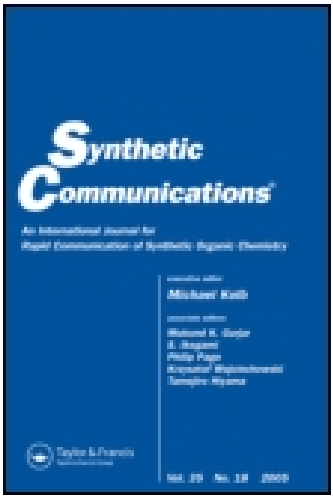

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Synthesis of Some Substituted 2H-Pyrano[3,2-c]pyridine-2,5(6H)-diones. Reaction of Their 3-Acetyl Derivatives with Methyl 3-Amino-2-butenoate

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SYNTHESIS OF SOME SUBSTITUTED 2*H*-PYRANO[3,2-*c*]PYRIDINE-2,5(6*H*)-DIONES. REACTION OF THEIR 3-ACETYL DERIVATIVES WITH METHYL 3-AMINO-2-BUTENOATE

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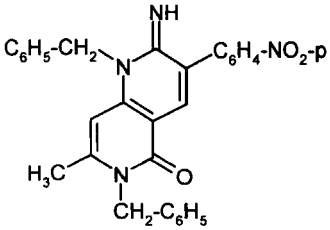
Abstract. Formylation of 4-hydroxy-6-methyl-2(1*H*)-pyridones and subsequent cyclization with a *Wittig* reagent or with CH-acidic esters gave a series of title compounds. The same starting pyridones reacted with methyl 3-amino-2-butenoate directly to the corresponding 4,7-dimethylpyrano[3,2-*c*]pyridines.

In connection with our recent studies[1-3] on pharmaceutically interesting N-heterocyclic systems we needed to develop a convenient general method for the preparation of a series of 2*H*-pyrano[3,2-*c*]pyridine-2,5(6*H*)-diones which are oxygen analogues to some 1,6-naphthyridines (*e.g.* **A**) with antituberculosis activity[2]. The title compounds are also well-known as fluorescent agents of technical importance as optical bleachers[4].



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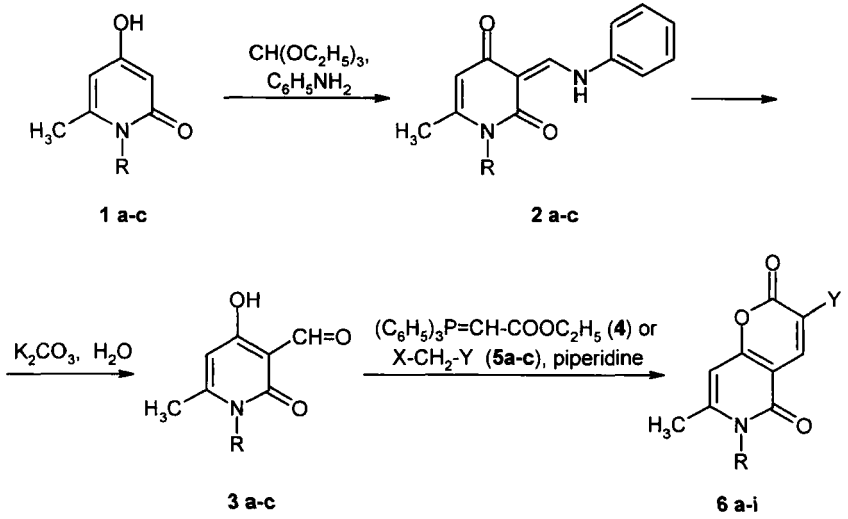
The known methods for the synthesis of this class of compounds start either from 4-hydroxy-2-pyridones[5] (**1**) or from their 3-arylaminomethylidene derivatives[6] (**2**) and allow introducing of only cyano or alkoxycarbonyl group in position 3. The preparation of otherwise 3-substituted or of 3,4-unsubstituted derivatives has not been described up to now.

Scheme 1



1, 2, 3	R
a	H
b	$CH_2C_6H_5$
c	$CH_2CH_2C_6H_5$

5	X	Y
a	$COOC_2H_5$	$COCH_3$
b	$COOC_2H_5$	C_6H_4-NO_2-*p*
c	CN	C_6H_4-NO_2-*p*

6	R	Y
a	H	H
b	$CH_2C_6H_5$	H
c	$CH_2CH_2C_6H_5$	H
d	H	$COCH_3$
e	$CH_2C_6H_5$	$COCH_3$
f	$CH_2CH_2C_6H_5$	$COCH_3$
g	H	C_6H_4-NO_2-*p*
h	$CH_2C_6H_5$	C_6H_4-NO_2-*p*
i	$CH_2CH_2C_6H_5$	C_6H_4-NO_2-*p*

In our previous work we employed the cyclizing *Knoevenagel* reaction in order to obtain [1]benzopyrano[4,3-*b*]pyridines[1] or 1,6-naphthyridines[2] of type **A**. Similarly, the synthesis of a pyrano[4,3-*b*]pyran-2,5-dione from dehydroacetic acid and ethyl acetoacetate has been reported by *Hassan* et al.[7] In the present study we applied the same approach as well as the *Wittig* reaction to prepare a series of title compounds (**6a-i**) (Scheme 1) starting from the 2-oxopyridine-3-carbaldehydes **3**. The aldehydes **3a-c** were obtained in 20-79 % overall yield from **1a-c** *via* the anilino derivatives **2a-c** by means of the "three-component reaction" recommended by *Ollinger* et al.[8] Treatment of **3a-c** with the *Wittig* reagent **4** in refluxing toluene led directly to the formation of the corresponding 3,4-unsubstituted pyranopyridines **6a-c** (Table 1) under spontaneous lactonization. The cyclization to the desired 3-substituted pyrano[3,2-*c*]pyridine-2,5-diones **6d-i** was achieved by reaction of **3a-c** either with an excess of ethyl acetoacetate (**5a**) at ambient temperature or with one equivalent of ethyl *p*-nitrophenylacetate (**5b**) in boiling ethanol, both in the presence of few drops of piperidine. The latter reaction succeeded also with *p*-nitrobenzyl cyanide (**5c**) under the same conditions but it needed acidic hydrolysis (18% HCl) of the initially formed iminolactone and gave lower yields (*e. g.* 13% of **6i** compared to 38 % with **5b**).

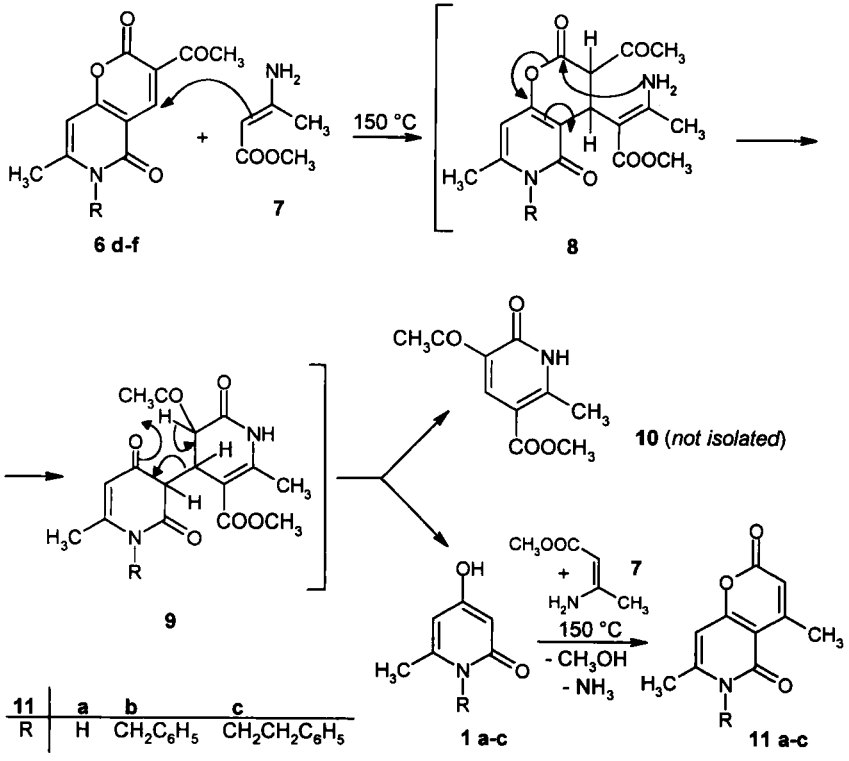
The structure of **6a-i** was confirmed by means of their IR and NMR spectra. The presence of lactone (1755-1734 cm^{-1}) and lactam (1661-1624 cm^{-1}) carbonyl bands is typical in all IR spectra (Table 1). In the ^{1}H-NMR spectra of **6a-i** signals for 4-H (δ = 7.92-8.54), 8-H (δ = 6.21-6.55) and the 7-methyl group (δ = 2.26-

Table 1. 3-Substituted 7-methylpyrano[3,2-*c*]pyridine-2,5(6*H*)-diones **6a-i** and 4,7-dimethylpyrano[3,2-*c*]pyridine-2,5(6*H*)-diones **11a-c**

Product	Yield [a] (%)	M.p. [°C] (solvent)	TLC[b] R_F	Mol. formula (Mol. mass)	Calcd./Found (%) C	H	N	IR (nujol), ν [cm^{-1}]
6a	70	317 (dec.) (BuOH)	0.10	$C_9H_7NO_3$ (177.2) [c]	61.02 60.74	3.98 4.21	7.91 7.58	1755, 1651, 1626 [d]
6b	44	175-177 (MeOH)	0.52	$C_{16}H_{13}NO_3$ (267.3)	71.90 71.83	4.90 5.00	5.24 5.05	1732, 1659
6c	38	161-163 (MeOH)	0.56	$C_{17}H_{15}NO_3$ (281.3)	72.58 72.29	5.37 5.49	4.98 4.81	1742, 1657
6d	89	289 (dec.) (DMF)	0.12	$C_{11}H_9NO_4$ (219.2) [c]	60.28 59.84	4.14 4.16	6.39 6.25	1755, 1682, 1656, 1622 [d]
6e	83	170-172 (MeOH)	0.52	$C_{18}H_{15}NO_4$ (309.3) [c]	69.89 69.38	4.89 4.88	4.53 4.45	1738, 1674, 1659
6f	57	220-222 (EtOH)	0.56	$C_{19}H_{17}NO_4$ (323.3)	70.58 70.25	5.30 5.31	4.33 4.22	1734, 1680, 1664
6g	63	312 (dec.) (DMSO)	0.10	$C_{15}H_{10}N_2O_5$ (298.3) [c]	60.41 60.31	3.38 3.44	9.39 9.09	1736, 1674, 1624 [d]
6h	38	223-225 (EtOH)	0.68	$C_{22}H_{16}N_2O_5$ (388.4) [c]	68.04 67.60	4.15 4.11	7.21 7.07	1734, 1661
6i	59	236-237 (EtOH)	0.70	$C_{23}H_{18}N_2O_5$ (402.4)	68.65 68.10	4.51 4.44	6.96 6.76	1736, 1647
11a [e]	8 (**6d**) 88 (**1a**)	>315(dec.) (MeOH)	0.21	$C_{10}H_9NO_3$ (191.2)	62.82 62.45	4.74 4.84	7.33 7.04	1740, 1664, 1634 [d]
11b	55 (**6e**) 80 (**1b**)	176-178 (EtOH)	0.54	$C_{17}H_{15}NO_3$ (281.3)	72.58 72.58	5.37 5.46	4.98 4.95	1734, 1659
11c	43 (**6f**) 79 (**1c**)	220-221 [f] (EtOH)	0.56	$C_{18}H_{17}NO_3$ (295.3)	73.20 73.06	5.80 5.95	4.74 4.49	1746, 1655

[a] The corresponding starting compound for preparation of **11a-c** is shown in parentheses. - [b] Solvent: toluene-acetone (8:2); more details in exp. part. - [c] Confirmed by EI-MS. - [d] Broad band due to NH (assoc.) of **6a,d,g** and **11a** at 2400-3200 cm^{-1} is also typical. - [e] Dec. point and spectral data are in good agreement with data of **11a** described in the literature[12] - [f] Mixed m. p. with the starting ketone **6f** gave depression: 190-195 °C.

Scheme 2



2.41) are observed, besides the signals of the substituents R and Y (Table 2). As an example, the assignment of the ^{13}C-NMR spectral data of the *N*-benzyl derivative **6e** is given in Figure 1.

Since the compounds **6a-i** could be regarded as 3-substituted 6-aza-coumarins we attempted to carry out a *Michael* addition of an enaminoester to the respective position 4. This reaction was earlier successfully applied by us[10,11] to some couma-

Table 2. ^{1}H-NMR chemical shifts for the pyrano[3,2-*c*]pyridines **6a-f,h,i** and **11a-c** in [D]$_6$DMSO[a,b]

Product	3-X or 3-H	4-H or 4-CH_3	6-R	7-CH_3	8-H
6a	6.21 d (J = 9.5)	7.92 d (J = 9.5)	12.00 br.	2.26 s	6.21 s
6b	6.28 d (J = 9.6)	8.01 d (J = 9.6)	5.34 s, 7.1-7.4 m	2.37 s	6.45 s
6c	6.26 d (J = 9.6)	8.00 d (J = 9.6)	2.92 t, 4.17 t ($J \approx 7.7$) [c], 7.2-7.4 m	2.34 s	6.35 s
6d [b]	2.86 s	9.14 s	*H/D-exchanged*	2.62 s	6.65 s
6e	2.54 s	8.54 s	5.36 s, 7.1-7.4 m	2.41 s	6.55 s
6f	2.54 s	8.54 s	2.93 t, 4.19 t ($J \approx 7.6$) [c] 7.2-7.4 m	2.37 s	6.45 s
6h	8.05 d, 8.27 d (J = 8.3)	8.27 s	5.38 s, 7.1-7.4 m	2.41 s	6.55 s
6I	8.03 d, 8.29 d (J = 8.8)	8.28 s	2.95 t, 4.21 t ($J \approx 7.6$) [c] 7.2-7.4 m	2.37 s	6.45 s
11a	6.16 s	2.50 s [d]	10.87 br.	2.23 s	5.99 s
11b	6.39 s	2.53 s	5.30 s, 7.1-7.4 m	2.35 s	6.08 s
11c	6.31 s	2.56 s	2.90 t, 4.13 t ($J \approx 7.6$) [c] 7.1-7.3 m	2.34 s	6.06 s

[a] The spectrum of **6g** could not be measured because of very poor solubility. - [b] Compound **6d** is measured in CF_3COOD. - [c] A triplet-like structure in CH_2CH_2Ph due to a more complicated AA'BB' coupling system. - [d] Overlapped by the solvent signal.

rins with electron-withdrawing 3-substitutents. Thus, reaction of the 3-acetyl derivatives **6d-f** with 2 equivalents of methyl 3-amino-2-butenoate (**7**) at 150 °C gave products whose molecular masses (determined by MS) were with 28 units less than the masses of the corresponding starting compounds. This fact could be mis-

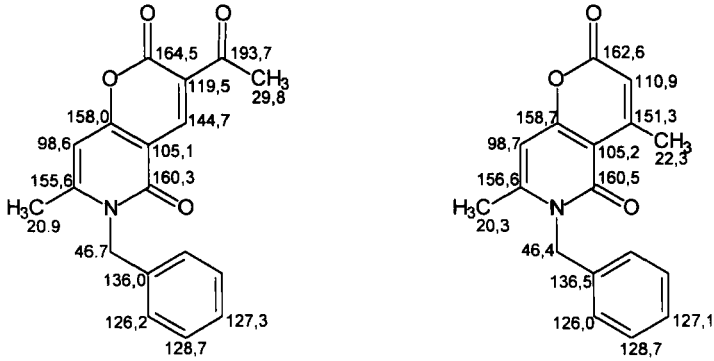
interpreted as a decarbonylation. However, in the ^{1}H-NMR spectra these products displayed signals for two -CH= groups at δ = 6.16-6.39 and 5.99-6.08, as well as for two methyl groups at δ = 2.50-2.56 and 2.23-2.35. In addition, two carbonyl bands (lactone at 1734-1746 and lactam at 1655-1664 cm^{-1}) and lack of an acetyl band were observed in their IR spectra. The only possible structure that matches these spectral properties should be a 4,6-dimethylpyrano[3,2-*c*]pyridine of type **11**.

We succeeded in independently preparing compounds **11a-c** (details in Table 1 and 2) from the pyridones **1a-c** and the enaminoester **7**, according to the *Kappe*'s modification of the *Pechmann* synthesis[12,13] (Scheme 2), and these turned out to be identical with the products obtained from **6d-f**. The assignment of the ^{13}C-NMR chemical shifts of the pyrano[3,2-*c*]pyridine **11b** is shown in Figure 1 as an example. The probable mechanism of this specific degradation of the aza-coumarins **6d-f** under the action of the enamine **7** is depicted in Scheme 2. The initially formed *Michael* adduct **8** might undergo intramolecular opening of the lactone ring to afford the intermediate **9** which splits further into the 2-pyridone **10** and the 4-hydroxy-2-pyridones **1a-c**. The latter pyridones (**1a-c**) are then being trapped by means of a second molecule enaminoester **7** to yield the final products **11a-c**.

This sequence is partially supported by analogous steps (addition and ring-opening) in the already known reactions of 3-substituted coumarins with enaminoesters[10,11] as well as by the fact that the starting aza-coumarins **6d-f** are stable

against heating up to 200 °C either neat or in a solution (in DMF, DMSO, pyridine or triethylamine), therefore, they react with the enamine **7** specifically.

Figure 1. ^{13}C-NMR chemical shifts for compounds **6b** and **11b** in [D_6]DMSO



Compounds **6a-f** and **11a-c** show intense blue to violet fluorescence when irradiated by UV light (λ = 366 nm).

EXPERIMENTAL

General notes. Melting points: open capillaries, Büchi 535 apparatus. IR (nujol): *Shimadzu* FTIR 8101M spectrometer. ^{1}H-NMR: *Bruker* ARX-300 instrument at 300 MHz ; δ (ppm) referenced to TMS (internal). TLC monitoring: precoated aluminium sheets, 0.2 mm layer of silica gel GF_{254} (*E. Merck*, Germany); detection by *Camag* UV lamp (λ = 254/366 nm). Yields of isolated, TLC homogeneous products are given.

The starting **4-hydroxy-2-pyridones 1a-c** were prepared according to the literature method[3,9]. The **intermediate compounds 2a-c**, which have not been previously described, were prepared after *Ollinger* et al.[8] from **1a-c**, triethyl orthoformate and aniline at 140 °C for 60 min.:

3-Anilinomethylidene-6-methyl-2,4(1*H*)-pyridinedione (2a)

Yellow crystals with m. p. 235 °C (dec.) (methanol). - $C_{13}H_{12}N_2O_2$: mol. mass calcd. 228.3; found 228.1 (MS); calcd. C 68.41, H 5.30, N 12.27; found C 68.30, H 5.25, N 12.02. - IR: 3173, 2200-3500, 1688, 1607, 1578 cm^{-1}.

3-Anilinomethylidene-1-benzyl-6-methyl-2,4(1*H*)-pyridinedione (2b)

Pale yellow crystals with m. p. 150-152 °C (methanol). - $C_{20}H_{18}N_2O_2$ (318.4): calcd. C 75.45, H 5.70, N 8.80; found C 75.31, H 5.66, N 8.74. - IR: 1653, 1628, 1595, 1572, 1555 cm^{-1}.

3-Anilinomethylidene-6-methyl-1-phenethyl-2,4(1*H*)-pyridinedione (2c)

Cream-coloured crystals with m. p. 133-135 °C (methanol). - $C_{21}H_{20}N_2O_2$ (332.4): calcd. C 75.88, H 6.06, N 8.43; found C 75.66, H 6.11, N 8.38. - IR: 1655, 1630, 1595, 1582, 1557 cm^{-1}.

Compounds **4-Hydroxy-2-oxo-1,2-dihydro-3-pyridinecarbaldehydes (3a-c)** were prepared after *Ollinger* at al.[8] from **2a-c**, respectively, by hydrolysis with 5% aqueous solution of K_2CO_3 at 100 °C for 30 min.; they have not been previously obtained:

4-Hydroxy-6-methyl-2-oxo-1,2-dihydro-3-pyridinecarbaldehyde (3a)

After recrystallization from methanol, yellow crystals with m. p. 260 °C (dec.); yield 79 % referred to **1a**. - $C_7H_7NO_3$ (153.1): calcd. C 54.90, H 4.61, N 9.15; found C 54.81, H 4.56, N 9.07. - IR: 3156, 2050-3300, 1669, 1615, 1570, 1501 cm^{-1}. - ^1H-NMR ([D_6]DMSO): δ = 2.18 (s, 3H, 6-CH_3), 5.84 (s, 1H, 5-H), 9.82 (s, 1H, -CHO), 11.73 (br. s, NH/OH).

1-Benzyl-4-hydroxy-6-methyl-2-oxo-1,2-dihydro-3-pyridinecarbaldehyde (3b)

After recrystallization from methanol, pale yellow crystals with m. p. 118-119 °C; yield 30 % referred to **1b**. - $C_{14}H_{13}NO_3$ (243.3): calcd. C 69.12, H 5.39, N 5.76; found C 69.16, H 5.43, N 5.72. - IR: 3069, 2000-3300, 1651, 1630, 1582 cm^{-1}.

4-Hydroxy-6-methyl-2-oxo-1-phenethyl-1,2-dihydro-3-pyridinecarbaldehyde (3c)

After recrystallization from methanol, yellow crystals with m. p. 122-123 °C; yield 20 % referred to **1c**. - $C_{15}H_{15}NO_3$ (257.3): calcd. C 70.02, H 5.88, N 5.44; found C 69.39, H 5.86, N 5.33. - IR: 3260, 2700-3500, 1655, 1624, 1565 cm^{-1}.

7-Methyl-2*H*-pyrano[3,2-*c*]pyridine-2,5(6*H*)-diones (6a-i)

Method A (preparation of **6a-c** using the *Wittig* reagent **4**): A mixture of an aldehyde **3a-c** (2.0 mmol) and the *Wittig* reagent **4** (2.0 mmol) in toluene (5.0 ml) was refluxed under stirring for 2 hours. On cooling, the formed precipitate was

filtered and recrystallized from methanol or butanol. Yield 38-70 %, yellow crystals of **6a-c** (Table 1). ^{1}H-NMR spectral data are given in Table 2.

Method B (preparation of **6d-i** using the *Knoevenagel* reaction): A mixture of an aldehyde **3a-c** (2.0 mmol), ethyl acetoacetate (**5a**; 5.0 mmol) or ethyl *p*-nitrophenylacetate (**5b**; 2.0 mmol) and 1-2 drops of piperidine was allowed to stay at ambient temperature for 48 hours (→ **6d-f**) or was stirred under reflux in ethanol (6.0 ml) for 3 hours (→ **6g-i**). The mixture was cooled, the separated crystals were filtered and recrystallized from the solvent given in Table 2. Yield 38-89 %, yellow to orange crystals of **6d-h** or brown crystals of **6i** (Table 1). ^{1}H-NMR data are displayed in Table 2. ^{13}C-NMR data for compound **6e** are given in Figure 1.

4,7-Dimethyl-2*H*-pyrano[3,2-*c*]pyridine-2,5(6*H*)-diones (11a-c)

Method A (starting from the pyrano[3,2-*c*]pyridine-2,5-diones **6d-f**): Crystals of the corresponding pyrano[3,2-*c*]pyridine **6d-f** (1.0 mmol) and of 3-amino-2-butenoate (7; 230 mg, 2.0 mmol) were ground together in a mortar and the resulted mixture was heated in an open reaction tube at 150 °C for 60 min. After cooling, the solidified reaction mixture was triturated with methanol, the separated brown precipitate was collected by filtration and chromatographed on a column (25 x 110 mm) of silica gel 60 (Merck, 70-230 mesh) by elution with hexane-chloroform-acetic acid (5:5:2, v/v parts). Yield 8-55 %, colourless crystals of **11a-c** (Table 1).

Method B: (starting from the 4-hydroxy-2(1*H*)-pyridones **1a-c**): Crystals of a 4-hydroxy-2-pyridone **1a-c** (1.0 mmol) and of 3-amino-2-butenoate **7** (230 mg, 2.0 mmol) were ground together in a mortar and the resulted mixture was heated in an open reaction tube at 150 °C for 60-90 min. (until evolution of methanol and ammonia ceased). After cooling, the resinoid mixture was triturated with methanol, the formed crystals were collected by filtration and, when necessary, recrystallized from the solvent given in Table 1. Yield 79-88 %, colourless crystals of **11a-c** (Table 1). ^{1}H-NMR spectral data are shown in Table 2. ^{13}C-NMR data for compound **11b** are given in Figure 1.

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