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Synthesis of Densely Substituted Trans-Configured 4-Acylated Piperidine-2,4-diones as 3:1 Adducts of Imines and Ketenes

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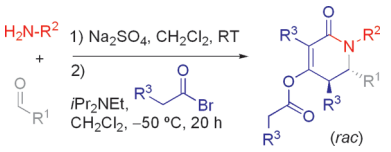
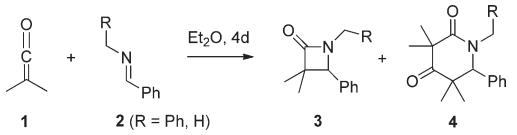


An operationally simple method is described to form densely substituted diastereomerically pure trans-configured and potentially biologically interesting 5,6-dihydropyridone derivatives as 3:1 adducts of ketenes formed in situ from acyl bromides and aromatic imines.

A hundred years ago, Staudinger et al. reported that benzaldehyde derived imines **2** carrying an *N*-Bn or *N*-Me substituent behaved differently from aromatic *N*-aryl imines on treatment with dimethylketene (**1**).[1] In addition to the expected β-lactam[2] products **3** they observed the formation of a product in which two ketene[3] units were incorporated and described them as piperidine-2,4-diones **4** (Scheme 1). Similar 2:1 adducts were also reported by Staudinger for quinoline.[1]

Half a century later reinvestigation by the Tennessee Eastman Company (Martin, Hoyle, and Brannock) revealed that the composition had been misassigned and that the 2:1 adducts are in fact 1,3-oxazin-6-ones **5** (Figure 1).[4] Huisgen later reported the related product with diphenylketene and

SCHEME 1. Proposed Formation of Piperidine-2,4-diones 4 as 2:1 Adducts of Dimethylketene (1) and Imines 2 As Reported by Staudinger



observed that either a β-lactam or the 2:1 adduct can be obtained in excess by variation of the reaction conditions.[5] He concluded that a common 1,4-dipolar intermediate **6** is involved[6] that can either cyclize to form a β-lactam or undergo a cycloaddition with a second ketene molecule.

In contrast to disubstituted ketenes, the parent ketene, prepared in situ from acetyl chloride (**7**, 2 equiv), provided 1,3-oxazin-4-ones **9** (Scheme 2). This was explained by the formation of diketene as the reactive intermediate and catalysis by NEt_3.[7]

During our ongoing investigations into the cycloadditions of ketenes or related reactive species,[8] we observed that acyl bromides preferentially formed diastereomerically pure 3:1 adducts with aromatic imines and that piperidine-2,4-dione products, related to those initially proposed by Staudinger, are apparently intermediates in their formation.[9] As a model system we investigated the reaction of propionyl bromide (**11**) and PMP-protected imine **10a** (PMP = *p*-MeO-C_6H_4). The ratio of 1:1, 2:1, and 3:1 adducts **12a**, **13a**, and **14a** mainly depended on the amounts of **11** and iPr$_2$NEt and the reaction temperature (Table 1).

An excess of propionyl bromide was required to obtain a useful imine conversion. Use of 3 equiv of both **11** and iPr$_2$NEt at −50 °C resulted in only moderate conversion (Table 1, entry 1). The product mixture contained 42% of the known β-lactam **12a**[10] and 58% of piperidine-2,4-dione **13a**, while the 3:1 adduct **14a** was not observed. Increasing the amount of acyl bromide led to improved conversion and the formation of **14a** as the major product (entries 2 and 6). In contrast, at 0 °C β-lactam **12a** was formed with high selectivity and **14a** was detected only in trace amounts (entry 3).

(1) Staudinger, H.; Klever, H. W.; Kober, P. *Annalen* **1910**, *374*, 1.
(2) (a) Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51. (b) Sheehan, J. C.; Corey, E. J. *Org. React.* **1957**, *9*, 388. (c) Mukerjee, A. K.; Singh, A. K. *Tetrahedron* **1978**, *34*, 1731. (d) Review on β-lactams: Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993; pp 295−368.
(3) Comprehensive reviews about ketene chemistry: (a) *Ketenes*; Tidwell, T. T. Wiley: Hoboken, NJ, 2006. (b) Tidwell, T. T. *Eur. J. Org. Chem.* **2006**, 563. (c) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771. (d) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545. (e) Ketene history: Tidwell, T. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5778.
(4) (a) Martin, J. C.; Hoyle, V. A., Jr.; Brannock, K. C. *Tetrahedron Lett.* **1965**, *6*, 3589. (b) Pratt, R. N.; Procter, S. A.; Taylor, G. A. *Chem. Commun.* **1965**, 575. (c) Martin, J. C.; Brannock, K. C.; Burpitt, R. D.; Gott, P. G.; Hoyle, V. A., Jr. *J. Org. Chem.* **1971**, *36*, 2211. (d) Moll, F.; Wieland, H. J. *Arch. Pharm.* **1975**, *308*, 481.
(5) Huisgen, R.; Davis, B. A.; Morikawa, M. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 826.
(6) Cossio, F. P.; Arrieta, A.; Sierra, M. A. *Acc. Chem. Res.* **2008**, *41*, 925.
(7) (a) Maujean, A.; Chuche, J. *Tetrahedron Lett.* **1976**, *17*, 2905. (b) Formation of a piperidine-2,4-dione as side product, using dimeric *tert*-butylcyanoketene: Schaumann, E.; Mrotzek, H. *Chem. Ber.* **1978**, *111*, 661. (c) Daneshtalab, M.; Micetich, R. G.; Forghanifar, S. *Heterocycles* **1988**, *27*, 713.
(8) (a) Tiseni, P. S.; Peters, R. *Chem.—Eur. J.* **2010**, *16*, 2503. (b) Zajac, M.; Peters, R. *Chem.—Eur. J.* **2009**, *15*, 8204. (c) Kull, T.; Peters, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 5461. (d) Tiseni, P. S.; Peters, R. *Org. Lett.* **2008**, *10*, 2019. (e) Kull, T.; Peters, R. *Adv. Synth. Catal.* **2007**, *349*, 1647. (f) Tiseni, P. S.; Peters, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 5325. (g) Zajac, M.; Peters, R. *Org. Lett.* **2007**, *9*, 2007. (h) Koch, F. M.; Peters, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 2685.
(9) The formation of a related 2:1 adduct has been observed as a side product in a β-lactam formation: (a) Fetter, J.; Bertha, F.; Czuppon, T.; Kajtar-Peredy, M.; Konkoly-Thege, M.; Lempert, K. *J. Chem. Res., Synop.* **1995**, *11*, 446. (b) For the formation of a 3:1 adduct as side product in a β-lactam formation at 110 °C in toluene (no yield given) see: Afonso, A.; Rosenblum, S. B.; Puar, M. S.; McPhail, A. T. *Tetrahedron Lett.* **1998**, *39*, 7431.
(10) The trans-configuration of **12a** was assigned by comparison with literature data: Townes, J. A.; Evans, M. A.; Queffelec, J.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2002**, *4*, 2537.

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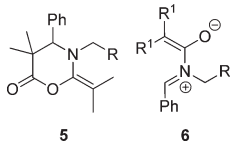
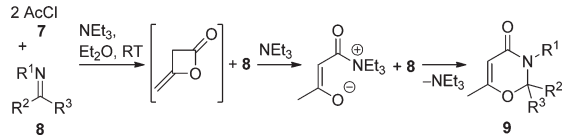


5 **6**

FIGURE 1. Revised structure **5** of the 2:1 adducts obtained by Staudinger and structure of the reactive 1,4-dipolar intermediate **6**.

SCHEME 2. Formation of 1,3-Oxazin-4-ones 9 as 2:1 Adducts of Ketene Prepared in Situ from Acetyl Chloride (7) and Imines 8



With a larger amount of base at −50 °C, the imine reacted completely (entries 7 and 9). The optimized conditions make use of 9 equiv of **11** and 6 equiv of *i*Pr_2NEt, with another 2 equiv of base added after 16 h to fully convert **13a** into **14a**.[11] Reactions at −70 °C resulted in lower conversion and product selectivity was not further improved (entries 5, 8, and 10). No product was detected when **12a** was treated with **11** under the reaction conditions in the absence of imine **10a**.

Various imines provided similar results under the optimized reaction conditions (Table 2). The imines were readily formed by mixing the corresponding aromatic aldehydes **15** and amines **16** and were used directly after filtration (to remove Na_2SO_4) without any further purification. Product **14a** was isolated in 68% yield over two steps (entry 1). Better product selectivity and higher yields were obtained for *N*-PMP-imines derived from benzaldehyde derivatives carrying electron-withdrawing groups like cyanide (entry 2) or chloride (entries 3−5). Ortho-, meta-, and para-substitution patterns were all well-tolerated (entries 3−5). A similar result was also obtained with a *p*-Me group as an example of a σ-donor substituent (entry 6), while a *p*-MeO group as an example of a π-donor-substituent impeded formation of **14g** (entry 7) despite full conversion of the imine. Changing the N substituent to phenyl resulted in slightly better product selectivity (entry 8). In contrast, with nonaromatic N substituents the reaction was found to be problematic. An *i*Pr group still allowed for product formation, albeit in a moderate yield of 46% (entry 9), whereas imines carrying a CH_2R group (*n*-Pr, *n*-Bu, and Bn) gave complex product mixtures but neither products **12** nor **14**. This is surprising given the fact that the initial studies on 2:1 adduct formation with disubstituted ketenes were limited to the use of *N*-CH_2R substituted aromatic imines.[1,2,4,5] The special behavior of acyl bromides is also evident from entry 10: in contrast to acetyl chloride, which formed a masked β-ketoamide protected as an *N*,*O*-acetal (see Scheme 2), acetyl bromide (**17**) still provided δ-lactam **14j** as the major product. Compared to the result with propionyl bromide both selectivity and yield were slightly improved. Furthermore, in CH_2Cl_2 at −50 °C with propionyl chloride only traces of **14a** were detectable. While the previously reported 2:1 adduct formations were performed at room temperature, the studies presented herein were all carried out at considerably lower temperatures, still providing significant product quantities at −70 °C.

The relative configuration of the racemic reaction products is evident from NMR studies (Scheme 3). The slightly puckered ring containing four sp^2-hybridized ring atoms should adopt the typical half-chair conformation. Since there is no significant NOE interaction between the Me group at C5 and the Ph at C6, a cis arrangement of these two substituents can be ruled out. This is confirmed by NOE interactions between H(5) and the Ph substituent at C(6) and H(6) and the Me at C(5). The coupling constants $J_{H(5)/H(6)}$ = ca. 1.2−1.5 Hz for all synthesized derivatives[12] furthermore reveal that both H atoms are in the equatorial position while the substituents at C5 and C6 consequently adopt a trans-diaxial orientation. This is not surprising as there are no severe 1,3-diaxial interactions in the otherwise flat ring.

The different reactivity profile of acyl bromides as a source of a mono- or unsubstituted ketene as compared to disubstituted ketenes may be explained by an enhanced steric accessibility of the nucleophilic enolate C-atom of the ketene/imine adduct **18** favoring the reaction of **18** as a *C*-nucleophile (Scheme 4) while **6** acted as an *O*-nucleophile in the formation of 2:1 adducts. Stepwise reaction with another equivalent of the corresponding ketene rather than cyclization to β-lactam **12** would generate 1,6-dipole **19**. This nucleophilic attack is expected to occur selectively trans to the ketene residue R^3 to minimize repulsive interactions,[3] thus selectively forming the *Z*-configured enolate **19**. Cyclization via a half-chair-like transition state **20** would explain the exclusive formation of trans-isomers which are subsequently *O*-acylated by the third equivalent of a ketene. The different reaction outcome, as compared to the results with acetyl chloride, might be explained by a lower concentration of ketene dimers under the reaction conditions, i.e., at lower temperature and using a less nucleophilic base than NEt_3.

In conclusion, an operationally simple new method was found to form densely substituted diastereomerically pure trans-configured piperidine-2,4-dione derivatives as 3:1 adducts of monosubstituted ketenes, formed in situ from acyl bromides and aromatic imines. Closely related heterocycles have recently been actively investigated because of their interesting biological properties.[13] Moreover, related heterocycles, which have often been plagued by laborious multistep syntheses in the past, have been found to be useful intermediates in a number of syntheses.[14] Our results nicely complement the previously reported methods to form 2:1 adducts possessing different ring atom patterns and might provide further impetus in the search for new physiologically active dihydropyridones.

Experimental Section

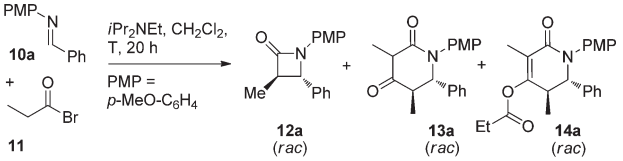
General Procedure for the Formation of 4-Acylated Piperidine-2,4-diones 14. To a stirred solution of the corresponding aldehyde

(11) Starting directly with 8 equiv of base, **13a** was not completely transformed into **14a** and results very similar to entries 7 and 8 in Table 1 were obtained.

(12) Related monocyclic 5,6-dihydropyridones with a cis-configuration show coupling constants $J_{H(5)/H(6)}$ of ca. 4−6 Hz, while the corresponding trans-isomer gave singlets for H(6) (Ph substituent at C(6), Me at C(5)): Bennett, D. M.; Okamoto, I.; Danheiser, R. L. *Org. Lett.* **1999**, *1*, 641.

(13) Selected examples: (a) Treatment of hepatitis C virus infections: Ellis, D.; Li, L.; Tran, C. V.; Ruebsam, F.; Zhou, Y. *U.S. Pat. Appl. Publ.*, US 2009062263, 2009. (b) Hypoglycemic activity: Xie, Y.; Raffo, A.; Ichise, M.; Deng, S.; Harris, P. E.; Landry, D. W. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5111. (c) Metabolism of strychnine: Mishima, M.; Tanimoto, Y.; Oguri, K.; Yoshimura, H. *Drug Metab. Dispos.* **1985**, *13*, 716.

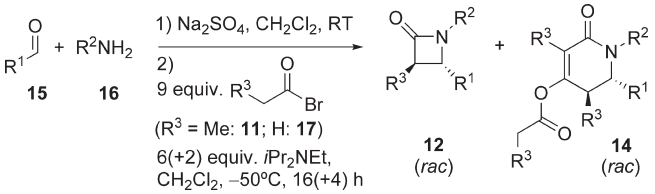
TABLE 1. Optimization of the Synthesis of 3:1 Adduct 14a



entry no.	equiv of **11**	equiv of iPr$_2$NEt	T (°C)	conv of **10a** (%)[a]	**12a**:**13a**:**14a** ratio[a]
1	3	3	−50	38	42/58/00
2	6	3	−50	65	22/10/68
3	6	3	0	100[b]	93/00/07
4	6	4.5	−50	90	15/27/58
5	6	3	−70	40	10/12/78
6	9	3	−50	70	27/00/73
7	9	6	−50	100	11/23/66
8	9	6	−70	78	08/24/68
9	9	6 (+2[c])	−50	100	16/00/84
10	10	6 (+2[c])	−70	100	20/23/57

[a]Determined by ^{1}H NMR. [b]Reaction time 1 h. [c]Added after 16 h.

TABLE 2. Investigation of Scope and Limitations for the Synthesis of Trans-Configured 4-Acylated Piperidine-2,4-diones 14



entry no.	R^1	R^2	R^3	conv (%)[a]	**12**:**14** ratio[a]	yield of **14** (%)[b]	dr[a] of **14**
1	Ph	p-MeOC$_6$H$_4$	Me	100	16:84	**14a**: 68	>98:2
2	p-NCC$_6$H$_4$	p-MeOC$_6$H$_4$	Me	100	06:94	**14b**: 82	>98:2
3	p-ClC$_6$H$_4$	p-MeOC$_6$H$_4$	Me	100	08:92	**14c**: 76	>98:2
4	o-ClC$_6$H$_4$	p-MeOC$_6$H$_4$	Me	100	12:88	**14d**: 80	>98:2
5	m-ClC$_6$H$_4$	p-MeOC$_6$H$_4$	Me	100	11:89	**14e**: 74	>98:2
6	p-MeC$_6$H$_4$	p-MeOC$_6$H$_4$	Me	100	10:90	**14f**: 65	>98:2
7	p-MeOC$_6$H$_4$	p-MeOC$_6$H$_4$	Me	100		**14g**: −[c]	−
8	Ph	Ph	Me	100	10:90	**14h**: 70	>98:2
9	Ph	iPr	Me	100	12:88	**14i**: 46	>98:2
10	Ph	p-MeOC$_6$H$_4$	H	100	10:90	**14j**: 77	>98:2

[a]Determined by ^{1}H NMR. [b]Yield of isolated product over 2 steps after column chromatography. [c]A complex mixture was formed.

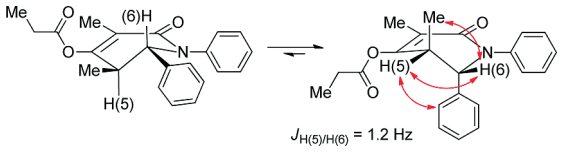
15 (0.50 mmol) and amine **16** (0.50 mmol) in CH_2Cl_2 (4 mL) was added anhydrous sodium sulfate. After the reaction mixture was stirred for 4 h at room temperature, the solution was filtered and the solvent was subsequently removed in vacuo. Anhydrous CH_2Cl_2 (2 mL) was added and the mixture was cooled to −50 °C. The corresponding acyl bromide (4.5 mmol) and diisopropylethylamine (496.1 μL, 3.00 mmol) were successively added at −50 °C. After the reaction mixture was stirred for 16 h at −50 °C, more diisopropylethylamine (165.4 μL, 1.00 mmol) was added. The mixture was stirred for an additional 4 h, poured into aqueous 1 M HCl (10 mL), and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried over $MgSO_4$ and filtered and the solvent was removed in vacuo. The crude product mixtures were purified by flash chromatography.

***trans*-3,5-Dimethyl-1-(4-methoxyphenyl)-6-phenyl-4-propionyloxy-5,6-dihydro-1*H*-pyridin-2-one (14a):** yield 68%, colorless oil, EtOAc/petroleum ether 1:2; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ 7.29−7.16 (m, 5H), 7.00 (d, J = 9.0 Hz, 2H), 6.73 (d, J = 9.0 Hz, 2H), 4.54 (d, J = 1.5 Hz, 1H), 3.67 (m, 3H), 2.70 (br q, J = 6.9 Hz, 1H), 2.35 (q, J = 7.5 Hz, 2H), 1.74 (d, J = 0.9 Hz, 3H), 1.40 (d, J = 6.9 Hz, 3 H), 1.09 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ 170.8, 165.2, 157.9, 155.9, 140.4, 135.3, 128.5, 127.7, 127.5, 126.5, 118.9, 114.2, 68.8, 55.4, 40.7, 27.4, 18.6, 10.2, 9.0; IR (neat) ν 2932, 1760, 1643, 1509, 1240, 1135, 1061, 699; HRMS (EI) m/z calcd for $C_{23}H_{25}NO_4$ 379.1784, found 379.1763.

***trans*-3,5-Dimethyl-6-(4-cyanophenyl)-1-(4-methoxyphenyl)-4-propionyloxy-5,6-dihydro-1*H*-pyridin-2-one (14b):** yield 82%,

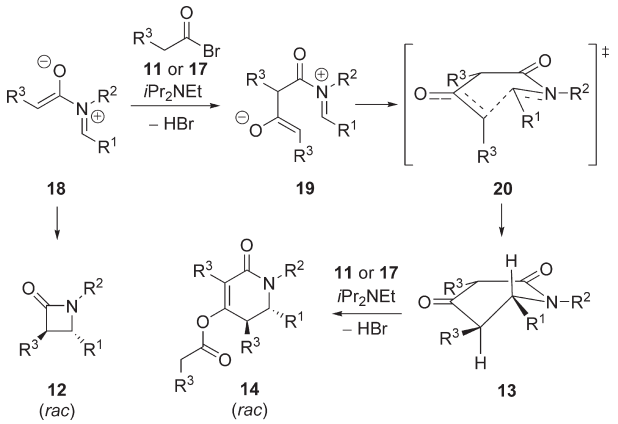
(14) Selected examples: (a) Padwa, A.; Danca, M. D. *Org. Lett.* **2002**, *4*, 715. (b) Padwa, A.; Danca, M. D.; Hardcastle, K. I.; McClure, M. S. *J. Org. Chem.* **2003**, *68*, 929. (c) Sasaki, Y.; Niida, A.; Tsuji, T.; Shigenaga, A.; Fujii, N.; Otaka, A. *J. Org. Chem.* **2006**, *71*, 4969. (d) Sasaki, Y.; Niida, A.; Tsuji, T.; Fujii, N.; Otaka, A. *Pept. Sci.* **2006**, *42*, 89. (e) Menichincheri, M.; Bargiotti, A.; Berthelsen, J.; Bertrand, J. A.; Bossi, R.; Ciavolella, A.; Cirla, A.; Cristiani, C.; Croci, V.; D'Alessio, R.; Fasolini, M.; Fiorentini, F.; Forte, B.; Isacchi, A.; Martina, K.; Molinari, A.; Montagnoli, A.; Orsini, P.; Orzi, F.; Pesenti, E.; Pezzetta, D.; Pillan, A.; Poggesi, I.; Roletto, F.; Scolaro, A.; Tato, M.; Tibolla, M.; Valsasina, B.; Varasi, M.; Volpi, D.; Santocanale, C.; Vanotti, E. *J. Med. Chem.* **2009**, *52*, 293. (f) Chaloin, O.; Cabart, F.; Marin, J.; Zhang, H.; Guichard, G.; Shibasaki, M.; Mihara, H. *Org. Synth.* **2008**, *85*, 147. (g) Kim, D.-I.; Deutsch, H. M.; Ye, X.; Schweri, M. M. *J. Med. Chem.* **2007**, *50*, 2718. (h) Marin, J.; Didierjean, C.; Aubry, A.; Casimir, J.-R.; Briand, J.-P.; Guichard, G. *J. Org. Chem.* **2004**, *69*, 130. (i) Lee, Y.-g.; McGee, K. F., Jr.; Chen, J.; Rucando, D.; Sieburth, S. *J. Org. Chem.* **2000**, *65*, 6676. (j) Padwa, A.; Coats, S. J.; Harring, S. R.; Hadjiarapoglou, L.; Semones, M. A. *Synthesis* **1995**, 973. (k) Rohloff, J. C.; Dyson, N. H.; Gardner, J. O.; Alfredson, T. V.; Sparacino, M. L.; Robinson, J., III *J. Org. Chem.* **1993**, *58*, 1935. (l) Akiba, K.; Nakatani, M.; Wada, M.; Yamamoto, Y. *J. Org. Chem.* **1985**, *50*, 63.

SCHEME 3. Determination of the Relative Configuration and the Preferred Trans-Diaxial Conformation by NOE Studies of 14h[a]



[a]Relevant NOE interactions are indicated by the red arrows.

SCHEME 4. Mechanistic Rationale for the Formation of Trans-Configured 4-Acylated Piperidine-2,4-diones 14



colorless oil, EtOAc/petroleum ether 1:2); ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ 7.63 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H), 7.82 (d, J = 9.0 Hz, 2H), 4.67 (d, J = 1.2 Hz, 1H), 3.75 (m, 3H), 2.76 (br q, J = 6.9 Hz, 1H), 2.43 (q, J = 7.5 Hz, 2H), 1.81 (d, J = 1.2 Hz, 3H), 1.50 (d, J = 6.9 Hz, 3 H), 1.15 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ 171.1, 164.8, 158.2, 155.8, 145.8, 134.7, 132.4, 127.4, 127.4, 119.2, 118.5, 114.4, 111.9, 68.4, 55.4, 40.1, 27.4, 18.7, 10.0, 8.9; IR (neat) ν 2975, 2228, 1760, 1642, 1509, 1243, 1122, 1091, 728; HRMS (EI) m/z calcd for $C_{24}H_{24}N_2O_4Na$ 427.1634, found 427.1637.

***trans*-3,5-Dimethyl-6-(4-chlorophenyl)-1-(4-methoxyphenyl)-4-propionyloxy-5,6-dihydro-1*H*-pyridin-2-one (14c):** yield 76%, colorless oil, EtOAc/petroleum ether 1:2; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ 7.30 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 9.0 Hz, 2H), 6.81 (d, J = 9.0 Hz, 2H), 4.58 (d, J = 1.5 Hz, 1H), 3.75 (m, 3H), 2.74 (br q, J = 6.9 Hz, 1H), 2.44 (q, J = 7.5 Hz, 2H), 1.81 (d, J = 0.6 Hz, 3H), 1.47 (d, J = 6.9 Hz, 3 H), 1.17 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ 171.0, 165.0, 158.0, 155.9, 140.0, 135.0, 133.6, 128.7, 127.9, 127.5, 118.9, 114.2, 68.3, 55.3, 40.4, 27.4, 18.6, 10.1, 9.0; IR (neat) ν 2976, 1760, 1643, 1509, 1243, 1125, 1090, 830; HRMS (EI) m/z calcd for $C_{23}H_{24}ClNO_4Na$ 436.1292, found 436.1286.

***trans*-3,5-Dimethyl-6-(2-chlorophenyl)-1-(4-methoxyphenyl)-4-propionyloxy-5,6-dihydro-1*H*-pyridin-2-one (14d):** yield 80%, colorless oil, EtOAc/petroleum ether 1:3; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ 7.33−7.00 (m, 5H), 7.01 (d, J = 9.0 Hz, 2H), 6.74 (d, J = 9.0 Hz, 2H), 4.96 (d, J = 1.2 Hz, 1H), 3.68 (m, 3H), 2.71 (br q, J = 6.9 Hz, 1H), 2.34 (q, J = 7.5 Hz, 2H), 1.74 (d, J = 0.6 Hz, 3H), 1.45 (d, J = 6.9 Hz, 3 H), 1.07 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C δ 170.9, 165.6, 158.0, 156.0, 137.2, 135.2, 132.1, 130.1, 129.0, 127.9, 127.2, 126.8, 118.7, 114.3, 65.4, 55.3, 38.5, 27.4, 18.2, 10.1, 9.0; IR (neat) ν 2943, 1754, 1645, 1509, 1239, 1125, 1079, 760; HRMS (ESI) m/z calcd for $C_{23}H_{25}ClNO_4$ 414.1472, found 414.1471.

***trans*-3,5-Dimethyl-6-(3-chlorophenyl)-1-(4-methoxyphenyl)-4-propionyloxy-5,6-dihydro-1*H*-pyridin-2-one (14e):** yield 74%, colorless oil, EtOAc/petroleum ether 1:3; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ 7.30−6.96 (m, 5H), 6.98 (d, J = 9.0 Hz, 2H), 6.74 (d, J = 9.0 Hz, 2H), 4.51 (d, J = 1.2 Hz, 1H), 3.68 (m, 3H), 2.67 (br q, J = 6.9 Hz, 1H), 2.36 (q, J = 7.5 Hz, 2H), 1.74 (d, J = 0.9 Hz, 3H), 1.41 (d, J = 6.9 Hz, 3 H), 1.10 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ 170.8, 165.0, 158.0, 155.7, 142.5, 134.9, 134.4, 129.8, 128.0, 127.5, 126.8, 124.7, 119.0, 114.3, 68.3, 55.3, 40.4, 27.4, 18.6, 10.1, 9.0; IR (neat) ν 2975, 1760, 1642, 1509, 1243, 1124, 1092, 829; HRMS (ESI) m/z calcd for $C_{23}H_{25}ClNO_4$ 414.1472, found 414.1465.

***trans*-3,5-Dimethyl-1-(4-methoxyphenyl)-6-(4-methylphenyl)-4-propionyloxy-5,6-dihydro-1*H*-pyridin-2-one (14f):** yield 65%, colorless oil, EtOAc/petroleum ether 1:2); ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ 7.13 (m, 4H), 7.06 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 4.58 (d, J = 1.5 Hz, 1H), 3.75 (m, 3H), 2.75 (br q, J = 6.9 Hz, 1H), 2.43 (q, J = 7.5 Hz, 2H), 2.33 (s, 3H), 1.81 (d, J = 0.9 Hz, 3H), 1.46 (d, J = 6.9 Hz, 3 H), 1.17 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ 170.9, 165.2, 157.9, 155.9, 137.5, 137.4, 135.4, 129.2, 127.5, 126.4, 118.9, 114.2, 68.6, 55.4, 40.8, 27.4, 21.1, 18.6, 10.2, 9.0; IR (neat) ν 2929, 1761, 1642, 1509, 1242, 1123, 1091, 830; HRMS (EI) m/z calcd for $C_{24}H_{27}NO_4$ 393.1940, found 393.1940.

***trans*-3,5-Dimethyl-1,6-diphenyl-4-propionyloxy-5,6-dihydro-1*H*-pyridin-2-one (14h):** yield 70% colorless oil, EtOAc/petroleum ether 1:4; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ 7.27−7.08 (m, 5H), 4.62 (d, J = 1.2 Hz, 1H), 2.73 (br q, J = 6.9 Hz, 1H), 2.35 (q, J = 7.5 Hz, 2H), 1.74 (d, J = 1.2 Hz, 3H), 1.41 (d, J = 6.9 Hz, 3 H), 1.09 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ 170.8, 165.1, 156.0, 142.5, 140.4, 128.9, 128.5, 127.7, 126.4, 126.1, 119.0, 68.4, 40.9, 27.4, 18.5, 10.1, 9.0; IR (neat) ν 2975, 1761, 1644, 1122, 1093, 758, 694; HRMS (EI) m/z calcd for $C_{22}H_{23}NO_3Na$ 372.1576, found 372.1578.

***trans*-3,5-Dimethyl-1-isopropyl-6-phenyl-4-propionyl-oxy-5,6-dihydro-1*H*-pyridin-2-one (14i):** yield 46%, colorless oil, EtOAc/petroleum ether 1:4 (difficult purification); ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ 7.26−7.08 (m, 5H), 4.85 (hept, J = 6.9 Hz, 1H), 4.28 (br s, 1H), 2.50 (br q, J = 6.9 Hz, 1H), 2.28 (q, J = 7.5 Hz, 2H), 1.7 (d, J = 0.6 Hz, 3H), 1.25 (d, J = 6.9 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 1.04 (t, J = 6.9 Hz, 3H), 0.77 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ 170.8, 165.0, 154.4, 142.0, 128.2, 127.3, 126.1, 119.0, 59.5, 44.9, 40.8, 27.4, 20.5, 20.0, 19.9, 18.5, 18.6, 10.2, 9.0; IR (neat) ν 2975, 1761, 1626, 1434, 1114, 700; HRMS (ESI) m/z calcd for $C_{19}H_{25}NO_3Na$ 338.1732, found 338.1727.

4-Acetyloxy-1-(4-methoxyphenyl)-6-phenyl-5,6-dihydro-1*H*-pyridin-2-one (14j): yield 77%, colorless oil, EtOAc/petroleum ether 1:2); ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ 7.27−7.18 (m, 5H), 7.00 (d, J = 9.0 Hz, 2H), 6.71 (d, J = 9.0 Hz, 2H), 6.00 (d, J = 2.4 Hz, 1H), 4.97 (dd, J = 7.2, 2.7 Hz, 1H), 3.66 (m, 3H), 3.49 (ddd, J = 17.2, 7.2, 2.1 Hz, 1H), 2.57 (dd, J = 17.2, 3.0 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ 167.4, 164.8, 157.9, 157.1, 140.2, 134.2, 128.7, 127.9, 127.5, 126.6, 114.1, 111.6, 62.0, 55.3, 35.9, 21.0;IR (neat) ν 2934, 1765, 1634, 1509, 1242, 1180, 1128, 1030, 830, 699; HRMS (ESI) m/z calcd for $C_{20}H_{19}NO_4Na$ 360.1212, found 360.1192.

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Supporting Information Available: General experimental information and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.