An Expedient, Flexible and Convergent Access to Selectively Protected 1,5-Dicarbonyl Compounds. Applications to the Synthesis of 2,6-Disubstituted Pyridines and Thiopyridines

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Abstract: Intermolecular addition of 2-oxoalkyl radicals generated from the corresponding S-alkyl-O-ethyl dithiocarbonates on vinyl ketals afforded selectively protected 1,5-dicarbonyl compounds in good yields. These key-intermediates can be converted into a plethora of useful substances. Transformations to pyridines and thiopyridines were given as examples.

Key words: ketals, alkenes, ketones, pyridines, radical reactions

The powerful radical chemistry of the xanthate group was nicely developed by Barton, Zard and their co-workers during the last two decades.1,2 Many radical processes that would be otherwise difficult to realize by classical methods because of unavoidable and useless side reactions could be achieved. Besides the reduction to the corresponding alkane,3 a special mention must be made to intermolecular addition of 2-oxoalkyl radicals to unactivated olefins that produces xanthate adducts in generally good yields and tolerates many functional groups. This method has become an easy and efficient way to form carbon–carbon bonds under smooth conditions. In most cases the xanthate moiety present in the adduct becomes useless and is reduced to an alkane.3,4 In this paper, we wish to describe an approach in which a carbon skeleton is assembled by addition of a 2-oxoalkyl radical to a vinyl ketal that produces a selectively protected 1,5-dicarbonyl compound. The strategy we have developed for this purpose is summarized in Figure 1. It is worthy of note that, by suitably choosing the starting materials, i.e. A and B, or B′ and A′, two different mono-protected diketones, C and C′ respectively, can be obtained. Upon hydrolysis both C and C′ furnish diketone D. Moreover, because intermolecular radical additions tolerate an ample substitution pattern in both xanthate and olefin moieties and also display a high chemoselectivity, the range of molecules C, C′ and D is infinitely sizeable.

The chemistry of these molecules is exceptionally rich and important: selectively protected 1,5-diketones have been used as building blocks mainly in the synthesis of carbocycles5,6 and 1,5-diketones intervene in many synthetic processes aimed to elaborate carbocycles7 and heterocycles.8a

Figure 1 a) intermolecular radical addition; b) reduction; c) hydrolysis; d) ammonia source in the presence of dioxygen; e) ammonia source in the absence of dioxygen; f) reductive amination.

To illustrate the potential of our strategy, we chose to convert compounds D into 2,6-disubstituted pyridines E. Of course, an interesting chemistry leading to dihydropyridines F, tetrahydropyridines H, and piperidines I from synthons C or C′ might have been also envisioned (Figure 1). Incidentally, the chirality might be introduced in a reductive amination step (f) or through oxazolopiperidines J, highly valuable intermediates in the CN(R,S) method.8b

At least in the case of pyridines many synthetic methods rely on the transformation of the preexisting nucleus under rather harsh conditions poorly adapted to sensitive functions. A stepwise construction of the pyridine nucleus requires also rather drastic reaction conditions.9 Organometallic chemistry might be an interesting alternative.
Thus, cycloaddition of two alkynes and a nitrile to a pyridine, catalyzed with organocobalt complexes under mild conditions, was published recently.16 However, in many instances, ring closure of a convenient precursor is considered as a more flexible and smooth process.11,12

Radical chemistry usually operates under neutral conditions and therefore is appropriate to wield sensitive compounds. In a preceding paper, we showed that addition of a 2-oxoalkyl radical to an allylic amine constitutes an attractive, flexible, and high-yielding way to gain access to these molecules under very mild conditions.13 This approach was utilized recently in a synthesis of precursors of Eburna and Lupin alkaloids.14

Xanthates derivatives 2a–c used in the present paper were prepared quantitatively by displacement of the corresponding halides 1a–c in the usual way (Scheme 1).

Intermolecular additions of xanthates 2 to olefins 6, catalyzed by dilauroyl peroxide (DLP), in refluxing cyclohexane proceeded smoothly under inert atmosphere and were performed as usual,13 affording the corresponding adducts 7 (Scheme 3, Table 1). In most experiments, we used catalytic amounts of 2,6-lutidine to prevent a putative hydrolysis of the ketal group because of the formation of lauric acid, a by-product from the decomposition of DLP. In fact, further experiments proved that this precaution was useless, mainly because only very small amounts of DLP were introduced [typically 5–10% (mol/mol xanthate)]. The results are summarized in Table 1. Entries 1–6 show that additions of xanthates 2a–c onto olefins 6a and 6b gave fair to good yields of adducts 7a–f.

In order to gain access later to 2,6-disubstituted pyridines, we had to proceed to the cleavage of the ketal group and to the reductive removal of the xanthate group. Hence a two-step process, i.e., reduction–hydrolysis or hydrolysis–reduction was applied to adducts 7 to reach diketones 10 (Tables 2 and 3). Hydrolysis with a mixture of trifluoroacetic acid/water/dichloromethane at room temperature permitted to prepare 2-oxoalkyl xanthates 9a–d (Scheme 3) from the corresponding ketals 7a–d in good yields (Table 2, entries 1–4).

As for reductive cleavage of the xanthate group, procedures based on Bu3SnH/AIBN in refluxing toluene (Method A) or on propan-2-ol as hydrogen atom donor in the presence of stoichiometric amounts of dilauroyl peroxide (Method B) were utilized (Table 3). In some instances, isopropyl acetate was used instead of propan-2-ol because of its lower nucleophilicity. Reduction of the xanthate group was accomplished from ethylene ketals 4a, 7d, 7e, and 7f to produce compounds 8a–d (Scheme 3, Table 3, entries 1–5). Compounds 8a, 8c, and 8d were hydrolyzed as above to give diketones 10a, 10d, and 10e (Table 2, entries 5–7). Alternatively, the method described by Huet et al. (oxalic acid on silica gel, entry 6) gave similar results.17

### Table 1  Intermolecular Addition of Xanthates onto Vinyl Ketals in the Presence of Catalytic Amounts of DLPa and 2,6-Lutidineb in Refluxing Cyclohexane

<table>
<thead>
<tr>
<th>Entry</th>
<th>Xanthate</th>
<th>Olefin (equiv vs xanthate)</th>
<th>Adduct (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>6a (0.66)</td>
<td>7a (82)</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>6b (0.66)</td>
<td>7b (52)</td>
</tr>
<tr>
<td>3</td>
<td>2b</td>
<td>6a (0.66)</td>
<td>7c (71)</td>
</tr>
<tr>
<td>4</td>
<td>2b</td>
<td>6b (0.66)</td>
<td>7d (58)</td>
</tr>
<tr>
<td>5</td>
<td>2c</td>
<td>6a (0.66)</td>
<td>7e (83)</td>
</tr>
<tr>
<td>6</td>
<td>2c</td>
<td>6b (0.66)</td>
<td>7f (69)</td>
</tr>
<tr>
<td>7</td>
<td>9a</td>
<td>6b (0.66)</td>
<td>13a (32)c</td>
</tr>
</tbody>
</table>

a 5–15% mol vs xanthate.

b 0.2 equiv vs olefin.

c 65% conversion.
Much of the work reported herein was achieved when we discovered that reduction based on phosphorous derivatives (Method C) was generally far more efficient. Hence, the yields given for reduction with $\text{Bu}_3\text{SnH}$ or propan-2-ol would have been certainly much higher if the hypophosphorous method had been used, as shown by comparison between entries 9 and 10 (Table 3).

**Scheme 3** Reagents and conditions: (a) DLP (5–15% mol vs xanthate) and 2,6-lutidine (0.2 equiv vs olefin) in refluxing cyclohexane; (b) see Table 2 (c) see Table 3.

Table 2 Hydrolysis of Ketals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketal</th>
<th>Ketone (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a</td>
<td>9a (78)</td>
</tr>
<tr>
<td>2</td>
<td>7b</td>
<td>9b (81)</td>
</tr>
<tr>
<td>3</td>
<td>7c</td>
<td>9c (83)</td>
</tr>
<tr>
<td>4</td>
<td>7d</td>
<td>9d (87)</td>
</tr>
<tr>
<td>5</td>
<td>8a</td>
<td>10a (51)</td>
</tr>
<tr>
<td>6</td>
<td>8c</td>
<td>10d (57)</td>
</tr>
<tr>
<td>7</td>
<td>8d</td>
<td>10e (99)</td>
</tr>
</tbody>
</table>

Hydrolysis with a mixture of $\text{F}_{3}\text{CCOOH}$–$\text{H}_2\text{O}$–$\text{CH}_2\text{Cl}_2$ (3.5:0.35:10, $c = 100 \text{ mg/mL}$) at r.t. (4 h).

Hydrolysis performed by treatment with oxalic acid on silica gel.

Table 3 Reduction of Xanthates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Xanthate</th>
<th>Alkane (yield%)</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a</td>
<td>8a (63)</td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td>7d</td>
<td>8b (93)</td>
<td>C</td>
</tr>
<tr>
<td>3</td>
<td>7f</td>
<td>8d (78)</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>7e</td>
<td>8a (31)</td>
<td>D</td>
</tr>
<tr>
<td>5</td>
<td>7f</td>
<td>8d (78)</td>
<td>A</td>
</tr>
<tr>
<td>6</td>
<td>7c</td>
<td>10b (22)</td>
<td>A</td>
</tr>
<tr>
<td>7</td>
<td>7c</td>
<td>10b (58)</td>
<td>B</td>
</tr>
<tr>
<td>8</td>
<td>9d</td>
<td>10c (63)</td>
<td>B</td>
</tr>
<tr>
<td>9</td>
<td>13a</td>
<td>13b (89)</td>
<td>C</td>
</tr>
<tr>
<td>10</td>
<td>13a</td>
<td>13b (56)</td>
<td>A</td>
</tr>
</tbody>
</table>

*Method A: $\text{Bu}_3\text{SnH}$, AIBN in refluxing toluene; Method B: Stoichiometric amount of DLP (1–1.2 equiv vs xanthate) in propan-2-ol; Method C: $\text{H}_2\text{PO}_3$, Et$_3$N, AIBN, dioxane; Method D: stoichiometric amounts of DLP (1–1.2 equiv vs xanthate) in isopropyl acetate.*

Table 4 Formation of pyridines 11, 12, and 14 from Diketones 10, 9, and 13b in the Presence of Ammonium Acetate in AcOH

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diketone</th>
<th>Pyridine (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>11a (62)</td>
</tr>
<tr>
<td>2</td>
<td>10b</td>
<td>11c (47)</td>
</tr>
<tr>
<td>3</td>
<td>10c</td>
<td>11b (31)</td>
</tr>
<tr>
<td>4</td>
<td>10d</td>
<td>11d (93)</td>
</tr>
<tr>
<td>5</td>
<td>10e</td>
<td>11e (24)</td>
</tr>
<tr>
<td>6</td>
<td>9b</td>
<td>12a (91)</td>
</tr>
<tr>
<td>7</td>
<td>9d</td>
<td>12b (32)</td>
</tr>
<tr>
<td>8</td>
<td>13b</td>
<td>14 (66)</td>
</tr>
</tbody>
</table>

Diketones 10a,c,d,e were converted to the corresponding pyridines by heating in AcOH in the presence of ammonium acetate, according to Pchelintseva’s method. Spontaneous oxidation with air afforded the corresponding 2,6-disubstituted pyridines 11a–e in non-optimized 24–93% yields (Scheme 4, Table 4, entries 1–5).

Interestingly, when the reaction with ammonium acetate was performed on diketones 9a and 9d, respectively, without prior reduction of the xanthate moiety, thiopyridines 12a and 12b were isolated in 91 and 32% yields, respectively (Scheme 4, Table 4, entries 6 and 7). To our knowledge these compounds represent the first example of pyridines bearing a xanthate function. The latter of course could be hydrolyzed to the corresponding thiol.
Few methods describe the preparation of 3-thiopyridines. Most of them start from the corresponding 3-halo derivative. Noteworthy, 3-mercaptopicolinic acid displays an interesting antidiabetic activity and some analogues have also been synthesized.

As emphasized above, compounds 9 possess a xanthate moiety in α position to a carbonyl group. Therefore, an iterative addition from a newly formed electrophilic, stabilized carbon radical to an olefin can be foreseen. α-Keto xanthates 7 can be considered as sources of nucleophilic carbon radicals. Such radicals have been used to achieve cyclications onto aromatic rings. These reactions lead to the formation of α-tetralones, indanes, indolines, etc. In these cases, stoichiometric amounts of peroxide are needed as the rearromatization step does not allow a radical chain mechanism and harsh reaction conditions are required because of an impeded process that demands much energy.

To illustrate this possibility, we reacted xanthate 9a with vinyl dioxyxane 6b under usual conditions (catalytic amounts of DLP in refluxing cyclohexane) (Scheme 4). Adduct 13a was formed in a modest but not optimized 32% yield. After desulfurization (Table 3, entries 9 and 10), compound 13b was converted into pyridine 14 in a fair 66% yield (Table 4, entry 6). Interestingly, no cyclization of the transient xanthate 13a on the phenyl group was observed. The hydrolysis of the ketal group occurred during the purification over silica gel as proven by the NMR spectrum of the crude. This explains that only one regiosomer was formed.

The preliminary results reported herein suggest that the scope of this strategy can be widely generalized. Because of the smoothness of the reaction conditions, intermolecular addition of 2-oxoalkyl radical onto terminal olefin containing a masked carbonyl group may represent a very efficient way to produce differentiated dicarbonyl compounds and hence, a plethora of useful transformations can be envisioned. We are currently working along these lines.

FTIR spectra were recorded on a PerkinElmer BX FT-IR instrument. Absorptions are given in cm⁻¹. ¹H and ¹³C NMR spectra were measured using either a Bruker AM-300, AM-400 or AC-250 instrument with chemical shifts reported as δ (ppm) downfield from TMS (δ = 0.00) using the residual solvent signal of CHCl₃. (¹H NMR: δ = 7.27, singlet; ¹³C NMR: δ = 77.0, triplet) as internal standard. Mass spectra were recorded on a ThermoQuest Navigator mass spectrometer with electrospray ionization (ESI). Electron impact (EI) mass spectra were obtained with an AEI MS-50 instrument. Chemical ionization (CI) mass spectra were recorded on a HP5989B spectrometer. Melting points were determined with the aid of a Büchi B-540 apparatus. Analytical TLC was performed using F254 pre-coated silica gel plates. After elution, UV active materials were visualized by UV illumination at 254 nm while non-active materials were visualized by staining with ethanolic vanillin solution (5% w/v solution of H₂SO₄ in EtOH), followed by charring with a heat gun. Silica gel (Kieselgel 60, Merck) was used for flash chromatography. All reactions were performed under argon unless otherwise stated. Commercial reagents were used as received and anhydrous solvents were either distilled from suitable drying agent or purchased.

**Dithiocarbonic Acid S-(3,3-Dimethyl-2-oxobutyl) Ester O-Ethyl Ester (2a)**

This known compound was obtained from chloropinacolone in 97% yield according to the procedure described for the preparation of compound 2b (see below).

**Dithiocarbonic Acid S-[2-(Biphenyl-4-yl)-2-oxoethyl] Ester O-Ethyl Ester (2b)**

Potassium O-ethylxanthate (10.58 g, 66 mmol) was added to a stirred solution of 1-bromo-4-phenylacetophenone (16.5 g, 60 mmol) in acetone (170 mL) at 0 °C. At the end of the addition, the mixture was allowed to warm to r.t. and then poured into H₂O. The white precipitate was collected by filtration and dried. Crystallization from EtOAc gave the title compound 2b; yield: 11.39 g (60%).

**Dithiocarbonic Acid O-Ethyl Ester S-[2-(4-Methoxyphenyl)-2-oxoethyl] Ester (2c)**

Potassium ethylxanthogenate (10.38 g, 66 mmol) was added slowly to a solution of 1-bromo-(4-methoxy)acetophenone (5.72 g, 25 mmol) in anhydrous acetone (50 mL). Upon addition of H₂O (200 mL), the title compound 2c precipitated. The solid was collected by
filtration and dried affording 2e as a white powder; yield: 6.07 g (89%).

IR (Nujol): 1664, 1598, 1574, 1255, 1214, 1174, 1109, 1056, 1032 cm⁻¹

¹H NMR (CDCl₃): δ = 7.96 (d, J = 8.4 Hz, 2 H), 7.66–7.32 (m, 12 H), 4.56 (q, J = 7.1 Hz, 2 H), 4.13 (m, 2 H), 3.85 (m, 2 H), 3.14 (m, 2 H), 2.29 (m, 1 H), 1.9 (m, 1 H), 1.37 (t, J = 7.1 Hz, 3 H).

¹C NMR (CDCl₃): δ = 214.6, 199.0, 145.7, 140.2, 140.0, 135.6, 129.0, 128.7, 128.5, 128.2, 127.3, 126.5, 110.5, 70.3, 65.7, 65.3, 59.0, 36.0, 24.7, 13.8.


Dithiocarbonic Acid S-[4-(Biphenyl-4-yl)-1-(2-ethyl[1,3]dioxolan-2-yl)-4-oxo-1]butyl Ester O-Ethyl Ester (7f)
A solution of xanthate 2b (0.679 g, 2.51 mmol), olefin 6a (0.664 g, 3.767 mmol) and 2,6-lutidine (0.088 mL, 0.2 equiv vs olefin) in cyclohexane (3 mL) was treated as above to furnish the title compound 7f (2.266 g, 58%) as white crystals; mp 53–57.8 °C (EtOH).

IR (Nujol): 1664, 1598, 1574, 1255, 1214, 1174, 1109, 1056, 1032 cm⁻¹.

¹H NMR (CDCl₃): δ = 7.85 (dd, J = 2.0, 6.9 Hz, 2 H), 7.52 (dd, J = 2.0, 7.6 Hz, 2 H), 7.32 (m, 3 H), 6.88 (dd, J = 2.0, 6.9 Hz, 2 H), 4.56 (m, 3 H), 4.09 (2 d, 2 H), 3.83 (s, 3 H), 3.88–3.76 (m, 3 H), 3.04 (m, 2 H), 2.23 (m, 1 H), 1.87 (m, 1 H), 1.35 (t, J = 7.3 Hz, 3 H).

¹C NMR (CDCl₃): δ = 214.3, 197.6, 163.2, 140.1, 130.1 C, 128.2, 127.9, 126.3, 113.5, 110.4, 70.0, 65.4, 65.1, 58.8, 55.3, 53.4, 24.6, 13.5.

HRMS-ESI: m/z calcd for C₂₃H₃₉O₂S₂ + Na [M + Na]⁺: 469.1199; found: 469.1136.

Dithiocarbonic Acid O-Ethyl Ester S-[4-(4-Methoxyphenyl)-1-(2-ethyl[1,3]dioxolan-2-yl)-4-oxo-1]butyl Ester (7e)
A solution of xanthate 2e (0.628 g, 2.323 mmol), olefin 6a (0.447 g, 3.40 mmol) and 2,6-lutidine (0.081 mL, 0.2 equiv vs olefin) in cyclohexane (3 mL) was treated as above to furnish the title compound 7e (0.93 g, 83%) as a viscous oil.

IR (film): 2983, 2838, 1676, 1600, 1575, 1509, 1447, 1418, 1364, 1213, 1259, 1217, 1170, 1111, 1049, 991 cm⁻¹.

¹H NMR (CDCl₃): δ = 7.85 (dd, J = 2.0, 6.9 Hz, 2 H), 7.52 (dd, J = 2.0, 7.6 Hz, 2 H), 7.32 (m, 3 H), 6.88 (dd, J = 2.0, 6.9 Hz, 2 H), 4.56 (m, 3 H), 4.09 (2 d, 2 H), 3.83 (s, 3 H), 3.88–3.76 (m, 3 H), 3.04 (m, 2 H), 2.23 (m, 1 H), 1.87 (m, 1 H), 1.35 (t, J = 7.3 Hz, 3 H).

¹C NMR (CDCl₃): δ = 214.3, 197.6, 163.2, 140.1, 130.1 C, 128.2, 127.9, 126.3, 113.5, 110.4, 70.0, 65.4, 65.1, 58.8, 55.3, 53.4, 24.6, 13.5.

HRMS-ESI: m/z calcd for C₂₃H₃₉O₂S₂ + Na [M + Na]⁺: 469.1199; found: 469.1136.
Dithiocarbonic Acid S-(1-Benzoyl-5,5-dimethyl-4-oxohexyl) Ester O-Ethyl Ester (9a); Typical Procedure

To a solution of ketal 7a (1.564g, 3.94 mmol) in CH2Cl2 (10 mL) was added a solution of 3% trifluoroacetic acid to reach completion as indicated by TLC monitoring. After removal of the solvent under reduced pressure, the crude mixture was subjected to column chromatography over silica gel. Elution with a mixture of hexane–EtOAc (9:1) gave the title compound 9a (1.077 g, 78%) as pale-yellow oil.


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silica gel column chromatography. Elution with a gradient of heptane–EtOAc (from 9:1 to 8:2) afforded the title compound 8c (0.45 g, 92%) as white crystals; mp 63.2–65.0 °C.

IR (Nujol): 3390, 2956, 2925, 2342, 1672, 1596, 1508, 1459, 1254, 1186, 1170, 1031, 896 cm⁻¹.

¹H NMR (CDCl₃); δ = 7.90 (d, J = 8.8 Hz, 2 H), 7.46 (d, J = 7.4 Hz, 2 H), 7.31 (m, 3 H), 6.91 (d, J = 8.8 Hz, 2 H), 4.03 (t, J = 6.8 Hz, 2 H), 3.89 (s, 3 H), 3.77 (t, J = 6.8 Hz, 2 H), 2.90 (t, J = 7.4 Hz, 2 H), 1.99 (m, 2 H), 1.80 (m, 2 H).

¹C NMR (CDCl₃); δ = 198.6, 163.2, 142.4, 130.2, 128.0, 127.7, 125.6, 113.6, 64.4, 55.3, 39.8, 38.0, 18.7.


(1-Biphenyl-4-yl)heptane-1,5-dione (10c)

Reduction with Propan-2-ol

The same procedure was used as for the preparation of 8a; yield: 63%; mp 129.1–129.7 °C.

IR (Nujol): 3424, 2924, 2854, 1710, 1681, 1604, 1459, 1417, 1376, 1266, 1198, 1117, 987 cm⁻¹.

¹H NMR (CDCl₃); δ = 8.04 (s, J = 8.2 Hz, 2 H), 7.68 (d, J = 8.2 Hz, 2 H), 7.62 (d, J = 7.7 Hz, 2 H), 7.44 (m, 3 H), 3.04 (t, J = 6.9 Hz, 2 H), 2.56 (q, J = 7.0 Hz, 2 H), 2.44 (q, J = 7.3 Hz, 2 H), 2.05 (m, 2 H), 1.07 (t, J = 7.3 Hz, 3 H, H-7).

¹C NMR (CDCl₃); δ = 211.2, 199.4, 144.5, 139.8, 138.5, 128.9, 128.6, 128.2, 127.2, 126.8, 41.2, 37.7, 35.9, 29.7, 18.4, 7.8.


(1-Methoxyphenyl)-5-phenylpentane-1,5-dione (10d)

The title compound 10d was obtained from 8c according to the procedure described by Huet et al.; yield: 57%; mp 85.4–85.6 °C.

IR (Nujol): 3433, 2923, 2854, 1682, 1670, 1600, 1577, 1506, 1450, 1415, 1375, 1281, 1256, 1192, 1175, 1027, 987 cm⁻¹.

¹H NMR (CDCl₃); δ = 7.95 (d, J = 7.1 Hz, 4 H), 7.48 (m, 3 H), 6.91 (d, J = 8.7 Hz, 2 H), 3.09 (t, J = 6.9 Hz, 2 H), 3.04 (t, J = 6.9 Hz, 2 H), 2.17 (m, 2 H).

¹C NMR (CDCl₃); δ = 199.9, 198.9, 163.4, 133.0, 130.3, 130.0, 128.5, 128.0, 113.7, 55.4, 37.7, 37.2, 18.9.

MS (EI); m/z: 282, 163, 150, 136, 135, 107, 105, 92, 78, 77, 76, 64, 63, 55, 51.


1-(4-Methoxyphenyl)-5-phenylpentane-1,5-dione (10e)

The title compound 10e was obtained from 8d according to the same procedure as for preparation of 9a; yield: 99%; mp 76.8–77.3 °C (EtOH).

IR (Nujol): 3433, 2923, 2853, 1706, 1664, 1602, 1510, 1452, 1420, 1375, 1257, 1208, 1180, 1111, 1030 cm⁻¹.

¹H NMR (CDCl₃); δ = 7.95 (d, J = 8.9 Hz, 2 H), 6.93 (d, J = 8.9 Hz, 2 H), 3.87 (s, 3 H), 2.96 (t, J = 7.0 Hz, 2 H), 2.54 (t, J = 7.0 Hz, 2 H), 2.43 (q, J = 7.3 Hz, 2 H), 2.01 (m, 2 H), 1.06 (t, J = 7.3 Hz, 3 H, H-7).

¹C NMR (CDCl₃); δ = 211.0, 198.2, 163.3, 130.1, 129.8, 113.6, 55.3, 41.1, 37.0, 35.7, 18.4, 7.7.


6-tert-Butyl-2-phenylpyridine (11a); Typical Procedure

A solution of compound 10a (0.09 g, 0.38 mmol) in AcOH (2 mL), containing NH₂OAc (0.24 g, 3.10 mmol) was refluxed for 5 h. The solvent was evaporated under reduced pressure and the residue was taken up in Et₂O. The organic layer was washed successively with 2 N aq NaOH and brine, then dried (MgSO₄). The residue was chromatographed over silica gel column chromatography. Elution with heptane–EtOAc (from 9:1) afforded the title compound 11a (0.04 g, 22%) as white crystals.

Reduction with Propan-2-ol: Same procedure was used as for the preparation of 9a: yield: 58%; mp 107.9–108.7 °C.

IR (Nujol): 3424, 2924, 2853, 1708, 1679, 1651, 1605, 1557, 1447, 1407, 1366, 1283, 1224, 1112, 1048, 987 cm⁻¹.
2-(Biphenyl-4-yl)-6-ethylpyridine (11b)
A solution of compound 10c (0.591 g, 1.395 mmol) in AcOH (6 mL), containing NH₂OAc (0.86 g, 11.16 mmol) was refluxed for 90 min. The solvent was evaporated under reduced pressure and the residue was taken up in Et₂O. The organic layer was washed successively with 2 N aq NaOH and brine, then dried (MgSO₄). The residue was chromatographed over silica gel (eluent: gradient heptane- EtOAc) to yield the title compound 11b; oil; yield: 31%.

IR (film): 2968, 2933, 1600, 1567, 1547, 1487, 1461, 1449, 1431, 1408, 1378, 1363, 1264, 1235, 1188, 1109, 1039, 1023, 1006 cm⁻¹.

HRMS-ESI: m/z calcd for C₁₈H₁₆NO [M + H]+: 262.1232; found: 262.1313.

1H NMR (CDCl₃): δ = 8.00 (d, J = 8.7 Hz, 2 H), 7.76 (m, 1 H), 7.62 (d, J = 7.7 Hz, 2 H), 7.45 (m, 3 H), 7.02 (d, J = 8.8 Hz, 2 H), 3.87 (s, 3 H).

13C NMR (CDCl₃): δ = 164.0, 156.6, 156.4, 139.6, 137.3, 132.1, 128.8, 128.6, 128.2, 126.9, 117.8, 114.0, 55.3.

HRMS-ESI: m/z calcd for C₁₈H₁₆NO [M + H]+: 262.1232; found: 262.1212.

1,2-Ethyl-6-(4-methoxyphenyl)pyridine (11e)
The title compound 11e was obtained from 10b according to the procedure described for the preparation of 11b; oil; yield: 93%; mp 133 °C.

IR (Nujol): 2923, 2853, 1631, 1607, 1587, 1377, 1247, 1188, 1162, 1112, 1083, 1028 cm⁻¹.

1H NMR (CDCl₃): δ = 7.86 (m, 6 H), 7.24 (d, J = 7.7 Hz, 2 H), 2.53 (t, J = 7.7 Hz, 2 H), 2.30 (q, J = 7.3 Hz, 2 H), 1.38 (s, 9 H), 0.98 (t, J = 7.3 Hz, 3 H).

13C NMR (CDCl₃): δ = 161.0, 156.2, 139.6, 137.3, 132.1, 128.8, 128.6, 128.2, 117.8, 114.0, 55.3.


1-(6-Tert-Butyl-2-phenylpyridin-3-yl)pentan-3-one (14)
The title compound 14 was obtained from 13b according to the procedure described for the preparation of 11b; oil; yield: 66%.

IR (film): 2957, 2872, 1715, 1640, 1589, 1547, 1450, 1380, 1362, 1186, 1102, 1086, 1065 cm⁻¹.

1H NMR (CDCl₃): δ = 7.47 (m, 6 H), 7.24 (d, J = 8.0 Hz, 1 H), 2.96 (t, J = 7.7 Hz, 2 H), 2.30 (q, J = 7.3 Hz, 2 H), 1.38 (s, 9 H), 0.98 (t, J = 7.3 Hz, 3 H).

13C NMR (CDCl₃): δ = 210.4, 166.6, 156.8, 141.1, 137.4, 130.3, 129.0, 128.1, 127.6, 117.4, 42.8, 37.1, 35.8, 30.2, 29.6, 26.3, 25.9, 7.9.


Dithiocarboxylic Acid S-[6-(6-Tert-Butyl-2-phenylpyridin-3-yl)pentan-3-yl] Ester O-Ethyl Ester (12a)
The title compound 12a was obtained from 9a according to the procedure described for the preparation of 11b; yellow oil; yield: 91%.

IR (film): 2958, 2925, 2854, 1566, 1548, 1422, 1149, 1110, 1047, 1031, 1020 cm⁻¹.

1H NMR (CDCl₃): δ = 7.79 (d, J = 8.3 Hz, 1 H), 7.65 (m, 2 H), 7.41 (m, 3 H), 7.34 (d, J = 8.3 Hz, 1 H), 4.49 (q, J = 7.2 Hz, 2 H), 1.40 (s, 9 H), 1.25 (t, J = 7.2 Hz, 3 H).

13C NMR (CDCl₃): δ = 212.1, 170.9, 160.0, 145.3, 139.9, 129.5, 128.4, 127.7, 125.5, 121.6, 118.0, 70.3, 65.8, 37.8, 38.1, 30.0, 15.2, 13.5.


Dithiocarboxylic Acid S-[6-(Biphenyl-4-yl)-2-ethylpyridin-3-yl] Ester O-Ethyl Ester (12b)
The title compound 12b was obtained from 9d according to the procedure described for the preparation of 11b; yellow oil; yield: 32%.

IR (film): 2930, 1567, 1432, 1365, 1226, 1110, 1040, 824 cm⁻¹.

1H NMR (CDCl₃): δ = 8.17 (d, J = 8.5 Hz, 2 H), 7.80 (d, J = 8.1 Hz, 1 H), 7.71 (d, J = 8.5 Hz, 2 H), 7.66 (m, 4 H), 7.46 (t, J = 7.2 Hz, 1 H), 7.28 (m, 5 H), 7.21 (d, J = 7.7 Hz, 2 H), 4.84 (m, 2 H), 3.77 (t, J = 7.7 Hz, 2 H), 1.37 (m, 9 H), 1.23 (t, J = 7.2 Hz, 3 H).


