



# An unexpected reaction of pyridine with acetyl chloride to give dihydropyridine and piperidine derivatives



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## ARTICLE INFO

### Article history:

Received 30 September 2013

Revised 3 February 2014

Accepted 4 February 2014

Available online 12 February 2014

### Keywords:

*N*-Acyl pyridinium salts

Zwitterionic ketene enolate

Dihydropyridine

Piperidine

## ABSTRACT

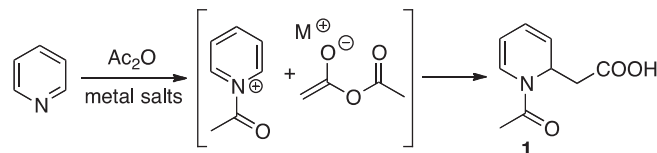
An unexpected reaction of pyridine with acetyl chloride to give *N*-acetyl-1,2 and 1,4-dihydropyridyl acetic acid (**1**, **2**) in high yield and regioselectivity has been reported. The key step is the formation of a zwitterionic pyridinium ketene enolate. The effect of different activating agents on the reaction yield and selectivity has been studied. Platinum(IV) mediated hydrogenation of the corresponding methyl esters (**7**, **8**) gave piperidine derivatives (**9**, **10**).

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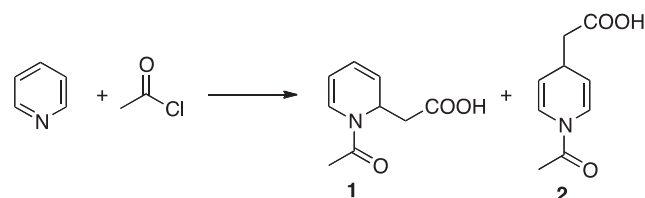
*N*-Acyl pyridinium salts have shown a remarkable importance as building blocks in organic synthesis. They are generated by reaction of pyridines with acyl chlorides or chloroformates and their utility in synthesis is determined either by the easy nucleophilic 1,2- or 1,4-addition reactions to give dihydropyridine derivatives, or by acyl transfer reactions involving nucleophilic addition on carbonyl carbon. Dihydropyridines and their derivatives are key intermediates for the synthesis of several biological active compounds as alkaloids,<sup>1</sup> calcium channel blockers,<sup>2</sup> P-gp inhibitors,<sup>3</sup> NADH model,<sup>4</sup> and antiviral compounds.<sup>5</sup> Several combinations of activating agents and nucleophiles have been reported, even in asymmetric fashion,<sup>6</sup> and the reactivity of *N*-activated pyridinium salts toward nucleophiles has been extensively exploited in Reissert type reactions.<sup>7</sup>

Recently, a simple synthesis of dihydropyridine **1** was reported via a copper-catalyzed Perkin-acyl-Mannich reaction of acetic anhydride with pyridine (Scheme 1).<sup>8,9</sup> In this reaction the proposed mechanism involves the nucleophilic addition of the in situ generated copper enolate of the acetic anhydride to the *N*-acetyl pyridinium salt.<sup>10</sup>

In the present work we report our early results about a new and regioselective synthesis of *N*-acetyl-1,2- and 1,4-dihydropyridyl acetic acid by simple reaction of pyridine with acetyl chloride through an unusual mechanism, which involves the formation of a zwitterionic ketene enolate intermediate of the *N*-acetyl pyridinium ion (Schemes 2 and 3).<sup>11</sup>



**Scheme 1.** Synthesis of *N*-acetyl-1,2-pyridyl acetic acid via copper-catalyzed Perkin-acyl-Mannich addition.



**Scheme 2.** Synthesis of *N*-acetyl-1,2 and *N*-acetyl-1,4-pyridyl acetic acid by reaction of pyridine with acetyl chloride.

While performing some experiments for an alcohol protection with different acylating agents we observed, the unexpected formation of a mixture of *N*-acetyl-1,2- and *N*-acetyl-1,4-dihydropyridyl acetic acid when acetyl chloride was used in pyridine. The same result was obtained when adding only acetyl chloride to an excess of pyridine and stirring the reaction mixture for two hours. After acetyl chloride addition to dry pyridine, at 0 °C under nitrogen, we observed at first the formation of a white compound slightly soluble in pyridine. When the reaction mixture was stirred

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at room temperature the white solid was slowly dissolved, and after quenching the reaction with water, a mixture of *N*-acetyl-1,2- and *N*-acetyl-1,4-dihydropyridyl acetic acid was recovered although in low yield and selectivity (Table 1, entry 1). Unlike the Perkin-acyl-Mannich reaction of acetic anhydride with pyridine, the reaction proceeded even in the absence of Lewis acid catalysis, providing so a first evidence of a different reaction mechanistic pathway.<sup>12,13</sup>

With the aim of improving yields and regioselectivity as well as of shedding some light on the mechanism we explored different reaction conditions.

A high conversion but almost no regioselectivity was obtained when the reaction mixture was stirred overnight at room temperature after addition of acetyl chloride to an excess of pyridine at 0 °C (Table 1, entry 2).<sup>14–16</sup> An excess of pyridine is mandatory in order to promote the formation of the products. In fact, when only one equivalent of pyridine with respect to the acetyl-chloride was added neat or in CH<sub>2</sub>Cl<sub>2</sub>, only the *N*-acetyl-pyridinium ion was formed as expected (Table 1, entry 3).<sup>17</sup> The same result was obtained when an excess of acetyl chloride was added (Table 1, entry 4).

In order to test the effect of different and stronger bases than pyridine, one equivalent of sodium hydride was added to a solution of *N*-acetyl-pyridinium chloride obtained from the reaction of pyridine and acetyl chloride in a 1:1 ratio in CH<sub>2</sub>Cl<sub>2</sub>. The formation of the *N*-acetyl-1,2- and *N*-acetyl-1,4-pyridyl acetic acid was confirmed by <sup>1</sup>H NMR spectra in a very low yield. Unfortunately, even if the effect of the base was clear, the low solubility of pyridinium salt and sodium hydride in CH<sub>2</sub>Cl<sub>2</sub> does not make this system suitable to obtain high conversions.

On the basis of these experiments a reaction mechanism can be proposed where the first step is the formation of the *N*-acetyl pyridinium chloride **3**, then the pyridine excess in the reaction mixture generates the zwitterionic ketene enolate intermediate **4** via deprotonation of the acetyl fragment of the *N*-acetyl-pyridinium ion (Scheme 3).

Similar pyridinium zwitterionic ketene enolates have been postulated as intermediates in catalytic reactions of ketene with aldehydes or imines and in very few cases they have been isolated.<sup>11,18</sup> Nucleophilic addition of the intermediate **4** on C-2 or C-4 of the electrophilic *N*-acetyl-pyridinium ion gives compounds **5** and **6**, that after hydrolysis provide a mixture of *N*-acetyl-1,2- and *N*-acetyl-1,4-pyridyl acetic acid **1** and **2** (Scheme 3).<sup>19</sup>

In order to improve yield and selectivity of the reaction performed in excess of pyridine we then added different activating agents able to increase the concentration of the nucleophilic or electrophilic species in the solution (Table 2).

**Table 1**Effect of pyridine/acetyl chloride molar ratio on the formation of **1** and **2**

Entry	Temp	Time (h)	Py <sup>a</sup>	Selectivity 1,4/1,2 <sup>b</sup>	Yield (%)
1	rt <sup>c</sup>	2	21	47/53	24
2	rt <sup>c</sup>	20	21	52/48	66
3	rt <sup>c</sup>	20	1	—	— <sup>d</sup>
4	rt <sup>c</sup>	20	0.15	—	— <sup>d</sup>

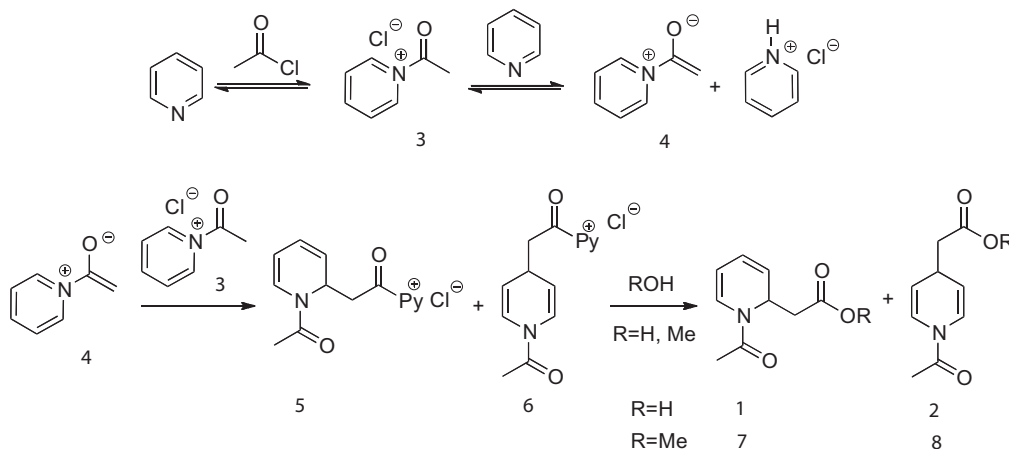
<sup>a</sup> Equivalents of pyridine with respect to acetyl chloride.<sup>b</sup> Calculated via <sup>1</sup>H NMR.<sup>c</sup> Acetyl chloride was added at 0 °C then the mixture was stirred at rt.<sup>d</sup> Only *N*-acetyl pyridinium chloride was recovered.

We mixed the usual excess of pyridine with acetyl chloride (20:1) at 0 °C and added one equivalent of NaH (Table 2, entry 2). The reaction mixture was stirred at room temperature for 20 h and quenched with water. <sup>1</sup>H NMR analysis confirmed the highly predominant formation of the *N*-acetyl-1,2-pyridyl acetic acid (82/18 isomer ratio) in a good 70% yield. The increasing of the nucleophile concentration in the reaction mixture by adding a stronger base than pyridine allowed to highly improve the 1,2-selectivity and to increase the yield. We also performed the same reaction at 0 °C (Table 2, entry 7), and despite the low yield (15%) a higher selectivity toward the 1,2-addition product was observed. The same temperature effect on the selectivity was more evident comparing the experiments performed without the addition of activating agents (Table 2, entries 1 and 6).<sup>20</sup>

We then studied the effect of *N*-acetyl pyridinium ion availability on the reaction. Since it is known that the amount of *N*-acetyl-pyridinium ion in solution can be increased by changing the chloride counterion with the less-nucleophilic triflate, we added Me<sub>3</sub>SiOTf to the reaction mixture.<sup>21</sup>

Under these conditions, the desired product was obtained in a high 80% yield and good 1,4-regioselectivity in only 5 h (Table 2, entry 3), whereas a slight decrease of the 1,4-regioselectivity was obtained stirring the reaction mixture at 0 °C (Table 2, entry 8).

Finally, we explored the effect of Lewis acids by adding catalytic amount of CuI and MgCl<sub>2</sub> to the reaction mixture (Table 2, entries 4 and 5). Although a soft enolization of the nucleophile precursor was demonstrated not to be essential for the reaction, we hoped that the metal coordination might be useful to increase the concentration of the nucleophile. The results highlight an effect on regioselectivity when a catalytic amount of MgCl<sub>2</sub> was added to the reaction mixture. Although a lower yield is observed with respect to the experiment without activating agents (Table 2, entry 1), a preferential 1,2-regioselectivity is obtained (Table 2, entry 4).

**Scheme 3.** Proposed mechanism for the formation of *N*-acetyl-pyridyl acetic acids and corresponding esters.

**Table 2**  
Effect of activating agents on the formation of **1** and **2**

Entry	Temp	Time (h)	Py <sup>a</sup>	Activating agent	Selectivity 1,4/1,2 <sup>b</sup>	Yield (%)
1	rt <sup>c</sup>	20	21	—	52/48	66
2	rt <sup>c</sup>	20	21	NaH	<b>18/82</b>	<b>70</b>
3	rt <sup>c</sup>	5	21	TMSOTf	<b>63/37</b>	<b>80</b>
4	rt <sup>c</sup>	20	21	MgCl <sub>2</sub> <sup>d</sup>	31/69	58
5	rt <sup>c</sup>	20	21	CuI <sup>d</sup>	50/50	— <sup>e</sup>
6	0 °C	8	21	—	10/90	<5
7	0 °C	8	21	NaH	10/90	15
8	0 °C	5	21	TMSOTf	60/40	80

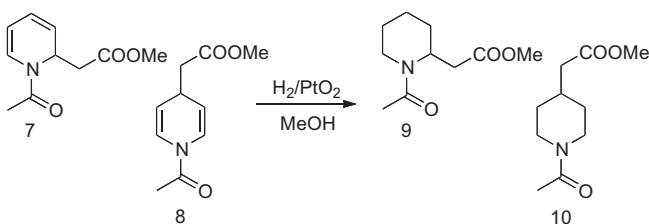
<sup>a</sup> Equivalents of pyridine with respect to acetyl chloride.

<sup>b</sup> Calculated via <sup>1</sup>H NMR.

<sup>c</sup> Acetyl chloride was added at 0 °C then the mixture was stirred at rt.

<sup>d</sup> Amount of Lewis acid 5% with respect to acetyl chloride.

<sup>e</sup> Yield not determined because of the presence of copper complexes.



**Scheme 4.** Synthesis of piperidine derivatives.

On the basis of the proposed mechanism, we thought that quenching the reaction with MeOH instead of water could allow the direct synthesis of the methyl esters **7** and **8** (Scheme 3). As supposed, the addition of anhydrous methanol to the reaction gave a mixture of the more stable esters **7** and **8** which were purified by flash chromatography on silica gel eluting with AcOEt/hexanes 2/3.<sup>22</sup>

Afterward, starting from the pure dihydropyridine methyl esters **7** and **8**, we carried out the simple synthesis of the corresponding piperidine derivatives by catalytic hydrogenation. Piperidines **9** and **10** were obtained in quantitative yield (Scheme 4).<sup>23</sup>

The piperidine products obtained are analogues of an important class of piperidine alkaloids of the *sedum* family, that showed biological activity against cognitive disorders and respiratory illness.<sup>24</sup> Furthermore *N*-acetyl-4-piperidyl derivatives have been employed as key intermediates in antidepressant drug synthesis.<sup>25</sup>

In summary we carried out a novel synthesis of dihydropyridyl acetic acid derivatives with high yields and 1,2 or 1,4-regioselectivity by an unexpected reaction between acetyl chloride and pyridine. A reaction mechanism, which postulates the formation of a pyridinium zwitterionic ketene enolate intermediate, has been proposed on the basis of a detailed study of different reaction conditions. This reaction shows a new nucleophilic reactivity of *N*-acetyl pyridinium salts under basic conditions.

By addition of activating agents to the reaction mixture it was possible to obtain a divergent access to both dihydropyridines. In fact, increasing the concentration of the nucleophilic species, through addition of a stronger base than pyridine, highly improves 1,2-selectivity and yield. While when a triflate counterion has been employed in order to increase the *N*-acetyl-pyridinium ion amount in solution, high yield and 1,4-selectivity were obtained. Catalytic hydrogenation of the dihydropyridine methyl esters gives the corresponding piperidine derivatives in a quantitative yield.

## Acknowledgments

The authors thank the Regione Autonoma della Sardegna for financial support (Ricerca Fondamentale o di Base 2012-L.R. 7 Agosto 2007, n. 7 and Master and Back program PRR-MAB-A2011-19282).

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2014.02.006>.

## References and notes

- (a) Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587–596; (b) Sinclair, A.; Stockman, R. A. *Nat. Prod. Rep.* **2007**, 298–326.
- (a) Gordeev, M. F.; Patel, D. V.; England, B. P.; Jonnalagadda, S.; Combs, J. D.; Gordon, E. M. *Bioorg. Med. Chem.* **1998**, 883–889; (b) Goldmann, S.; Stoltzfuss, J. *Angew. Chem., Int. Ed. Engl.* **1991**, 1559–1578.
- Baumert, C.; Gunthel, M.; Krawczyk, S.; Hemmer, M.; Wersig, T.; Langner, A.; Molnár, J.; Lage, H.; Hilgeroth, A. *Bioorg. Med. Chem.* **2013**, 166–177.
- Burgess, V. A.; Davies, S. G.; Skerlj, R. T. *Tetrahedron: Asymmetry* **1991**, 299–328.
- Stonans, I.; Jansone, I.; Jonane-Osa, I.; Bisenieks, E.; Duburs, G.; Kalvins, I.; Vigante, B.; Uldrikis, J.; Bruvere, I.; Zuka, L.; Poikans, J.; Neidere, Z. Patent WO10276 A1, 2012.
- (a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, 2642–2713; (b) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Pure Appl. Chem.* **2005**, 2047–2052; (c) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, 4719–4728; (d) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc.* **1999**, 2651–2652; (e) Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, 5219–5231; (f) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, 11829–11830; (g) Hoesl, C. E.; Maurus, M.; Pabel, J.; Polborn, K.; Wanner, K. Th. *Tetrahedron* **2002**, 6757–6770; (h) Yamada, S.; Morita, C. *J. Am. Chem. Soc.* **2002**, 8184–8185; (i) Yamada, S.; Jahan, I. *Tetrahedron Lett.* **2005**, 8673–8676; (j) Ichikawa, E.; Suzuki, M.; Yabu, K.; Albert, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, 11808–11809; (k) Murugan, R.; Scriven, E. F. V. *Aldrichimica Acta* **2003**, 21–27.
- (a) Kiehl, N.; Lavilla, R. *Top. Heterocycl. Chem.* **2010**, 127–168; (b) Ahamed, M.; Todd, M. H. *Eur. J. Org. Chem.* **2010**, 5935–5942.
- Crotti, S.; Berti, F.; Pineschi, M. *Org. Lett.* **2011**, 5152–5155.
- Dihydropyridyl acetic acid derivatives have shown their utility as building blocks for the synthesis of unconventional piperidine and pyrrole derivatives. See Ref. 8 and Berti, F.; Di Bussolo, V.; Pineschi, M. *J. Org. Chem.* **2013**, 78, 7324–7329.
- The reaction was performed by using a 1/1 equivalent ratio Ac<sub>2</sub>O/Py.
- Pyridinium zwitterionic ketene enolate intermediates have been postulated in a catalytic asymmetric Staudinger reaction of ketenes with imines and nucleophile-catalyzed [2+2] cycloadditions of disubstituted ketenes with aldehydes. See: (a) Fu, G. C. *Acc. Chem. Res.* **2004**, 542–547; (b) Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, 11586–11587; (c) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2004**, 6358–6360; (d) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, 6771–6803.
- We performed the reaction of Ac<sub>2</sub>O with an excess of pyridine without addition of catalyst, and after water quenching not any dihydropyridine derivative was obtained.
- It was unlikely that the final product was obtained by reaction of the acetyl chloride enolate with the *N*-acetyl-pyridinium ion because the formation of this enolate was proposed only in the presence of a Lewis acid catalyst. See: Nelson, S. G.; Peelen, T. J.; Wan, Z. *Tetrahedron Lett.* **1999**, 6541–6543.
- General experimental procedure for the synthesis of *N*-acetyl-1,2- and *N*-acetyl-1,4-pyridyl acetic acid **1** and **2**: To a solution of pyridine (2.5 mL, 30 mmol, 21 equiv), acetyl chloride (0.11 g, 1.4 mmol, 1 equiv) was added dropwise under nitrogen at 0 °C. The mixture was stirred under nitrogen for the time and the temperature specified in Table 1 and then quenched with an acidic water solution (pH = 4). The pyridine was evaporated under air flow and the residue orange oil washed with Et<sub>2</sub>O. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to afford a mixture of *N*-acetyl-1,2- and 1,4-dihydropyridyl acetic acid as a dark orange powder. Isolation of *N*-acetyl-

- dihydropyridyl-acetic acids was not possible due to their low stability during chromatography. See Ref. 8.
15. Mixture of 2-(1-acetyl-1,2-dihydropyridin-2-yl)acetic acid (**1**) and 2-(1-acetyl-1,4-dihydropyridin-4-yl)acetic acid (**2**): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.13 (d, *J* = 8.4 Hz, 1Ha), 6.50 (d, *J* = 8.4 Hz, 1Ha) 6.48 (dd, *J* = 7.2, 0.4 Hz, 1Hb), 6.0 (dd, *J* = 9.4, 5.6 Hz, 1Hb), 5.94–5.76 (m, 1Hb), 5.60–5.50 (m, 1Hb), 5.42–5.38 (m, 1Hb), 5.07–4.89 (bs, 2Ha), 3.41 (m, 1Ha), 2.69 (dd, *J* = 15.4, 8.8 Hz, 1Ha), 2.57 (dd, *J* = 14.8, 8.0 Hz, 1Hb), 2.50 (dd, *J* = 14.4, 6.0 Hz, 1Hb), 2.19 (s, 3Hb), 2.49 (dd, *J* = 16.2, 5.2 Hz, 1Ha). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 176.2, 174.9, 171.2, 169.8, 124.7, 124.1, 123.2, 121.9, 121.6, 110.5, 110.1, 107.7, 46.9, 42.5, 37.5, 29.7, 21.3.
  16. NMR studies showed that *N*-acetyl-1,2- and 1,4-dihydropyridyl acetic acids are present as a mixture of rotamers in equilibrium. A similar equilibrium was observed in the case of different *N*-acetyl-1,2-piperidyl esters. See: Liljeblad, A.; Kavenius, H.-M.; Tahtinen, P.; Kanerva, L. *Tetrahedron: Asymmetry* **2007**, 181–191.
  17. It is known that acetyl chloride reacts at low temperature with one equivalent of pyridine under anhydrous conditions to give the corresponding *N*-acetylpyridinium chloride. See: Sauer, J. C. *J. Am. Chem. Soc.* **1947**, 2444–2448.
  18. Kollenz, G.; Holzer, S.; Oliver Kappe, C.; Dalvi, T. S.; Fabian, W. M. F.; Sterk, H.; Wong, M. W.; Wentrup, C. *Eur. J. Org. Chem.* **2001**, 1315–1322.
  19. We excluded that the formation of the pyridinium zwitterionic ketene enolates proceeded via reaction of the ketene intermediate with the pyridine because the dehydrohalogenation of the acetyl chloride to give the corresponding ketene was never observed in previous experiments see Ref. 17.
  20. Damji, S.; Fyfe, C. A. *J. Org. Chem.* **1979**, 44, 1757.
  21. Pabel, J.; Hösl, C. E.; Maurus, M.; Ege, M.; Wanner, K. T. *J. Org. Chem.* **2000**, 9272–9275.
  22. Methyl-2-(1-acetyl-1,2-dihydropyridin-2-yl)-acetate (**7**): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.46 (dq, *J* = 7.6, 0.8 Hz, 1H), 5.96 (qt, *J* = 9.2, 5.2, 0.8 Hz, 1H), 5.80 (qt, *J* = 9.2, 5.6, 1.2 Hz, 1H), 5.51 (m, 1H), 5.35 (ddd, *J* = 7.6, 5.6, 1.2 Hz, 1H), 3.69 (s, 3H), 2.51 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.42 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.15 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 170.7, 169.2, 124.9, 123.04, 121.9, 107.2, 51.7, 47.0, 37.4, 21.3. Anal. calcd for C<sub>10</sub>H<sub>13</sub>NO<sub>3</sub>: C, 61.53, H, 6.71, N, 7.18; Found: C 61.69, H, 6.81, N, 7.11. Methyl-2-(1-acetyl-1,4-dihydropyridin-4-yl)-acetate (**8**): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.17 (dt, *J* = 8.6, 1.6 Hz, 1H), 6.54 (dt, *J* = 8.0, 1.6 Hz, 1H), 5.06 (ddd, *J* = 8.4, 6.0, 2.4 Hz, 1H), 4.92 (ddd, *J* = 8.4, 6.0, 2.8 Hz, 1H), 3.69 (m, 3H), 3.46–3.40 (m, 1H) 2.42 (bs, 1H), 2.40 (bs, 1H), 2.19 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.8, 166.0, 124.0, 122.0, 110.2, 109.6, 51.7, 42.6, 29.9, 21.3. Anal. calcd for C<sub>10</sub>H<sub>13</sub>NO<sub>3</sub>: C, 61.53, H, 6.71, N, 7.18; found: C, 61.70, H, 6.72, N, 7.22.
  23. Methyl-2-(1-acetyl-piperidin-2-yl)acetate (**9**): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, mixture of rotamers) δ 5.22–5.12 (m, 1Hb), 4.57–4.51 (m, 1H, Ha), 4.48–4.40 (m, 1H, Ha), 3.67 (s, 3Hb), 3.63 (s, 3Ha), 3.61 (m, 1Hb), 3.19–3.07 (m, 1Hb), 2.77 (dd, *J* = 15.2, 8.0 Hz, 1Ha), 2.65–2.60 (m, Ha), 2.64–2.45 (m, 1Ha, 2Hb), 2.14 (s, 3Ha), 2.05 (s, 3Hb), 1.80–1.30 (m, 6Ha, 6Hb). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.6, 169.5, 51.4, 50.2, 45.8, 41.9, 36.4, 35.1, 34.1, 28.9, 27.1, 25.2, 21.4, 19.0. Anal. calcd for C<sub>10</sub>H<sub>17</sub>NO<sub>3</sub>: C, 60.29, H, 8.60, N, 7.03; Found: C, 60.48, H, 8.71, N, 7.11. Methyl-2-(1-acetyl-piperidin-4-yl)acetate (**10**): (rotamer mixture) <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.62–4.57 (m, 1H), 3.81–3.77 (m, 1H), 3.68 (s, 3H), 3.10–3.00 (m, 1H), 2.63–2.50 (m, 1H), 2.30–2.28 (m, 2H), 2.08 (s, 3H), 2.05–1.96 (m, 1H), 1.80–1.50 (m, 2H), 1.25–1.10 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.4, 171.3, 169.5, 52.0, 51.8, 50.7, 45.2, 42.3, 38.6, 35.6, 34.9, 29.5, 28.1, 25.9, 25.4, 22.8, 22.0, 18.9, 18.7. Anal. calcd for C<sub>10</sub>H<sub>17</sub>NO<sub>3</sub>: C, 60.29, H, 8.60, N, 7.03; found: C, 60.49, H, 8.80, N, 7.10.
  24. (a) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, 10192–10213; (b) Meth-Cohn, O.; Yau, C. C.; Yu, C.-Y. *J. Heterocycl. Chem.* **1999**, 1549–1553; (c) Gershwin, M. E.; Terr, A. *Clin. Rev. Allergy* **1996**, 241–245.
  25. Orjales, A.; Mosquera, R.; Toledo, A.; Pumar, M. C.; Garcia, N.; Cortizo, L.; Labeaga, L.; Innerarity, A. *J. Med. Chem.* **2003**, 5512–5532.