SYNTHESIS AND SPECTRAL PROPERTIES OF METHYL 6-ACETYL- OR 6-CYANO-3-AMINO-2-BENZOYL-7-FURYL-5-METHYL-INDOLIZINE-8-CARBOXYLATES

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Good yields of methyl 6-acetyl- or 6-cyano-3-amino-2-benzoyl-5-methyl-7-(5-substituted-2-furyl)-indolizine-8-carboxylates (**5a**–**5f**) were obtained in the reaction of corresponding 5-acetyl- or 5-cyano-2-formyl-4-(5-substituted-2-furyl)-6-methyl-1,4-dihydropyridine-3-carboxylated (**4a**–**4f**) with 3-phenyl-3-oxopropanenitrile. Spectral properties of the indolizines **5** are discussed.

Key words: 1,4-Dihydropyridines; Indolizines; 2-Formyl-1,4-dihydropyridines; 3-Aminoindolizines; Intramolecular cyclization.

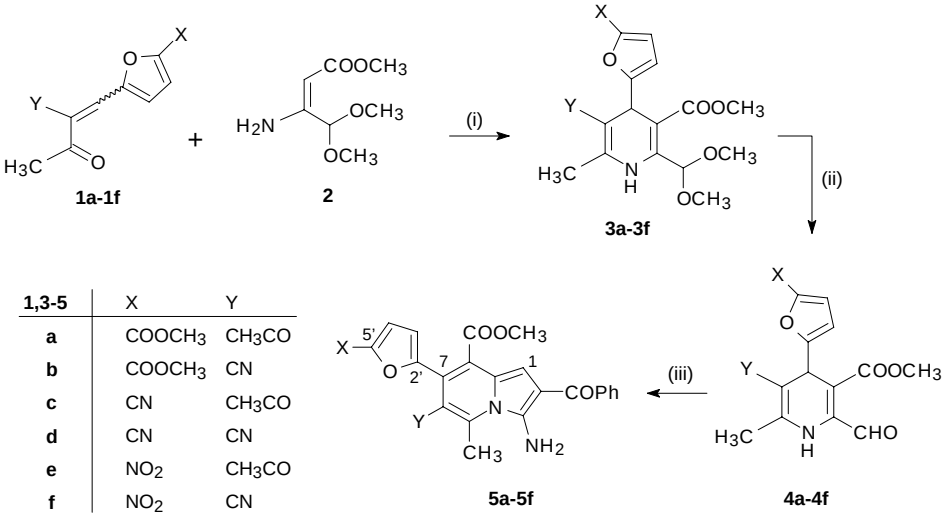
Substituted pyrrolo[1,2-*a*]pyridines known as indolizines are used as photographic sensitisers and dyes[1,2]. Some indolizine derivatives are calcium entry blockers[3] and they showed effectiveness in treatment of angina pectoris[4]. Also the indolizine ring system is present in many natural alkaloids[5].

3-Aminoindolizines can be prepared by the reaction of 2-bromomethylpyridine with phenylacetonitrile in the presence of sodium amide[6], Michael addition of substituted acetonitriles on 2-pyridylchalcones, followed by an intramolecular cyclization[7], electrochemical reduction[8] of appropriate substituted pyridines or pyridinium salts, or by reduction of corresponding nitro-, azo- or nitrosoindolizine[9].

The scrutiny of the reactivity of 2-substituted 1,4-dihydropyridine derivatives led us to discover a novel simple and efficient method for the synthesis of dialkyl 3-amino-7-aryl-5-methylindolizine-6,8-dicarboxylates from the easily available dialkyl 4-aryl-2-formyl-6-methyl-1,4-dihydropyridine-3,5-dicarboxylates and 3-phenyl-3-oxopropanenitrile[10,11]. In this paper we report the synthesis of methyl 6-acetyl- or 6-cyano-3-amino-2-benzoyl-7-(5-substituted-2-furyl)-5-methylindolizine-8-carboxylates and influence of substituents in positions 4 and 5 of 1,4-dihydropyridines on reaction with 3-oxo-3-phenylpropanenitrile.

RESULTS AND DISCUSSION

The starting 2-(dimethoxymethyl)-1,4-dihydropyridines **3** were prepared by the modified Hantzsch synthesis (Scheme 1). Cyclocondensation of 2-[(5-substituted-2-furyl)methylene]-3-oxobutanenitriles **1a**, **1c**, **1e** with methyl 3-amino-4,4-dimethoxy- but-2-enoate (**2**) in propan-2-ol afforded 5-cyano-2-dimethoxymethyl-1,4-dihydropyridines **3a**, **3c**, **3e** in good yields (62–70%). Analogously, the reaction of 3-[(5-substituted-2-furyl)methylene]-pentane-2,4-diones **1b**, **1d**, **1f** with enamine **2** gave 5-acetyl-2-(dimethoxymethyl)-1,4-dihydropyridines **3b**, **3d**, **3f** in 55–67% yields. 2-Formyl-1,4-dihydropyridines **4a**–**4f** were prepared by acid hydrolysis of the correspoonding 2-(dimethoxymethyl)-1,4-dihydropyridines **3a**–**3f** in 56–80% yields.



1,3-5	X	Y
a	$COOCH_3$	CH_3CO
b	$COOCH_3$	CN
c	CN	CH_3CO
d	CN	CN
e	NO_2	CH_3CO
f	NO_2	CN

(i) iPrOH, reflux; (ii) 6 M HCl, acetone; (iii) $PhCOCH_2CN$, piperidine, EtOH, reflux

SCHEME 1

The synthesis of methyl 6-acetyl- and 6-cyano-3-amino-2-benzoyl-5-methyl-7-(5-substituted-2-furyl)indolizine-8-carboxylates was performed through a tandem reaction (Knoevenagel reaction, sigmatropic rearrangement and intramolecular nucleophilic addition)[10,11] of 2-formyl-1,4-dihydropyridines **4** with 3-oxo-3-phenylpropanenitrile. Thus, the corresponding 2-formyl-1,4-dihydropyridines **4a**–**4f** and 3-oxo-3-phenylpropanenitrile were refluxed in the presence of piperidine in ethanol. The target 3-aminoindolizines **5** (dark red crystals) were obtained in good yields (Table I). The formyl group in position 2 in compounds **4a**–**4f** is more reactive in comparison with 4-aryl-2-formyl-6-methyl-1,4-dihydropyridine-3,5-dicarboxylates. Contrary to the case of the latter compounds[10,11] we did not isolate at low temperature any 2-(2-benzoyl-2-cyanovinyl)-1,4-dihydropyridine as a primarily arising intermediate; in all cases, a direct intra-

TABLE I
Analytical and spectral data of 2-dimethoxymethyl-1,4-dihydropyridines **3a**–**3f**, 2-formyl-1,4-dihydropyridines **4a**–**4f** and 3-aminoindolizines **5a**–**5f**

Compound	X	Y	M.p. °C	Yield %	Calculated/Found			Mass spectra, *m/z*	IR (KBr) ν, cm^{-1}
					% C	% H	% N		
3a	CO_2CH_3	CH_3CO	95–96	62	58.01/57.92	5.89/5.84	3.56/3.56	393 ($M^{+\bullet}$), 361, 329, 318, 302	3 297, 1 677
3b	CO_2CH_3	CN	162–163	63	57.44/57.62	5.36/5.35	7.44/7.48	376 ($M^{+\bullet}$), 344, 329, 285, 75	3 349, 2 197, 1 686
3c	CN	CH_3CO	101–102	65	59.99/60.23	5.59/5.50	7.77/7.87	360 ($M^{+\bullet}$), 328, 298, 285, 281	3 322, 2 222, 1 671
3d	CN	CN	128–130	67	59.47/59.69	4.99/4.70	12.24/12.32	343 ($M^{+\bullet}$), 311, 296, 252, 75	3 323, 2 228, 2 206
3e	NO_2	CH_3CO	120–122	70	53.68/53.79	5.30/5.14	7.37/7.44	380 ($M^{+\bullet}$), 348, 331, 305, 289	3 353, 1 682
3f	NO_2	CN	134–136	55	52.89/52.73	4.72/4.63	11.57/11.57	363 ($M^{+\bullet}$), 331, 272, 219, 75	3 363, 2 207, 1 686
4a	CO_2CH_3	CH_3CO	124–125	56	58.79/58.55	4.93/5.02	4.03/3.93	347 ($M^{+\bullet}$), 304, 287, 272, 244	3 318, 1 699
4b	CO_2CH_3	CN	156–158	79	58.18/58.37	4.27/4.46	8.48/8.38	330 ($M^{+\bullet}$), 298, 270, 255, 239	3 325, 2 200, 1 712
4c	CN	CH_3CO	140–142	80	61.14/61.36	4.49/4.62	8.91/8.88	314 ($M^{+\bullet}$), 260, 254, 239, 211	3 351, 2 227, 1 702
4d	CN	CN	169–171	73	60.61/60.48	3.73/3.77	14.14/14.11	297 ($M^{+\bullet}$), 265, 237, 236, 209	3 291, 2 229, 2 202
4e	NO_2	CH_3CO	156–157	65	53.89/53.99	4.22/4.31	8.38/8.34	334 ($M^{+\bullet}$), 317, 285, 275, 244	3 321, 1 707
4f	NO_2	CN	160–161	63	53.00/53.11	3.49/3.76	13.24/12.96	317 ($M^{+\bullet}$), 300, 288, 268, 255	3 330, 2 201, 1 718
5a	CO_2CH_3	CH_3CO	171–172	64	65.82/65.65	4.67/4.70	5.90/5.85	474 ($M^{+\bullet}$), 369, 355, 105, 77	3 419, 1 729
5b	CO_2CH_3	CN	191–193	86	65.64/64.78	4.19/4.48	9.19/9.40	457 ($M^{+\bullet}$), 382, 352, 105, 77	3 436, 2 221, 1 734
5c	CN	CH_3CO	158–159	67	68.02/67.92	4.34/4.35	9.52/9.49	441 ($M^{+\bullet}$), 382, 336, 105, 77	3 435, 2 224, 1 733
5d	CN	CN	232–234	67	67.92/68.09	3.80/3.83	13.20/13.38	424 ($M^{+\bullet}$), 319, 289, 105, 77	3 480, 2 225, 1 732
5e	NO_2	CH_3CO	165–167	69	62.47/62.65	4.15/4.17	9.11/9.20	461 ($M^{+\bullet}$), 251, 105, 77, 51	3 414, 1 730
5f	NO_2	CN	246–247	91	62.16/62.19	3.63/3.66	12.61/12.70	444 ($M^{+\bullet}$), 383, 370, 105, 77	3 415, 2 223, 1 723

molecular cyclization affording indolizine took place. Unlike 5-alkoxycarbonyl-2-formyl-1,4-dihydropyridines (which need at least 5 h to complete reaction) in the case 5-acetyl and 5-cyano derivatives reaction is faster (1 h) and also at room temperature cyclization was observed. It seems that higher reactivity of 2-formyl-1,4-dihydropyridines **4a**–**4f** is a result of superposition both substitutions, acetyl or cyano group instead of alkoxycarbonyl[10,11] in the position 5 and 5-substituted-2-furyl instead of substituted phenyl in the position 4. We did not observe any differences in the reactivity of 5-acetyl and 5-cyano-2-formyl-1,4-dihydropyridines **4a**–**4f**. Also there was no influence of substituents in the position 5 of furan ring.

The structure of compounds **3**, **4** and **5** was proved by elemental analysis and spectral measurements. The IR spectra of 1,4-dihydropyridines **3a**–**3f** and **4a**–**4f** exhibit an (NH) vibration band at 3 291–3 363 cm^{-1}, (C=O) bands at 1 691–1 729 cm^{-1} and all the compounds containing nitrile group shows (C≡N) stretching vibration bands at 2 197–2 229 cm^{-1}. The indolizines **5a**–**5f** exhibit (NH_2) bands at 3 414–3 480 cm^{-1} and (C=O) at 1 723–1 734 cm^{-1} (Table I). The NMR spectra are also in accord with the structures **3**, **4** and **5**.

The ^{1}H NMR spectra of 1,4-dihydropyridine derivatives **3** and **4** display proton signals at δ 4.85–5.49 ppm (Table II), which are characteristic of hydrogens at C-4 of the 1,4-dihydropyridine ring[12]; these are, however, absent in spectra of 3-aminoindolizine derivatives **5** (Table IV). Generally, 5-acetyl-1,4-dihydropyridines **3a**, **3c**, **3e** and **4a**, **4c**, **4e** exhibit H-4 hydrogen signals at lower fields in comparison with 5-cyano derivatives **3b**, **3d**, **3f** and **4b**, **4d**, **4f** (Table II). The ^{1}H NMR spectra of 3-aminoindolizines

TABLE II
^{1}H NMR chemical shifts δ (ppm) of **3a**–**3f** and **4a**–**4f**

Proton	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**
CH_3	2.35	2.17	2.23	2.19	2.37	2.20	2.35	2.27	2.35	2.27	2.38	2.29
CH_3O	3.77	3.69	3.77	3.71	3.77	3.72	3.78	3.78	3.85	3.80	3.86	3.97
H-4	5.28	4.85	5.31	4.88	5.36	4.89	5.43	4.98	5.45	5.01	5.49	5.06
H-3′[a]	6.12	6.27	6.15	6.28	6.31	6.42	6.27	6.47	6.36	6.57	6.50	6.72
H-4′[a]	7.03	7.09	6.97	7.04	7.20	7.25	7.07	7.16	7.27	7.38	7.38	7.48
NH	7.04	7.19	7.13	7.22	7.17	7.23	8.33	8.66	8.40	8.75	8.47	8.83
2-R[b]	6.01	6.03	6.00	6.01	6.00	6.01	10.42	10.39	10.42	10.40	10.43	10.41
	3.42	3.44	3.41	3.43	3.44	3.45	–	–	–	–	–	–
	3.49	3.49	3.49	3.49	3.51	3.51	–	–	–	–	–	–
X	3.82	3.83	–	–	–	–	3.85	3.81	–	–	–	–
Y	2.36	–	2.38	–	2.39	–	2.49	–	2.51	–	2.53	–
$J_{3',4'}$[c]	3.4	3.4	3.5	3.5	3.7	3.6	3.4	3.3	3.6	3.6	3.7	3.6

[a] Doublet; [b] R = $(CH_3O)_2CH$ for compounds **3a**–**3f** and R = CHO for **4a**–**4f**; [c] coupling constant in Hz.

TABLE III
^{13}C NMR chemical shifts δ (ppm) of **3a**–**3f** and **4a**–**4f**

Carbon	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**
CH_3	20.5	18.3	20.4	18.3	20.6	18.4	20.4	18.2	20.4	18.4	20.5	18.5
2-R[a]	54.3	54.0	54.4	54.4	54.4	54.2	186.1	185.9	185.9	185.8	185.7	185.7
	55.7	55.6	55.6	55.6	55.8	55.8	–	–	–	–	–	–
	98.1	97.8	98.0	97.9	98.1	97.8	–	–	–	–	–	–
C-2	144.9	144.9	144.9	145.0	145.5	145.5	139.3	139.2	139.5	139.3	139.7	139.4
C-3	108.3	98.9	107.9	98.3	108.0	98.0	111.4	109.2	110.4	108.4	110.0	108.1
C-4	34.6	35.2	34.4	35.3	34.5	35.7	35.3	35.8	35.0	35.9	35.1	36.3
C-5	101.1	82.4	100.6	81.7	100.1	81.5	107.3	81.7	107.4	81.5	107.2	81.2
C-6	145.0	146.6	145.2	147.0	145.5	147.3	145.2	147.1	145.4	147.3	145.7	147.6
C-2′	161.8	160.0	163.0	161.1	161.0	158.9	160.0	158.5	161.3	159.5	159.2	157.3
C-3′	107.5	107.8	106.9	107.4	108.9	109.2	108.4	108.9	107.8	108.3	109.6	110.2
C-4′	119.0	119.0	123.0	123.1	112.9	112.7	119.0	119.0	123.1	123.2	112.7	112.6
C-5′	143.2	143.7	124.4	125.2	151.1	151.6	143.8	144.2	125.1	125.9	151.9	152.0
$CO_2\mathbf{C}H_3$	51.5	51.6	51.6	51.7	51.7	51.8	52.5	52.4	52.5	52.6	52.6	52.8
$\mathbf{C}O_2CH_3$	166.2	165.7	165.8	165.5	165.7	165.4	165.6	165.1	165.2	164.8	165.1	164.8
X	51.6	51.6	111.7	111.5	–	–	51.7	51.7	111.5	111.3	–	–
	159.0	158.8	–	–	–	–	158.9	158.5	–	–	–	–
Y	29.8	118.7	29.8	118.4	30.1	118.3	29.8	118.2	30.0	118.0	30.2	117.8
	197.0	–	196.2	–	195.9	–	196.6	–	195.9	–	195.7	–

[a] R = $(CH_3O)_2CH$ for compounds **3a**–**3f** and R = CHO for **4a**–**4f**.

5a–**5f** showed proton signals at δ 6.53–6.73 ppm (Table IV), typical for 3-aminoindolizines[8]. The ^{13}C NMR spectra (Tables III and V) show theoretical number of signals. The chemical shifts of the dihydropyridine, indolizine and furan carbon atoms were assigned by comparison with ^{13}C NMR spectra of other 2-formyl-1,4-dihydropyridines and 3-aminoindolizines[11] and using of additivity rule.

Typical signal in ^{13}C NMR spectra of 1,4-dihydropyridines is that of the C-4 of the pyridine ring at 34.4–36.3 ppm (Table III). The C-5 carbon of the 5-acetyl derivatives is shifted downfield by 19–27 ppm as compared with 5-cyano derivatives (Tables III and V), which is caused by the anisotropic effect of the cyano group. The chemical shift of C-1 at 102.8–105.9 ppm (Table V) is characteristic for 3-aminoindolizines[8]. The molecular ion $[M]^{+\cdot}$ observed in all the spectra of 3-aminoindolizines **5a**–**5f** lose the benzoyl cation (*m/z* = 105), the most intensive ionic species in spectra (Table I). The benzoyl cation decomposes to C=O and $C_6H_5^+$ (*m/z* = 77).

In summary, we found efficient and convenient method for preparation of 5-acetyl- and 5-cyano-3-aminoindolizines **5a**–**5f**. We observed that substituents in positions 4 and 5 have an important influence on rate of intramolecular cyclization. The electron-withdrawing substituents accelerate reaction.

EXPERIMENTAL

Melting points were measured on a Boetius micro hot-stage and are uncorrected. The infrared spectra were recorded on a Philips analytical PV 9800 FT IR spectrophotometer (KBr pellets). The NMR spectra were recorded on a Bruker AC-250 spectrometer (250 MHz) in $CDCl_3$ (**3a**–**3f** and **4a**–**4f**) and

TABLE IV
^1H NMR chemical shifts δ (ppm) of 3-aminoindolizines **5a**–**5f**

Proton	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**
CH_3	2.79	3.18	2.80	3.18	2.81	3.17
$CO_2\mathbf{C}H_3$	3.72	3.74	3.72	3.72	3.75	3.76
H-1	6.53	6.61	6.60	6.68	6.65	6.73
H-3′[a]	6.46	7.00	6.58	7.01	6.66	7.15
H-4′[a]	7.36	7.45	7.68	7.76	[b]	7.80
Ph	7.5–7.8	7.5–7.8	7.5–7.8	7.5–7.8	7.5–7.8	7.5–7.8
X	3.38	3.84	–	–	–	–
Y	2.27	–	2.22	–	2.35	–
NH_2	7.15	7.34	7.12	7.23	7.20	7.33
$J_{3',4'}$[c]	3.6	3.6	3.8	3.7	4.1	4.0

[a] Doublet; [b] not observed; [c] coupling constant in Hz.

in $(CD_3)_2SO$ (**5a**–**5f**) using tetramethylsilane as internal standard. Thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots were visualized using UV lamp or iodine vapour. Mass spectral measurements were recorded on an AEI MS 902 S spectrometer.

The Michael acceptors **1a–1f** were prepared by Knoevenagel condensation of the corresponding 2-furancarbaldehyde with 3-oxobutanenitrile[13] or pentane-2,4-dione[14], respectively. Methyl 3-amino-4,4-dimethoxybut-2-enoate was obtained from ammonia and methyl 4,4-dimethoxy-3-oxobutanoate[15], which was prepared in three steps from dichloroacetic acid[16].

TABLE V
^{13}C NMR chemical shifts δ (ppm) of 3-aminoindolizines **5a**–**5f**

Carbon	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**
CH_3	16.9	19.3	17.0	19.3	16.9	19.4
$CO_2\mathbf{C}H_3$	52.8	52.8	52.9	52.9	53.0	53.2
$\mathbf{C}O_2CH_3$	165.6	165.0	165.3	164.7	165.2	164.6
C-1a	112.9	112.7	112.4	112.4	111.3	111.2
C-1	102.8	104.4	103.5	105.1	104.3	105.9
C-2	108.3	108.3	108.5	108.4	108.7	108.7
C-3	144.9	145.2	145.0	145.2	145.2	145.5
C-5	133.5	148.3	133.9	148.3	133.8	148.4
C-6	122.1	95.1	121.9	95.3	122.0	94.8
C-7	124.4	123.3	124.5	123.9	125.1	124.4
C-8	123.9	121.7	124.3	121.4	124.0	121.5
C-2′	152.0	150.8	153.6	152.3	151.5	150.2
C-3′	111.8	112.6	111.5	112.3	113.3	114.1
C-4′	120.0	119.8	125.4	125.1	114.9	114.7
C-5′	143.2	143.5	124.3	124.7	151.0	150.8
C-1″	139.8	139.5	139.8	139.4	139.7	139.4
C-2″	128.5	128.6	128.5	128.6	128.5	128.5
C-3″	128.2	128.2	128.3	128.3	128.3	128.3
C-4″	131.4	131.6	131.4	131.6	131.5	131.7
X	52.0	52.0	111.5	111.5	–	–
	158.0	158.0	–	–	–	–
Y	32.0	116.7	32.1	116.4	32.4	116.5
	203.0	–	202.7	–	203.0	–
Ph**C**O	191.5	191.3	191.5	191.3	191.5	191.3

Phenyl group: C-1″, 2″, 3″ and 4″.

Methyl 5-Acetyl- and 5-Cyano-2-(dimethoxymethyl)-6-methyl-4-(5-substituted-2-furyl)-1,4-dihydropyridine-3-carboxylates (**3a**–**3f**). General Procedure

A mixture of Michael acceptor **1a–1f** (0.016 mol) and methyl 3-amino-4,4-dimethoxybut-2-enoate (**2**; 2.4 g, 0.017 mol) was refluxed in propan-2-ol (40 ml) for 3–5 h. After cooling, the solvent was removed *in vacuo* to give an oil, which was triturated with methanol to afford **3a**–**3f**. The separated solid was filtered off and recrystallized from propan-2-ol. The yields and analytical data are given in Table I.

Methyl 5-Acetyl- and 5-Cyano-2-formyl-6-methyl-4-(5-substituted-2-furyl)-1,4-dihydropyridine-3-carboxylates (**4a**–**4f**). General Procedure

To a solution of **3a**–**3f** (2.3 mmol) in acetone (10 ml) 6 M hydrochloric acid (1.5 ml) was added and the mixture was stirred for 5 h at room temperature. After the reaction was completed, the solvent was removed to give a residue, which was pulverized by adding water (10 ml). The suspension was extracted with ethyl acetate (20 ml) and the extract was washed with aqueous solution of sodium hydrogencarbonate (10%, 10 ml) to pH about 7 and then twice with brine (10 ml). The dried solution was concentrated to give **4a**–**4f** as an oil which was crystallized from a mixture of ethyl acetate–isohexane. The crystals were collected by filtration and dried. The yields and analytical data are given in Table I.

Methyl 3-Amino-6-acetyl- and 3-Amino-6-cyano-2-benzoyl-5-methyl-7-(5-substituted-2-furyl)-indolizine-8-carboxylates (**5a**–**5f**). General Procedure

A mixture of 2-formyl-1,4-dihydropyridines **4a**–**4f** (1.3 mmol), 3-oxo-3-phenylpropanenitrile (0.19 g, 1.3 mmol) and piperidine (3 drops) in ethanol (5 ml) was refluxed for 1 h. The reaction mixture turned from yellow to the dark red and after few minutes a precipitate was formed. After standing at 0 °C overnight, precipitates were filtered off, dried and recrystallized from ethanol. The yields and analytical data are given in Table I.

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