Stereoselective Synthesis of *trans*-4,5-Substituted 1,4,5,6-tetrahydropyridine-2-(olates)thiolates

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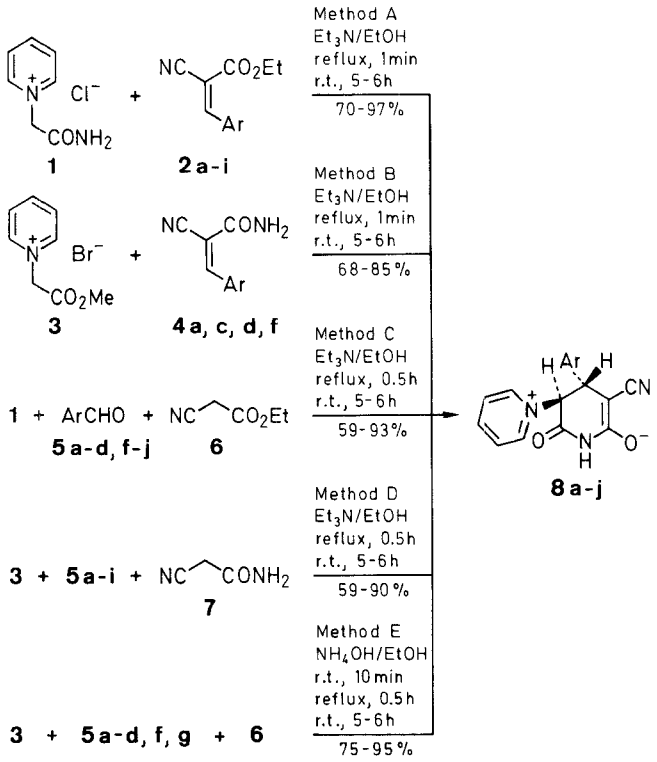
trans-4,5-Substituted 1,4,5,6-tetrahydropyridine-2-(olates)thiolates are prepared either from pyridinium salts and cyanoacetic acid derivatives or from pyridinium salts, aromatic aldehydes and ethyl cyanoacetate or cyanoacetamide in the presence of a base.

Pyridinium salts have found wide applications in the synthesis of substituted pyridines.[1-4] However, the use of pyridinium salts in the stereoselective synthesis of tetrahydropyridines has not been reported.

We describe here the applications of pyridinium salts in the stereoselective synthesis of substituted tetrahydropyridine-2-(olates)thiolates. The *N*-(carbomoylmethyl)pyridinium chloride (**1**) with 3-aryl-2-cyano-2-propenoates **2** in the presence of triethylamine in ethanol proceeds with the formation of substituted tetrahydropyridine-2-olates **8** (Method A, Table). Under similar conditions compounds **8** were also obtained from *N*-(methoxycarbonylmethyl)pyridinium bromide (**3**) and 3-aryl-2-cyanopropenamides **4** (Method B). The reactions proceed via pyridinium ylides, which are generated from pyridinium salts **1** and **3** in the presence of triethylamine (Scheme **1**).

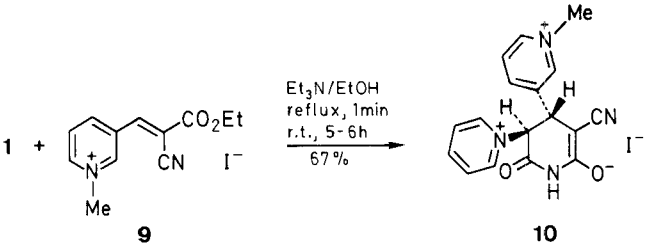


2, 4, 5, 8	Ar	2, 4, 5, 8	Ar
a	Ph	f	4-ClC_6H_4
b	2-FC_6H_4	g	4-BrC_6H_4
c	3-FC_6H_4	h	4-$MeOC_6H_4$
d	4-FC_6H_4	i	4-$EtOC_6H_4$
e	2-ClC_6H_4	j	4-$O_2NC_6H_4$

Scheme 1

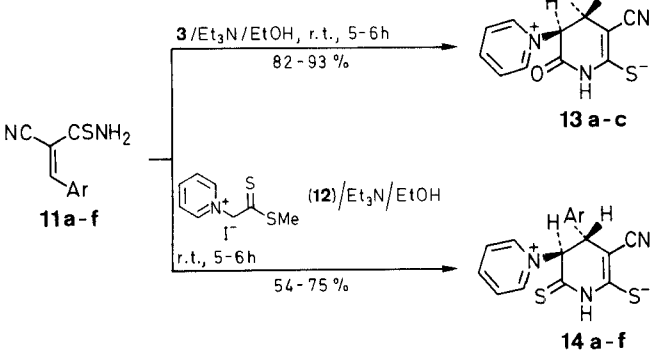
Analysing the above results obtained from the Methods A and B, we have worked out simple methods of obtaining compounds **8** by a one-pot procedure. Substituted tetrahydropyridine-2-olates **8** were formed in high yield by the condensation of pyridinium salts **1** or **3**, aromatic aldehydes **5** and ethyl cyanoacetate (**6**) or cyanoacetamide (**7**) (Methods C, D, and respectively). However, the most feasible and simple method for the synthesis of compounds **8** is the reaction of compounds **3**, **5** and **6** in ethanol in the presence of aqueous ammonia (Method E) (Scheme **1**).

The methods developed were successfully applied in the synthesis of compound **10**, which was obtained from *N*-(carbamoylmethyl)pyridinium chloride (**1**) and the pyridinium salt **9** (Scheme **2**).



Scheme 2

The reaction of salts **3** or **12** with compounds **11** in the presence of triethylamine is a general method for the preparation of tetrahydropyridine-2-thiolates **13** and **14** (Scheme **3**).

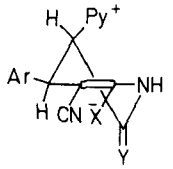


11, 13, 14	Ar	11, 13, 14	Ar
a	4-FC_6H_4	d	4-HOC_6H_4
b	4-ClC_6H_4	e	4-$MeOC_6H_4$
c	4-BrC_6H_4	f	3-pyridyl

Scheme 3

According to the spectral data, the above reactions proceed with a high selectivity (Table). Compounds **8**,

10, 13, 14 are stabilized in the form of betaines with the separation and delocalization of the positive and negative charges in Py^+ and $N{=}C{-}C{-}C{-}X^-$ (X = O, S) fragments. Partial delocalization of the negative charge shifts the frequency of vibration of the C≡N group lower energy ($\nu = 2168-2195\ cm^{-1}$) similar to the earlier observation on the salts of hydrated 3-cyanopyridine-2-thiolates.[5,6] The adsorption bands of the carbonyl group at $1693-1705\ cm^{-1}$ are characteristic of the uncoupled carbamoyl group and indicative of the C-2 atom leaving the surface of the coplanar N(1)–C(2) =C(3)–C(4) fragment as shown in the twist conformation **15**.



15 X,Y = O,S

Delocalization of the positive charge in the pyridinium cation leads to the shift of signals of its protons to lower field at $\delta = 7.98-8.95$ in analogy to quaternized pyridines.[7] Signals of H-5 and H-4 protons are obtained in the form of two doublets in the range of $\delta = 5.95-6.49$

Table. Compounds **8**, **10**, **13**, **14** Prepared

Product	Method	Yield (%)	mp (°C)	Molecular Formula[a]	IR (KBr) ν (cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS)
8a	A	70	233–235	$C_{17}H_{13}N_3O_2$	3420, 2963,	4.47 (d, 1 H, J = 13.1, H-4), 5.98 (d, 1 H, J = 13.1, H-5), 7.14 (m,
	B	68		(291.3)	2855, 2174,	$5H_{arom}$), 8.03 (t, $2H_{pyridyl}$, J = 6.4, 8), 8.51 (t, $1H_{pyridyl}$, J = 8),
	C	70			1703, 1634	8.86 (d, $2H_{pyridyl}$, J = 6.4), 9.88 (s, 1 H, NH)
	D	59				
	E	75				
8b	A	81	236–240	$C_{17}H_{12}FN_3O_2$	3418, 2963,	4.61 (d, 1 H, J = 13.4, H-4), 5.95 (d, 1 H, J = 13.4, H-5), 7.12 (m,
	C	85		(309.3)	2832, 2174,	$4H_{arom}$), 8.03 (t, $2H_{pyridyl}$, J = 6.3, 8.2), 8.48 (t, $1H_{pyridyl}$, J = 8.2),
	D	75			1702, 1637	8.83 (d, $2H_{pyridyl}$, J = 6.3), 9.79 (s, 1 H, NH)
	E	87				
8c	A	86	240–243	$C_{17}H_{12}FN_3O_2$	3429, 2945,	4.49 (d, 1 H, J = 13.1, H-4), 5.97 (d, 1 H, J = 13.1, H-5), 7.15 (m,
	B	80		(309.3)	2853, 2170,	$4H_{arom}$), 8.02 (t, $2H_{pyridyl}$, J = 6.2, 7.9), 8.46 (t, $1H_{pyridyl}$, J = 7.9),
	D	79			1706, 1632	8.84 (d, $2H_{pyridyl}$, J = 6.2), 9.92 (s, 1 H, NH)
	D	82				
	E	85				
8d	A	78	242–245	$C_{17}H_{12}FN_3O_2$	3428, 2968,	4.50 (d, 1 H, J = 13.4, H-4), 5.96 (d, 1 H, J = 13.4, H-5), 7.09 (m,
	B	75		(309.3)	2840, 2180,	$4H_{arom}$), 8.03 ($2H_{pyridyl}$, J = 6.3, 8), 8.48 (t, $1H_{pyridyl}$, J = 8), 8.85
	C	82			1694, 1638	(d, $2H_{pyridyl}$, J = 6.3), 9.94 (s, 1 H, NH)
	D	64				
	E	85				
8e	A	83	245–248	$C_{17}H_{12}ClN_3O_2$	3426, 2975,	4.57 (d, 1 H, J = 13.2, H-4), 5.96 (d, 1 H, J = 13.2, H-5), 7.23 (m,
	D	75		(325.8)	2836, 2172,	$4H_{arom}$), 8.02 (t, $2H_{pyridyl}$, J = 6.2, 7.9), 8.45 (t, $1H_{pyridyl}$, J = 7.9),
					1705, 1635	8.48 (d, $2H_{pyridyl}$, J = 6.2), 9.87 (s, 1 H, NH)
8f	A	80	246–248	$C_{17}H_{12}ClN_3O_2$	3417, 2963,	4.52 (d, 1 H, J = 13.2, H-4), 5.96 (d, 1 H, J = 13.2, H-5), 7.20 (d,
	B	82		(325.8)	2827, 2178,	$2H_{arom}$, J = 8.2), 7.53 (d, $2H_{arom}$, J = 8.2), 7.98 (t, $2H_{pyridyl}$,
	C	87			1700, 1635	J = 6.3, 8.1), 8.39 (t, $1H_{pyridyl}$, J = 8.1), 8.81 (d, $2H_{pyridyl}$,
	D	75				J = 6.3), 9.79 (s, 1 H, NH)
	E	83				
8g	A	88	243–245	$C_{17}H_{12}BrN_3O_2$	3420, 2974,	4.48 (d, 1 H, J = 12.9, H-4), 5.96 (d, 1 H, J = 12.9, H-5), 7.09 (d,
	C	93		(370.2)	2815, 2175,	$2H_{arom}$, J = 8.1), 7.35 (d, $2H_{arom}$, J = 8.1), 7.99 (t, $2H_{pyridyl}$,
	D	90			1703, 1638	J = 6.3, 8), 8.48 (t, $1H_{pyridyl}$, J = 8), 8.81 (t, $2H_{pyridyl}$, J = 6.3),
	E	95				9.78 (s, 1 H, NH)
8h	A	85	234–236	$C_{18}H_{15}N_3O_3$	3415, 2940,	3.82 (s, 3 H, CH_3), 4.38 (d, 1 H, J = 13.1, H-4), 5.95 (d, 1 H,
	C	93		(321.3)	2895, 2826,	J = 13.1, H-5), 7.12 (d, $2H_{arom}$, J = 8.7), 7.55 (d, $2H_{arom}$, J = 8.7),
	D	90			2183, 1695,	8.03 (t, $2H_{pyridyl}$, J = 6.3, 8), 8.53 (t, $1H_{pyridyl}$, J = 8), 8.84 (d,
					1638	$2H_{pyridyl}$, J = 6.3), 9.83 (s, 1 H, NH)
8i	A	97	237–240	$C_{19}H_{17}N_3O_3$	3420, 2929,	1.20 (t, 3 H, J = 7.2, CH_3), 3.84 (q, 2 H, J = 7.2, CH_2), 4.43 (d,
	C	88		(335.4)	2910, 2830,	1 H, J = 12.8, H-4), 5.98 (d, 1 H, J = 12.8, H-5), 7.13 (d, $2H_{arom}$,
	D	80			2172, 1700,	J = 8.6), 7.58 (d, $2H_{arom}$, J = 8.6), 8.02 (t, $2H_{pyridyl}$, J = 6.2, 8),
					1635	8.48 (t, $1H_{pyridyl}$, J = 8), 8.82 (d, $2H_{pyridyl}$, J = 6.2), 9.85 (s, 1 H,
						NH)
8j	C	59	238–242	$C_{17}H_{12}N_4O_4$	3426, 2925,	4.54 (d, 1 H, J = 13.4, H-4), 5.97 (d, 1 H, J = 13.4, H-5), 7.24 (d,
				(336.3)	2830, 2176,	$2H_{arom}$, J = 8.5), 7.62 (d, $2H_{arom}$, J = 8.5), 7.98 (t, $2H_{pyridyl}$,
					1698, 1635	J = 6.2, 7.9), 8.50 (t, $1H_{pyridyl}$, J = 7.9), 8.85 (d, $2H_{pyridyl}$,
						J = 6.2), 9.94 (s, 1 H, NH)
10	A	63	173–175	$C_{17}H_{15}IN_4O_2$	3418, 2929,	4.38 (s, 3 H, CH_3), 4.53 (d, 1 H, J = 12.0, H-4), 6.02 (d, 1 H,
				(434.2)	2826, 2173,	J = 12.0, H-5), 8.03–9.01 (m, $9H_{pyridyl}$), 9.20 (s, 1 H, NH)
					1690, 1632	

Table. (continued)

Product	Method	Yield (%)	mp (°C)	Molecular Formula[a]	IR (KBr) ν (cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS)
13a	–	82	189–193 (dec)	$C_{17}H_{12}FN_3OS$ (325.4)	3200, 3144, 2193, 1695, 1635	4.65 (d, 1H, J = 13.5, H-4), 6.21 (d, 1H, J = 13.5, H-5), 7.13 (m, $4H_{arom}$), 8.06 (t, $2H_{pyridyl}$, J = 6.2, 7.9), 8.53 (t, $1H_{pyridyl}$, J = 7.9), 8.87 (d, $2H_{pyridyl}$, J = 6.2), 10.14 (s, 1H, NH)
13b	–	82	229–234 (dec)	$C_{17}H_{12}ClN_3OS$ (341.3)	3200, 3150, 2195, 1693, 1635	4.66 (d, 1H, J = 13.5, H-4), 6.25 (d, 1H, J = 13.5, H-5), 7.18, 7.30 (d, $4H_{arom}$, J = 7.8), 8.10 (t, $2H_{pyridyl}$, J = 6.1, 7.9), 8.56 (t, $1H_{pyridyl}$, J = 7.9), 8.90 (d, $2H_{pyridyl}$, J = 6.1), 10.22 (s, 1H, NH)
13c	–	93	227–231 (dec)	$C_{17}H_{12}BrN_3OS$ (386.3)	3222, 3140, 2196, 1696, 1635	4.63 (d, 1H, J = 13.8, H-4), 6.21 (d, 1H, J = 13.8, H-5), 7.11, 7.41 (d, $4H_{arom}$, J = 8.1), 8.06 (t, $2H_{pyridyl}$, J = 6.1, 7.9), 8.49 (t, $1H_{pyridyl}$, J = 7.9), 8.87 (d, $2H_{pyridyl}$, J = 6.1), 10.08 (s, 1H, NH)
14a	–	75	223–224 (dec)	$C_{17}H_{12}FN_3S_2$ (341.4)	3460, 3308, 2172, 1630, 1200	4.68 (d, 1H, J = 13.5, H-4), 6.41 (d, 1H, J = 13.5, H-5), 7.00–7.38 (m, $4H_{arom}$), 8.03 (t, $2H_{pyridyl}$, J = 6.2, 8.1), 8.53 (t, $1H_{pyridyl}$, J = 8.1), 8.93 (d, $2H_{pyridyl}$, J = 6.2), 11.87 (s, 1H, NH)
14b	–	71	228–230 (dec)	$C_{17}H_{12}ClN_3S_2$ (357.9)	3440, 3284, 2176, 1630, 1204	4.72 (d, 1H, J = 13.7, H-4), 6.42 (d, 1H, J = 13.7, H-5), 7.18, 7.32 (d, $4H_{arom}$, J = 5.8), 8.09 (t, $2H_{pyridyl}$, J = 6.2, 8.2), 8.54 (t, $1H_{pyridyl}$, J = 8.2), 8.92 (d, $2H_{pyridyl}$, J = 6.2), 11.86 (s, 1H, NH)
14c	–	74	236–237 (dec)	$C_{17}H_{12}BrN_3S_2$ (402.3)	3435, 3296, 2178, 1632, 1202	4.67 (d, 1H, J = 14.0, H-4), 6.42 (d, 1H, J = 14.0, H-5), 7.18, 7.45 (d, $4H_{arom}$, J = 6.2), 8.09 (t, $2H_{pyridyl}$, J = 6.1, 8.2), 8.55 (t, $1H_{pyridyl}$, J = 8.2), 8.95 (d, $2H_{pyridyl}$, J = 6.1), 11.86 (s, 1H, NH)
14d	–	68	173–174 (dec)	$C_{17}H_{13}N_3OS_2$ (339.4)	3457, 3248, 2168, 1620, 1200	4.49 (d, 1H, J = 13.8, H-4), 6.25 (d, 1H, J = 13.8, H-5), 6.53, 6.97 (d, $4H_{arom}$, J = 7.8), 8.08 (t, $2H_{pyridyl}$, J = 6.0, 8.1), 8.51 (t, $1H_{pyridyl}$, J = 8.1), 8.88 (d, $2H_{pyridyl}$, J = 6.0), 9.36 (s, 1H, NH)
14e	–	62	193–195 (dec)	$C_{18}H_{15}N_3S_2O$ (353.5)	3427, 3295, 2165, 1632, 1203	3.65 (s, 3H, CH_3), 4.57 (d, 1H, J = 14.0, H-4), 6.35 (d, 1H, J = 14.0, H-5), 6.76, 7.12 (d, $4H_{arom}$, J = 8.8), 8.06 (t, $2H_{pyridyl}$, J = 6.3, 8.2), 8.52 (t, $1H_{pyridyl}$, J = 8.2), 8.92 (d, $2H_{pyridyl}$, J = 6.3), 11.84 (s, 1H, NH)
14f	–	54	224–226 (dec)	$C_{16}H_{12}N_4S_2$ (324.4)	3424, 3302, 2180, 1628, 1204	4.74 (d, 1H, J = 13.4, H-4), 6.49 (d, 1H, J = 13.4, H-5), 7.31–9.10 (m, $9H_{pyridyl}$), 11.93 (s, 1H, NH)

[a] Satisfactory microanalyses obtained: C ±0.21, H ±0.18, N ±0.15, S ±0.19.

and 4.38–4.74 with ^3J = 12.8–14.0 Hz. A torsion angle calculated according to the Carplus–Conroy[7] equation $\varphi \geqslant 173°$ indicates that H-5 and H-4 atoms are in a *trans*-pseudodiaxial position; therefore, the aryl/heteroaryl substituents at C-5 and C-4 atoms are in a *trans*-pseudodiequatorial position. These data support the assumption that the 6-membered ring in the tetrahydropyridines **8, 10, 13, 14** is in a twist conformation **15** as shown earlier for the salts of 3-cyano-tetrahydropyridine-2-thiolates.[8]

IR spectra were recorded on a Perkin-Elmer 577 spectrophotometer and ^{1}H-NMR spectra on a Bruker WM (250 MHz) spectrometer.

***trans*-4-Aryl-3-cyano-6-oxo-5-pyridinio-1,4,5,6-tetrahydropyridine-2-olates 8, 10; General Procedure:**

Method A, *for* **8a–i, 10**: A mixture of the salt **1** (1.72 g, 10 mmol), the appropriate 2-propenoate **2** (10 mmol) or **9** (3.44 g, 10 mmol) and Et_3N (1.01 g, 10 mmol) in EtOH (20–30 mL) is heated to the boiling point and filtered. The filtrate is stirred at r.t. for 5–6 h, the precipitate is filtered, washed with EtOH and hexane (Table).

Method B, *for* **8a,c,d,f**: Compounds **8a,c,d,f** are prepared starting from the pyridinium salt **3** and 2-propenamides **4a,c,d,f** adapting the same procedure as Method A (Table).

Method C, *for* **8a–d,f–j**: A mixture of **1** (1.73 g, 10 mmol), the appropriate aromatic aldehyde **5a–d,f–j** (10 mmol), ethyl cyanoacetate (**6**; 1.13 g, 10 mmol) and Et_3N (1.01 g, 10 mmol) in EtOH (20–30 mL) is refluxed with stirring for 0.5 h. The mixture is then stirred at r.t. for 5–6 h, the precipitate is filtered, washed with EtOH and hexane (Table).

Method D, *for* **8a–i**: Same as Method C, but starting from compounds **3**, **5a–i** and cyanoacetamide (**7**) (Table).

Method E, *for* **8a–d,f,g**: A mixture of pyridinium salt **3** (2.32 g, 10 mmol), the appropriate aromatic aldehyde **5a–d,f,g** (10 mmol) and ethyl cyanoacetate (**6**; 1.13 g, 10 mmol) is stirred in EtOH (20–30 mL) at r.t. 25% aq NH_4OH (17 mL, 25 mmol) is added dropwise to the mixture during 10 min. The mixture is refluxed with stirring for 0.5 and stirred at r.t. for 5–6 h. The precipitated product is isolated by filtration (Table).

***trans*-4-Aryl-3-cyano-6-(oxo)thio-5-pyridinio-1,4,5,6-tetrahydropyridine-2-thiolates 13 and 14; General Procedure:**

A mixture of the appropriate 2-propenthioamide **11** (10 mmol), pyridinium salt **3** (2.32 g, 10 mmol) or **12** (3.11 g, 10 mmol) and Et_3N (1.01 g, 10 mmol) in EtOH (20–30 mL) is stirred at r.t. for 5–6 h. The precipitated product is filtered, washed with EtOH and hexane (Table).

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