229–231 (DMF)	77.25	4.60	5.33	C <sub>33</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> S	77.32	4.72	5.46
<b>XIIh</b>	84/77	195–196 (BuOH)	61.02	3.71	7.84	C <sub>27</sub> H <sub>20</sub> BrN <sub>3</sub> O <sub>2</sub> S	61.14	3.80	7.92
<b>XIIo</b>	–/70	245–247 <sup>a</sup> (AcOH)	59.01	2.85	10.22	C <sub>20</sub> H <sub>12</sub> BrN <sub>3</sub> S	59.12	2.98	10.34

<sup>a</sup> 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,  $\nu$ , cm<sup>-1</sup>: 3380 (NH), 2228 (C≡N). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 3.84 s (3H, Me), 07.08 s (1H, C<sup>5</sup>N, pyridine), 7.12 m (1H, H<sub>Ar</sub>, *J* 8.1 Hz), 7.23 d (1H, H<sub>Ar</sub>, *J* 8.7 Hz), 7.39–7.63 m (5H, H<sub>Ar</sub>), 7.84 d (1H, H<sub>Ar</sub>, *J* 8.1 Hz), 3.8 m (1H, H<sub>Ar</sub>), 14.23 br. s (1H, NH). Found, %: C 71.52; H 4.29; N 8.71. C<sub>19</sub>H<sub>14</sub>N<sub>2</sub>OS. 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 **1b**. 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*<sub>rel</sub>, %): 467 (100) [*M*+1]<sup>+</sup>.

**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*<sub>rel</sub>, %): 467 (100) [*M*+1]<sup>+</sup>.

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

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

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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