ACETATE/ACETIC ACID-ASSISTED ONE-POT SYNTHESIS OF (DIARYLMETHYLENE)IMIDAZOLONE FROM AMIDE OR THIOAMIDE

Masahiro Ikejiri,* Atsufumi Watanabe, Mari Katsuda, Mayu Funakoshi, Aki Fujisaka, and Kazuyuki Miyashita*

Faculty of Pharmacy, Osaka Ohtani University, Nishikiori-Kita 3-11-1, Tondabayashi, Osaka 584-8540, Japan; E-mail: ikejim@osaka-ohtani.ac.jp; miyasik@osaka-ohtani.ac.jp.

Abstract – With the aim of extending the library of green fluorescent protein chromophore analogs, a facile one-pot synthesis of 5-(diarylmethylene)imidazolones from the corresponding amide or thioamide is described. Isolation of unstable imidate intermediates is not required, thereby circumventing the drawback of previous approaches. A reaction mechanism in which both acetate and acetic acid promote the imidazolone formation is proposed.

Imidazolone, also called imidazolinone, is a common heterocycle found in the chromophore structure of representative fluorescent proteins such as green fluorescent protein (GFP), blue fluorescent protein (BFP), cyan fluorescent protein (CFP), and Sirius protein (Figure 1). In addition, imidazolone is attractive as a constituent unit of bioactive agents including irbesartan and imazapic. Therefore, numerous imidazolone-containing compounds have been developed so far; especially, 5-arylmethylenated imidazolones have attracted significant attention because of its practical use as fluorescent dyes analogous to the GFP chromophore (GFPc).

Figure 1. Structures of green fluorescent protein chromophore (GFPc) and its analogs
We previously developed a diaryl analog of GFPc (X = Ar, Figure 1), namely, (diarylmethylene)imidazolinone (DAIN), which can act as a fluorescent molecular rotor. In particular, the diphenyl derivative 1 showed notable fluorescence properties such as viscosity-dependent emission and aggregation-induced emission. The DAIN structure was readily synthesized by a condensation reaction developed in our group (Scheme 1). This reaction produces the DAIN ring in moderate yields (about 40%–80%) by mixing imidate 2-O (or thioimidate 2-S) and iminoacetate 3 in the presence of acetic acid. This reaction proceeds most likely by migration of the diphenylmethylene moiety from nitrogen to the α-carbon of the same molecule via an aziridine intermediate. Acetic acid enhances the electrophilicity of the imidate by protonation to the imino nitrogen. Certainly, this condensation reaction is a promising tool for the DAIN synthesis; however, some drawbacks need to be overcome, particularly those regarding the hydrolytic instability of imidate 2. In addition, the low boiling point of small imidate molecules renders them more difficult to handle. Thus, we were interested in improving the synthetic method to DAIN 1 by circumventing the isolation of the unstable imidate 2. In this paper, we report an improved synthesis of DAIN from the corresponding amide or thioamide by a one-pot procedure that does not require isolation of an imidate intermediate.

As a first attempt, we added iminoacetate 3 to the methylation mixture with amide 4a-O and methyl triflate (MeOTf), as expecting that trifluoromethanesulfonic acid (TfOH) generated in situ could serve as a proton source to activate the imino nitrogen of 2a-O (run 1, Table 1). This hypothesis was based on the reaction mechanism of the DAIN synthesis, in which acetic acid enhances the electrophilicity of the
imidate. However, contrary to our expectation, DAIN 1a was not obtained under these conditions. We then sought to reduce the acidity of TfOH by adding a mild base such as pyridine or triethylamine to the reaction mixture after the methylation of 4a-O; however, these attempts were also ineffective (runs 2 and 3, Table 1). Considering then that an acetoxy group might be necessary for this reaction, acetoxy compounds were evaluated as additives (runs 4–6, Table 1). Consequently, basic acetoxy groups afforded a small amount of 1a, whereas acetic acid proved ineffective (runs 5 and 6 vs. 4, Table 1), which indicates that replacement of TfO− with AcO− was crucial for the reaction. Eventually, addition of the tetramethylammonium salt as acetoxy source gave the best result, although the yield was still quite low (run 6, Table 1).

**Table 1.** Effect of additives in the synthesis of 1a

<table>
<thead>
<tr>
<th>Run</th>
<th>Additive (1.0 equiv.)</th>
<th>TLC after 24 h</th>
<th>Yield after 48 h (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>not detected</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>pyridine</td>
<td>not detected</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Et3N</td>
<td>not detected</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>AcOH</td>
<td>not detected</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>AcONa</td>
<td>trace</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>6</td>
<td>AcONMe4</td>
<td>detected</td>
<td>8</td>
</tr>
</tbody>
</table>

To improve the product yield, we then added acetic acid to the reaction mixture described in run 6 in Table 1. The result is shown in Table 2. Notably, the addition of acetic acid was found to improve the yield effectively (runs 1–6, Table 2); in particular, around ten equivalents of acetic acid seemed the appropriate amount, affording a yield of 52% (run 4, Table 2). The yield could not be further improved by extending the reaction time (run 4 vs. 6, Table 2), but refluxing in 1,2-dichloroethane allowed shortening the reaction time (run 4 vs. 7, Table 2). Using a different carboxylic acid reduced the yield (run 4 vs. 8, Table 2). Under excess acetic acid conditions, 1a was yielded even without tetramethylammonium acetate; however, its yield was considerably low (run 9, Table 2). Since the previous method afforded 1a in 60% yield from isolated 2a-O, the yield of 52% obtained following the present procedure can be...
considered acceptable. In addition, the total yield of this one-pot method is superior to that of the corresponding stepwise synthesis from 4a-O (15% total yield; methylation: 25%; condensation: 60%).

Table 2. Effect of the addition of acetic acid for the synthesis of 1a

<table>
<thead>
<tr>
<th>Run</th>
<th>Equiv. of AcOH</th>
<th>Temp.</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>rt</td>
<td>48</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>rt</td>
<td>48</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>rt</td>
<td>48</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>rt</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>rt</td>
<td>48</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>rt</td>
<td>72</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>reflux</td>
<td>24</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td>10b</td>
<td>rt</td>
<td>48</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>11</td>
<td>rt</td>
<td>48</td>
<td>6c</td>
</tr>
</tbody>
</table>

*1,2-Dichloroethane was used as the solvent.

b EtCO₂H was used instead of AcOH.

c The reaction was performed without AcONMe₄.

Notably, the refluxing condition (run 7, Table 2) was also applicable to the corresponding thiolactam 4a-S, improving the yield of 1a to 76% (Scheme 2). Besides, the amount of thiolactam could be reduced to 1.1 equivalents due to the high nucleophilicity of the sulfur atom. Meanwhile, the room temperature conditions did not improve the yield of 1a (conditions: 10 equiv. of AcOH, rt, 48 h, 47% yield).

Scheme 2. Synthesis of 1a from thiolactam 4a-S

Next, a substrate screening was performed using the optimized one-pot methods, method A (from amide at rt or under reflux) and B (from thioamide under reflux). A variety of DAINs including
low-molecular-weight analogs 1b–e were prepared (Table 3). The products were obtained in moderate yields by either method. Although thioamides 4-S generally afforded good yields, amides 4-O also afforded acceptable yields in the case of cyclic structures. The use of amide is an efficient choice for the short synthesis of 1 because it does not require a thioamidation step. Low yields from acyclic amides such as 4c-O and 4d-O are presumably due to their weak reactivity to MeOTf. Notably, this one-pot reaction was applicable for the synthesis of not only diphenyl analogs but also diaryl analogs 1'h and 1'i using the corresponding iminoacetates.

Table 3. Examples of the one-pot synthesis of 1 from a variety of amides and/or thioamides

<table>
<thead>
<tr>
<th>Amide</th>
<th>DAIN</th>
<th>Yield (%) [method A/B]a</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Diagram" /></td>
<td><img src="image2.png" alt="Diagram" /></td>
<td>49 [A, rt] 49 [B]</td>
</tr>
<tr>
<td><img src="image3.png" alt="Diagram" /></td>
<td><img src="image4.png" alt="Diagram" /></td>
<td>15 [A, reflux] 47 [B]</td>
</tr>
<tr>
<td><img src="image5.png" alt="Diagram" /></td>
<td><img src="image6.png" alt="Diagram" /></td>
<td>14 [A, reflux] 41 [B]</td>
</tr>
<tr>
<td><img src="image7.png" alt="Diagram" /></td>
<td><img src="image8.png" alt="Diagram" /></td>
<td>50 [B]</td>
</tr>
<tr>
<td><img src="image9.png" alt="Diagram" /></td>
<td><img src="image10.png" alt="Diagram" /></td>
<td>63 [A, reflux]</td>
</tr>
<tr>
<td><img src="image11.png" alt="Diagram" /></td>
<td><img src="image12.png" alt="Diagram" /></td>
<td>54 [B]</td>
</tr>
<tr>
<td><img src="image13.png" alt="Diagram" /></td>
<td><img src="image14.png" alt="Diagram" /></td>
<td>51 [A, rt]</td>
</tr>
</tbody>
</table>

a Method A: from amide at rt or under reflux; method B: from thioamide under reflux.

A notable advantage of this reaction is the facile synthesis of small size analogs such as 1c and 1d, which can extend the library of GFPc analogs. For example, 1c can be utilized as a common substrate for aldol-type condensation reactions, affording red-Kaede-type chromophore analogs possessing an extended conjugation system at the 2-position. These analogs produce a red shift of fluorescence. An
example of this reaction is shown in Scheme 3-A; styryl analog 1j was successfully obtained by the condensation of 1c with benzaldehyde in the presence of zinc chloride in good yield. Furthermore, 1d was applicable to the click chemistry reaction shown in Scheme 3-B, which suggests that DAIN 1 can be applied to fluorescent probes in the chemical biology field.

![Scheme 3](image)

**Scheme 3.** Application of small size analogs 1c and 1d as substrates

According to our results, we reconsidered the reaction mechanism as follows (Figure 2). Since the first attempt using 2a·TFOH and 3 was unsuccessful, replacement of TFO⁻ as the counter anion with AcO⁻ seems critical to the process, which suggests that the formation of the aziridine ring is a rate-determining step. Basic acetate such as tetramethylammonium acetate would be more suitable for this anion exchange from 2a·TFOH to 2a·AcOH than acetic acid. Consequently, acetic acid in 2a·AcOH could work not only as a proton source for 2a but also as a mild base that contributes to the deprotonation from intermediate I to form aziridine intermediate II. The triflate anion would not be sufficiently basic for this deprotonation, which would explain its lack of reactivity for the present reaction. Excess addition of acetic acid would favor the formation of 2a·AcOH from 2a.

In conclusion, we developed a one-pot synthesis of DAINs from the corresponding amide or thioamide. In this reaction, the additive acetic acid is suggested to act not only as a proton source but also as a base. Using this one-pot method, we were able to synthesize several DAINs having a small molecular weight without difficulty. Among them, 1c and 1d are of particular interest because they can be expected to contribute to extend the library of GFPc analogs. Further studies of their applications are currently in progress in our laboratory.
Figure 2. An improved plausible reaction mechanism from 2 to 1

EXPERIMENTAL

General information

$^1$H- and $^{13}$C-NMR spectra were recorded on a JNM-ECZ400S spectrometer at 400 and 100 MHz, respectively, and chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane or the solvent signal. Mass spectra were recorded using a JEOL JMS-T100LP mass spectrometer in positive electrospray ionization (ESI) mode. Infrared (IR) spectra were recorded using a JASCO FT/IR-6600 spectrometer by attenuated total reflection (ATR). Melting points (Mp) values were measured using a Yanaco melting-point apparatus. Notably, the obtained Mp values were uncorrected. Column chromatography was performed using Fuji Silysia PSQ 100 silica gel or Teledyne Isco RediSep Rf silica gel. Compounds 4c-S,¹³ and 4d-O¹⁴ were synthesized according to literature procedures. The yields of DAINs were calculated based on the amount of MeOTf.

General procedures for the one-pot synthesis of 1:¹⁵ synthesis of 2-(diphenylmethylene)-2,5,6,7,8,9-hexahydro-3H-imidazo[1,2-a]azepin-3-one (1a)⁵

Method A (rt): Table 2, run 4—Methyl trifluoromethanesulfonate (67 µL, 0.61 mmol) was added to a stirred solution of 4a-O (103 mg, 0.91 mmol) in CH₂Cl₂ (3.0 mL) at rt, and the mixture thus obtained was stirred at rt for 24 h. Subsequently, tetramethylammonium acetate (81 mg, 0.61 mmol) was added to the mixture at rt, and the thus obtained mixture was stirred at rt for 20 min. Acetic acid (349 µL, 6.10 mmol) and glycinate 3 (815 mg, 3.05 mmol) were then added to the mixture at rt, and the resulting mixture was
stirred at rt for 48 h. Subsequent to the addition of 10% aqueous HCl and Et₂O to the mixture, the liquid layers thus obtained were shaken and separated. The organic layer was further extracted three times with 10% aqueous HCl, and the combined aqueous layer was neutralized with NaHCO₃ and then re-extracted twice with EtOAc. The combined EtOAc layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to yield 1a (100 mg, 52%) as a yellow solid. The ¹H-NMR spectrum was identical with that previously reported.

Method A (reflux): Table 2, run 7—Methyl trifluoromethanesulfonate (67 µL, 0.61 mmol) was added to a stirred solution of 4a-O (103 mg, 0.91 mmol) in 1,2-dichloroethane (3.0 mL) at rt, and the resulting mixture was stirred at rt for 24 h. Tetramethylammonium acetate (81 mg, 0.61 mmol) was then added to the mixture at rt, and the obtained mixture was stirred at rt for 20 min. Acetic acid (349 µL, 6.10 mmol) and glycinate 3 (815 mg, 3.05 mmol) were then added to the mixture at rt, and the mixture thus obtained was stirred under reflux conditions for 24 h. The rest of the procedure was the same as that described above, and it yielded 1a (100 mg, 52%).

Method B—Methyl trifluoromethanesulfonate (67 µL, 0.61 mmol) was added to a stirred solution of 4a-S (87 mg, 0.67 mmol) in 1,2-dichloroethane (3.0 mL) at ice-cooling temperature; the mixture was then stirred initially for 1 h at the same temperature and then for 6 h at rt. Tetramethylammonium acetate (81 mg, 0.61 mmol) was added to the mixture at rt, and the mixture thus obtained was stirred at rt for 20 min. Acetic acid (349 µL, 6.10 mmol) and glycinate 3 (815 mg, 3.05 mmol) were then added to the mixture at rt, and the resulting mixture was stirred for 24 h under reflux conditions. The rest of the procedure was the same as that described above, and it yielded 1a (146 mg, 76%).

2-(Diphenylmethylene)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3(2H)-one (1b)⁵

Method A (rt); reaction time for the condensation: 72 h; eluent for the silica gel column chromatography: hexane/EtOAc = 2/1; yield: 49%. Method B; eluent for the silica gel column chromatography: hexane/EtOAc = 2/1; yield: 49%. The ¹H-NMR spectrum was identical with that previously reported.⁵

5-(Diphenylmethylene)-2,3-dimethyl-3,5-dihydro-4H-imidazol-4-one (1c)

Method A (reflux); eluent for the silica gel column chromatography: hexane/EtOAc = 2/1 to 1/1; yield: 15%. Method B; reaction time for the methylation: 1 h at 0 ℃ and then 24 h at rt; eluent for the silica gel column chromatography: hexane/EtOAc = 3/2; yield: 47%. Yellow solid; Mp 131-132 ℃; IR (ATR) νmax: 1703, 1619; ¹H-NMR (CDCl₃) δ: 7.56-7.54 (2H, m), 7.42-7.28 (8H, m), 3.09 (3H, s), 2.33 (3H, s); ¹³C-NMR (CDCl₃) δ: 168.7, 160.6, 146.0, 139.1, 137.9, 136.1, 132.3, 130.3, 129.3, 128.8, 127.9, 127.7, 26.4, 15.5; HRMS (ESI) calcd for C₁₈H₁₇N₂O [M + H]⁺ 277.1335; found 277.1344.
3-(But-3-yn-1-yl)-5-(diphenylmethylene)-2-methyl-3,5-dihydro-4H-imidazol-4-one (1d)

Method A (reflux); eluent for the silica gel column chromatography: hexane/EtOAc = 2/1 to 1/1 and for PLC: CH₂Cl₂/EtOAc = 20/1; yield: 14%. Method B; reaction time for the methylation: 1 h at 0 ºC and then 1 h at rt; eluent for the silica gel column chromatography: hexane/EtOAc = 2/1; yield: 41%. Yellow solid; Mp 141-142 ºC; IR (ATR) νmax: 1217, 1264, 1151, 1552, 1264, 1151; 1H-NMR (CDCl₃) δ: 7.58-7.55 (2H, m), 7.43-7.29 (8H, m), 3.68 (2H, t, J = 6.6 Hz), 2.52 (2H, td, J = 6.6, 2.7 Hz), 2.42 (3H, s), 2.01 (1H, t, J = 2.7 Hz); ¹³C-NMR (CDCl₃) δ: 168.6, 160.2, 146.2, 139.1, 137.8, 135.7, 132.3, 130.4, 129.4, 128.9, 127.9, 127.8, 80.7, 70.7, 39.4, 18.5, 15.8; HRMS (ESI) calcd for C₂₁H₁₉N₂O [M + H]+ 315.1492; found 315.1495.

5-(Diphenylmethylene)-2-methyl-3,5-dihydro-4H-imidazol-4-one (1e)

Method B; eluent for the silica gel column chromatography: hexane/EtOAc = 1/2; yield: 50%. Pale yellow solid; Mp 216-217 ºC; IR (ATR) νmax: 3195 (br), 1707, 1617; ¹H-NMR (CDCl₃) δ: 9.60 (1H, br s), 7.50-7.48 (2H, m), 7.41-7.28 (8H, m), 2.09 (3H, s); ¹³C-NMR (CDCl₃) δ: 170.9, 159.3, 146.3, 139.3, 137.8, 136.8, 132.3, 130.6, 129.4, 128.9, 127.9, 127.8, 16.1; HRMS (ESI) calcd for C₁₇H₁₅N₂O [M + H]+ 263.1179; found 263.1182.

2-(Diphenylmethylen e)-5,6-dihydroimidazo[2,1-a]isoquinolin-3(2H)-one (1f)⁵

Method A (reflux); eluent for the silica gel column chromatography: hexane/EtOAc = 4/1; yield: 63%. Extraction with aqueous HCl was not performed. The ¹H-NMR spectrum was identical with that previously reported.⁵

5-(Diphenylmethylene)-2-(4-iodophenyl)-3-methyl-3,5-dihydro-4H-imidazol-4-one (1g)²

Method B; reaction time for the anion exchange: 45 min; eluent for the silica gel column chromatography: hexane/CH₂Cl₂ = 1/2 to CH₂Cl₂; yield: 54%. Extraction with aqueous HCl was not performed. The ¹H-NMR spectrum was identical with that previously reported.²

2-(Bis(4-methoxyphenyl)methylene)-2,5,6,7,8,9-hexahydro-3H-imidazo[1,2-a]azepin-3-one (1h)⁵

Method A (rt); eluent for the silica gel column chromatography: hexane/EtOAc = 2/1 to 1/1; yield: 51%. Ethyl 2-((bis(4-methoxyphenyl)methylene)amino)acetate⁵ was used instead of 3. Extraction with aqueous HCl was not performed. The ¹H-NMR spectrum was identical with that previously reported.⁵

2-(9H-Fluoren-9-ylidene)-2,5,6,7,8,9-hexahydro-3H-imidazo[1,2-a]azepin-3-one (1i)⁵

Method A (rt); eluent for the silica gel column chromatography: hexane/EtOAc = 20/1 to 9/1; yield: 41%. Methyl 2-(9H-fluoren-9-ylidene)amino)acetate,¹⁶ was used instead of 3. Extraction with aqueous HCl was not performed. The ¹H-NMR spectrum was identical with that previously reported.⁵

(E)-5-(Diphenylmethylene)-3-methyl-2-styryl-3,5-dihydro-4H-imidazol-4-one (1j)

A mixture of 1c (30 mg, 0.11 mmol), benzaldehyde (22 µL, 0.22 mmol), and zinc chloride (3.0 mg, 0.022 mmol) in THF (1.0 mL) was refluxed for 24 h. Subsequent to the addition of triethylamine (50 µL, 0.36
mmol), the mixture was stirred for 5 min at rt; the solvent was then evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to yield 1j (32 mg, 81%) as a yellow–orange solid. Mp 180.5-182 °C; 1H-NMR (CDCl3) δ: 7.97 (1H, d, J = 15.8 Hz), 7.69-7.67 (2H, m), 7.62-7.59 (2H, m), 7.44-7.32 (11H, m), 6.82 (1H, d, J = 15.8 Hz), 3.25 (3H, s); 13C-NMR (CDCl3) δ: 168.9, 158.2, 145.9, 140.4, 139.3, 138.3, 137.0, 135.2, 132.8, 130.5, 130.0, 129.4, 128.9, 128.8, 128.0, 127.8, 127.8, 113.0, 26.5; HRMS (ESI) calcd for C25H21N2O [M + H]+ 365.1648; found 365.1651.

3-(2-(1-Benzyl-1H-1,2,3-triazol-4-yl)ethyl)-5-(diphenylmethylen)-2-methyl-3,5-dihydro-4H-imidazol-4-one (1k)

A mixture of 1d (20 mg, 0.064 mmol), benzyl azide (24 µL, 0.19 mmol), N,N-diisopropylethylamine (32 µL, 0.19 mmol), and copper(I) iodide (1.8 mg, 0.0096 mmol) in THF (1.0 mL) was stirred for 16 h at rt. Subsequent to the addition of triethylamine (89 µL, 0.64 mmol), the solvent was evaporated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane/EtOAc = 1/4) to yield 1k (21 mg, 74%) as a yellow solid. Mp 121.5-123.5 ℃; 1H-NMR (CDCl3) δ: 7.52-7.50 (2H, m), 7.42-7.32 (9H, m), 7.27-7.20 (4H, m), 7.20 (1H, s), 5.47 (2H, s), 3.83 (2H, t, J = 7.2 Hz), 3.00 (2H, t, J = 7.2 Hz), 2.16 (3H, s); 13C-NMR (CDCl3) δ: 168.7, 160.4, 146.0, 144.2, 139.0, 137.8, 135.7, 134.5, 129.4, 128.9, 128.7, 127.7, 121.8, 54.1, 40.5, 24.9, 15.5; HRMS (ESI) calcd for C28H26N5O [M + H]+ 448.2132; found 448.2129.

N-(But-3-yn-1-yl)ethanethioamide (4d-S)

A mixture of amide 4d-O (300 mg, 2.70 mmol) and Lawesson’s reagent (765 mg, 1.89 mmol) in THF (30 mL) was refluxed for 2 h. After evaporation of the solvent under reduced pressure, the residue thus obtained was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to yield 4d-S (343 mg, 100%) as a white solid. Mp 46-48 °C; 1H-NMR (CDCl3) δ: 7.50 (1H, s), 3.83 (2H, q, J = 6.1 Hz), 2.60-2.56 (2H, m), 2.59 (3H, s), 2.07 (1H, t, J = 2.5 Hz); 13C-NMR (CDCl3) δ: 201.6, 80.9, 70.6, 44.2, 34.3, 17.6; HRMS (ESI) calcd for C6H10NS [M + H]+ 128.0529; found 128.0528.

REFERENCES AND NOTES


8. The use of excess AcONMe$_4$ (11 equiv.) and absence of AcOH did not afford 1a.


15. Details of the experimental procedures for 1b–g, 1'h, and 1'i are given in the supporting information.