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# One pot solid phase synthesis of 2-substituted 2,3-dihydropyridin-4(1*H*)-ones on Rinkamide-resin

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**Abstract**—A novel solid phase synthesis of 2-substituted 2,3-dihydropyridin-4(1*H*)-ones using Rinkamide-polystyrene-resin is described. The key step involves a hetero-Diels–Alder reaction of Danishefsky's diene with solid phase bound imines, which was carefully optimized. Using this method even ketones are transformed into 2,2-disubstituted dihydropyridones.


## 1. Introduction

Many natural and synthetic compounds with biological activity possess a basic centre in the form of a nitrogen containing heterocycle. Among these heterocycles the piperidine ring is of particular interest for drugs like biperidene, pethidine, haloperidol, dexoxadrol or etoxadrol.[1] Our interest has been focused on the development of a novel method, which provides straightforward access to 2-substituted piperidine precursors. In the process of drug development and/or lead structure optimization it is most welcome to use a method, which allows easy access to diverse compounds. In this article, we present a novel one pot solid phase procedure that can be conducted in parallel form.

Our particular interest was the solid phase synthesis of N-unsubstituted piperidine derivatives from carbonyl compounds (aldehydes, ketones; Fig. 1). In the literature, several methods for the synthesis of 2-substituted piperidine derivatives are described.[2–4] In the liquid phase, these piperidines are accessible by reaction of aldehydes and amines with methyl 4-nitrobutyrate to yield 1,6-disubstituted 5-nitropiperidin-2-ones (path A).[2] This reaction is usually performed in polar protic solvents like EtOH, which is a drawback for the application on solid phase since swelling properties of mostly used polystyrene resins in polar protic solvents are poor. Additionally acidic reaction conditions are necessary which limit the choice of the linker.

In another method, carbonyl compounds are reacted with the Wittig reagent 4-(4-methylphenylsulfonyl)-1-triphenylphosphoranylidene-butan-2-one and subsequently with amines to yield 1,2-disubstituted piperidin-4-ones in a stepwise conjugate addition/β-elimination/conjugate addition (path B).[3] This concept allows parallel synthesis by replacement of the amine component by an amine functionalized resin. As a consequence a variety of α,β-unsaturated ketones has to be synthesized in solution, employing various aldehydes as diversity element. The resin bound amine then functions as a scavenger. Alternatively the Wittig-reagent was bound to the solid phase. Subsequent derivatization with aldehydes followed by a cyclization-cleavage with amines delivers N-substituted piperidin-4-ones.[3b]

In a third approach, the hetero-Diels–Alder (=HDA) reaction[4] of imines with activated dienes like Danishefsky's diene[5] led to 1,2-disubstituted 2,3-dihydroypridin-4(1*H*)-ones (path C). This type of reaction has previously been performed on solid phase,[6] yielding only N-substituted piperidine derivatives with aryl residues in position 2, thus limiting the diversity of the substituents in this position.

There is only one solid phase method, that leads to N-unsubstituted 2,3-dihydropyridin-4(1*H*)-ones. In this method, polymer bound pyridinium salts are used instead of a HDA-reaction.[7] The key step of this strategy is the addition of Grignard reagents to these pyridinium salts. However, according to this strategy 2,2-disubstituted

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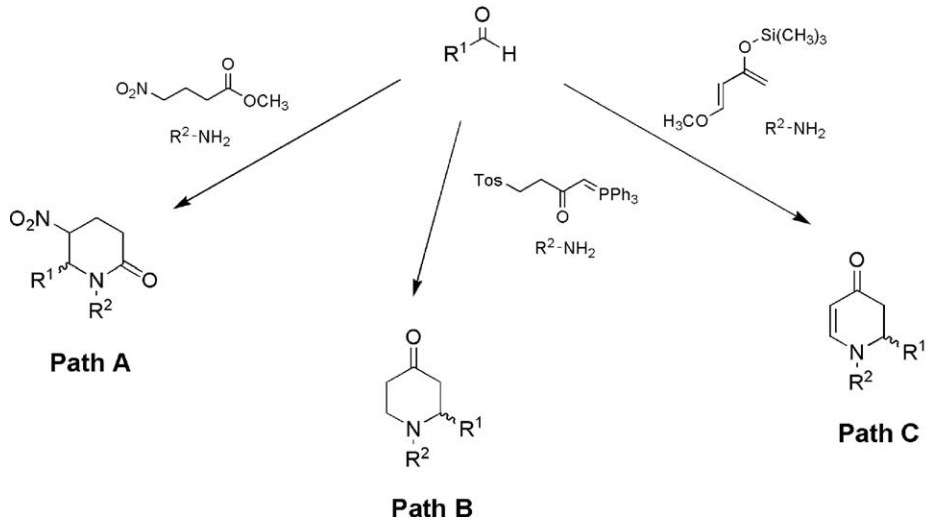



**Figure 1.**

piperidines or piperidines containing heteroatoms in the 2-substituent are not accessible.

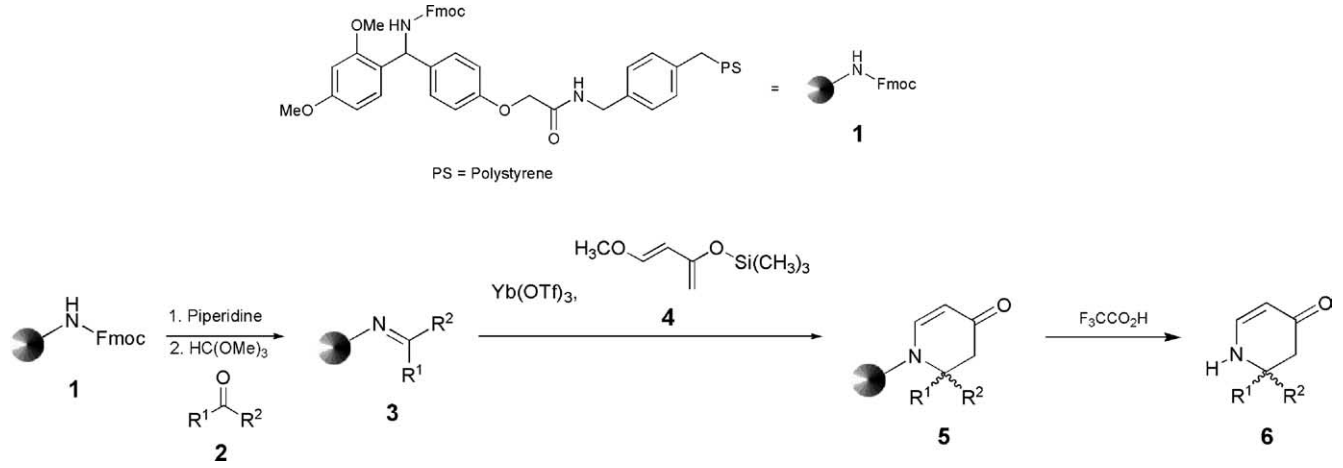
Thus, we decided to extend the HDA-concept to a new solid phase synthesis method to obtain N-unsubstituted pyridine derivatives with highly diverse 2-substituents including 2,2-disubstituion and heteroatom containing residues (e.g., ester, 2-bromophenyl).

As outlined in Scheme 1, Fmoc-protected Rinkamide-Resin **1** was used as amine component and therefore as N-donor. Deprotection with piperidine followed by condensation with various carbonyl compounds **2** using trimethyl orthoformate[8] led to the polymer bound imines **3**. Lewis acid catalyzed HDA-reaction with Danishefsky's-diene **4** provided the solid phase bound 2-substituted pyridones **5**. Finally, cleavage with trifluoroacetic acid yielded the N-unsubstituted 2,3-dihydropyridin-4(1*H*)-ones **6**.

In solution yields and diastereoselectivity of the HDA reaction (if chiral carbonyl compounds are used) are strongly dependent on the temperature and the solvent.[9] Additionally the kind of Lewis acid effects product yields. However, there are several reports showing ytterbium triflate $Yb(OTf)_3$ to be the most appropriate soluble catalyst.[6b,10] Therefore, the Lewis acid catalyst was not varied in our studies. A wide range of apolar as well as polar protic and aprotic solvents, including $CH_2Cl_2$,[11,12] THF,[10a,13] $CH_3CN$,[10b,14] MeOH[15] and even $H_2O$[16] has been used successfully. In most cases, the HDA-reaction has been performed at room temperature.[10,11b,15,16] However, performing the HDA-reaction at lower temperature has a positive effect on both diastereoselectivity and yield in solution.[9,11a,12–14]

On the other side, there are only few examples of the HDA-reaction on solid phase. These examples were always performed on polystyrene resins in THF, whereas the temperature varied from −60 °C to room temperature[6b] to +60 °C.[6a]

Obviously the HDA-reaction is the yield limiting step in this four step piperidine precursor synthesis. Therefore, we decided to optimize reaction conditions of the HDA-reaction. In particular, the solvent and the reaction temperature should be optimized. The optimized reaction




**Scheme 1.**

conditions then were applied to the synthesis of a small library.

## 2. Investigation of the solvent

In solid phase chemistry, THF is usually employed as solvent for the HDA-reaction with Danishefsky's diene **4**. However, it is described that in solution polar (protic) solvents (e.g. $CH_3OH$, $CH_3CN$) can increase yields in HDA-reactions, presumably by imine activation via hydrogen bonds[13,17] or by stabilization of a zwitterionic transition state, indicating that a nonconcerted stepwise Mannich–Michael reaction mechanism is operative.[10b,11a] According to poor swelling properties of polystyrene resins in polar (protic) solvents, THF/MeOH and THF/$CH_3CN$ mixtures (1:1) were used within the solvent effect examination. Additionally, pure DMF and a DMF/$CH_3CN$ mixture (1:1) were investigated (see Table 1).

Four different aldehydes were used, providing solid phase bound imines **3** differing in their reactivity in the HDA-reaction. At room temperature the resin bound imine **3** was preswelled in the dry solvent, the imine was activated by addition of 0.2 equiv of $Yb(OTf)_3$ and after 15 min, 5 equiv of freshly synthesized[18] Danishefsky's diene **4** were added and the mixture was agitated overnight at room temperature. The success of the HDA-reactions was evaluated by the product yields after $F_3CCO_2H$ cleavage and flash chromatographic isolation. The results are shown in Table 1.

In all cases, the highest yields of **6** were obtained by performing the HDA-reaction in dry THF (entries 1, 6, 11 and 16). As a rule, increasing the solvent polarity decreases yields of **6**. Sterically demanding imines (e.g., **3b**, **3c**) led to reduced yields. Efficient Lewis acid imine activation seems to be crucial for high yields of dihydropyridones **6**. Using the Lewis basic solvent DMF, binding of the Lewis acid $Yb(OTf)_3$ resulted in very low yields of dihydropyridones **6** (entries 5, 10, 15 and 20).

**Table 1.** Influence of the solvent on the yields of **6**

| Entry | $R^1$ | $R^2$ | Product | Solvent | Yield [%][a] |
|---|---|---|---|---|---|
| 1 | *i*Pr | H | **6a** | THF | 43 |
| 2 | | | **6a** | THF/MeOH=1:1 | 10 |
| 3 | | | **6a** | THF/$CH_3CN$=1:1 | 21 |
| 4 | | | **6a** | DMF/$CH_3CN$=1:1 | 26 |
| 5 | | | **6a** | DMF | 16 |
| 6 | Cy | H | **6b** | THF | 36 |
| 7 | | | **6b** | THF/MeOH=1:1 | 31 |
| 8 | | | **6b** | THF/$CH_3CN$=1:1 | 25 |
| 9 | | | **6b** | DMF/$CH_3CN$=1:1 | 17 |
| 10 | | | **6b** | DMF | 8 |
| 11 | *t*Bu | H | **6c** | THF | 25 |
| 12 | | | **6c** | THF/MeOH=1:1 | 0 |
| 13 | | | **6c** | THF/$CH_3CN$=1:1 | 0 |
| 14 | | | **6c** | DMF/$CH_3CN$=1:1 | 0 |
| 15 | | | **6c** | DMF | 0 |
| 16 | Ph | H | **6d** | THF | 58 |
| 17 | | | **6d** | THF/MeOH=1:1 | 17 |
| 18 | | | **6d** | THF/$CH_3CN$=1:1 | 37 |
| 19 | | | **6d** | DMF/$CH_3CN$=1:1 | 24 |
| 20 | | | **6d** | DMF | 9 |

[a] Yields are given after FC-purification and are related to pure products.

## 3. Investigation of temperature effects

After optimization of the solvent (THF) the influence of the temperature on the HDA-reaction was investigated. For this purpose the HDA-reaction was performed at 50, −10, and 0–25 °C. In the last case temperature was held at 0 °C for 4 h, then the reaction mixture was allowed to reach 25 °C overnight. All other reaction parameters were not altered.

The results in Table 2 demonstrate that the highest yields of dihydropyridones **6** were obtained by using the temperature gradient from 0 to 25 °C. However, temperature variation seems to be less important for the aromatic benzaldehyde imine **3d** (entries 13 and 15). Performing the HDA-reaction with sterically less demanding aliphatic aldehyde imines **3a** and **3b** at various temperatures (−10, 25, 50 °C) had only little influence on the dihydropyridone yields (entries 1–3 and 5–7). However, the temperature gradient led to a considerable improvement of product yields (entries 4 and 8).

**Table 2.** Influence of the temperature on the yields of **6**

| Entry | $R^1$ | $R^2$ | Product | Temp. [°C] | Yield [%][a] |
|---|---|---|---|---|---|
| 1 | *i*Pr | H | **6a** | 50 | 36 |
| 2 | | | **6a** | 25 | 43 |
| 3 | | | **6a** | −10 | 33 |
| 4 | | | **6a** | 0–25 | 55 |
| 5 | Cy | H | **6b** | 50 | 34 |
| 6 | | | **6b** | 25 | 36 |
| 7 | | | **6b** | −10 | 42 |
| 8 | | | **6b** | 0–25 | 74 |
| 9 | *t*Bu | H | **6c** | 50 | 0 |
| 10 | | | **6c** | 25 | 25 |
| 11 | | | **6c** | −10 | 42 |
| 12 | | | **6c** | 0–25 | 46 |
| 13 | Ph | H | **6d** | 50 | 69 |
| 14 | | | **6d** | 25 | 58 |
| 15 | | | **6d** | −10 | 71 |
| 16 | | | **6d** | 0–25 | 71 |

[a] Yields are given after FC-purification and are related to pure products.

In contrary to these results the yields of **6c** resulting from the HDA-reaction of the sterically demanding pivalaldehyde imine **3c** strongly depended on the reaction temperature (entries 9–12). Decreasing the temperature increased yields, and the temperature gradient represented optimal reaction conditions. Thus, even products which are difficult to obtain at room temperature were synthesized in satisfactory yields by the temperature gradient.

Obviously at higher temperatures side reactions seem to be faster than the HDA-reaction. They can be suppressed by using lower temperatures at the beginning of the reaction. In order to drive the reaction to completion, the temperature has to be raised to 25 °C.

## 4. Scope and limitations

Next, the optimized reaction conditions were applied to the synthesis of a small dihydropyridone **6** library. The imines **3** were formed by condensation of deprotected **1** with a series of aliphatic, aromatic and heteroaromatic aldehydes as well

**Table 3.** Scope and limitations of the solid phase synthesis of dihydropyridones **6**

| Entry | $R^1$ | $R^2$ | Product | Yield [%][a] |
|---|---|---|---|---|
| 1 | *i*Pr | H | **6a** | 61±5 ($n$=3)[b] |
| 2 | Cy | H | **6b** | 68±5 ($n$=3)[b] |
| 3 | *t*Bu | H | **6c** | 46±8 ($n$=3)[b] |
| 4 | *n*Bu | H | **6e** | 34 |
| 5 | *i*Bu | H | **6f** | 59 |
| 6 | Ph | H | **6d** | 52 |
| 7 | 4-$NO_2$–Ph | H | **6g** | 67 |
| 8 | 2-Br–Ph | H | **6h** | 63 |
| 9 | Furan-2-yl | H | **6i** | 26 |
| 10 | Thiophen-2-yl | H | **6k** | 30 |
| 11 | Pyridin-2-yl | H | **6l** | 40 |
| 12 | Me | $CO_2Et$ | **6m** | 33 |

[a] Yields are given after FC-purification and are related to pure products.
[b] Average yields±standard deviation of three independent experiments.

as a ketone. Reactions with the aliphatic aldehydes used for the solvent- and temperature optimizing were repeated twice ($n$=3) to prove reproducibility of the transformation. The results are summarized in Table 3.

All kinds of aldehydes **2a**–**2l** and even the ketone ethyl pyruvate **2m** reacted to afford the desired 2-substituted dihydropyridones **6a**–**m** in good yields.

In the case of aromatic aldehydes, electron withdrawing aryl substituents seem to be favorable to high product yields (entries 7 and 8). This observation is confirmed by low yields that were obtained after the reaction of electron rich heteroaromatic carbaldehydes **2i** and **2k** (entries 9 and 10). The product **6m** resulting from the ketone ethyl pyruvate (**2m**, entry 12) is of particular interest, since two substituents are introduced in position 2 of the dihydropyridone moiety. To the best of our knowledge this is the first solid phase method for the synthesis of 2,2-disubstituted dihydropyridones from ketones.

## 5. Conclusion

We have developed a new solid phase method for the parallel synthesis of 2-substituted 2,3-dihydropyridin-4(1*H*)-ones **6**. Reaction conditions for the key step, that is, Lewis acid catalyzed HDA-reaction, were optimized to obtain the desired products in up to 68% overall yield (entry 2, Table 3), which implies an average yield of 91% for each of the four reaction steps. The chosen reaction sequence is applicable to all kinds of aldehydes. Even activated ketones reacted to yield disubstituted products, which were not accessible by other known methods. The novel strategy allows the introduction of additional functional groups in position 2, thus offering the possibility to access diverse structures. All described compounds were isolated by flash chromatography and are analytically pure.

## 6. Experimental

### 6.1. General

Thin layer chromatography (TLC): silica gel 60 $F_{254}$ plates (Merck). Flash chromatography (FC):[19] Silica gel 60, 40–63 μm (Merck). MS: MAT GCQ (Thermo-Finnigan); EI=electron impact. Gas chromatography-high resolution MS (GC-HRMS): GCT (Waters-Micromass, Manchester, UK); EI=electron impact. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). $^1$H NMR (400 MHz), $^{13}$C NMR (100 MHz): Unity Mercury Plus 400 NMR spectrometer (Varian); $\delta$ in ppm related to tetramethylsilane, coupling constants are given with 0.5 Hz resolution; the assignments of $^{13}$C and $^1$H NMR signals were supported by 2D NMR techniques.

All dihydropyridone syntheses were performed in parallel on a 24-position Bohdan-MiniBlock (Mettler-Toledo). Temperature was controlled with a FP40-MV refrigerated circulator (Julabo). All solvents used were dried using standard procedures.

THF was dried over sodium and freshly distilled before use. Fmoc-Rinkamide-polystyrene-resin was purchased from Fluka and stored under $N_2$ at 4 °C. $Yb(OTf)_3$ (Aldrich) was stored in a desiccator over $P_2O_5$ in vacuo at room temperature. Danishefsky's diene **4** was stored under $N_2$ at −25 °C.

**6.1.1. *trans*-1-Methoxy-3-trimethylsilyloxy-1,3-butadiene (=Danishefsky's diene) (4).** Modified according to Ref. 20. Anhydrous LiBr (4.32 g, 49.8 mmol) was given to a 100 mL-Schlenk-flask, which was immediately sealed by a rubber septum, flushed with $N_2$ and heated to approx. 400 °C with a heat gun. The flask was allowed to cool down to room temperature under gentle $N_2$-flow, then 25 mL of dry THF were added. It was stirred until all LiBr was completely dissolved. Afterwards the mixture was cooled to −15 °C, 4.72 mL chlorotrimethylsilane (37.3 mmol) and 2.50 mL *trans*-4-methoxy-but-3-en-2-on (24.9 mmol) were added gradually and the mixture was stirred for 15 min. Then 5.18 mL triethylamine (37.3 mmol) were added directly into the solution, it was stirred at −15 °C for 1 h and another 24 h at 40 °C. After that the reaction mixture was transferred with 30 mL of cold (4 °C) pentane into a separating funnel loaded with 15 g ice, 15 mL cold saturated $NaHCO_3$, 15 mL cold brine and another 30 mL cold pentane (4 °C each). The organic layer was separated and the aqueous layer was extracted twice with 30 mL cold pentane. The combined organic layers were washed with 15 mL cold brine and five times with 15 mL cold water and dried over anhydrous $MgSO_4$. It was filtered, concentrated (400 mbar; 40 °C) and the resulting brownish oil was distilled in vacuo over a 10 cm-vigreux-column to yield 3.19 g (74%) of a clear colourless liquid, $bp._{10}$ 66–67 °C (Ref. 20 bp. 65–70 °C, 7 mm Hg).

### 6.2. General procedure for the one-pot parallel synthesis of 2,3-dihydropyridin-4(1*H*)-ones (6a–m)

Twelve glass-fritted tubes were loaded with 300 mg N-Fmoc-Rinkamide(aminomethyl)polystyrene-resin **1** (1.1 mmol/g, 0.33 mmol), suspended in 20% piperidine in DMF (3 mL) and shaken for 2 h at room temperature. It was filtered off and the resins were washed twice with 3 mL of DMF, $CH_2Cl_2$ and MeOH, respectively. Trimethylorthoformate (=$HC(OMe)_3$; 3 mL) was added to each tube, it was shaken for 15 min and filtered off. Another 3 mL of

$HC(OMe)_3$ were added as well as the carbonyl compounds **2a**–**m** (3.3 mmol each) and it was shaken for 18 h at room temperature (solid carbonyl compounds were dissolved in $HC(OMe)_3$ before use and if solubility was poor, $CH_3CN$ was added). It was filtered off and the resins were washed three times each with dry $CH_2Cl_2$ (3 mL) and dry MeOH (3 mL) and once with dry THF (3 mL). They were suspended in 2 mL of dry THF before 1.0 mL of a 0.066 mM solution of anhydrous $Yb(OTf)_3$ (0.066 mmol) in dry THF was added to each tube. It was shaken while the reaction mixtures were cooled down to 0 °C. Then 315 μL **4** (1.65 mmol) were added to each resin, it was agitated for 4 h at 0 °C, then the reaction mixtures were allowed to warm to room temperature while it was shaken for additional 16 h. The reactions were quenched with approximately the same volume of water and shaken for 15 min. It was filtered off and washed as follows (3 mL each time): 2×THF, 2×$CH_2Cl_2$, 2×MeOH, 1×$CH_2Cl_2$. Products were cleaved from the resins with 20% TFA in $CH_2Cl_2$ for 3 h at room temperature. It was filtered off, the resins were washed with $CH_2Cl_2$ (3×2 mL) and cleavage reaction was repeated once. The combined filtrates were concentrated in vacuo and the obtained crude products were purified by column flash chromatography (eluent = ethyl acetate, exceptions: **6h** eluent = ethyl acetate/petroleum ether = 75:25, **6l** eluent = ethyl acetate/methanol/dimethylethylamine = 87.5:10:2.5).

#### 6.2.1. 2-Isopropyl-2,3-dihydropyridin-4(1*H*)-one (6a).[7,21]

Yellow oil, $R_f$ = 0.12 (EtOAc); yield: 27.3 mg (60%); purity > 99% (GC); UV: $\lambda_{max}$ = 303 nm; IR (neat): 3284 (broad, –N–H), 3043 (w, –C=*C*–*H*), 2966 (m, –C–H), 1676 (s, amide I), 1561 (s, amide II), 1241 (s)/1212 (s)/1187 (s)/1138 $cm^{-1}$ (s, characteristic dihydropyridone fingerprint); $^1H$ NMR (DMSO-$d_6$): δ 7.49 (s broad, 1H, NH), 7.25 (t, *J* = 6.9 Hz, 1H, 6-H), 4.63 (d, *J* = 7.1 Hz, 1H, 5-H), 3.30 (dt, *J* = 13.0, 5.6 Hz, 1H, 2-H), 2.15 (dd, *J* = 16.0, 13.0 Hz, 1H, 3-H), 2.06 (dd, *J* = 15.2, 5.6 Hz, 1H, 3-H), 1.85–1.74 (m, 1H, –C*H*($CH_3$)$_2$), 0.87 (d, *J* = 6.8 Hz, 3H, –C*H*$_3$), 0.86 (d, *J* = 6.8 Hz, 3H, –C*H*$_3$); $^{13}C$ NMR (DMSO-$d_6$): δ 189.8 (C-4), 151.0 (C-6), 95.1 (C-5), 56.5 (C-2), 37.0 (C-3), 29.1 (–*C*H($CH_3$)$_2$), 17.0, 16.8 (2C, –*C*H$_3$); MS (70 eV) *m/e* (rel.int.): 139 (M, 22), 96 (M − *i*Pr, 100), 68 (M − *i*Pr–CO, 56); HRMS (70 eV) *m/e* calcd for $C_8H_{13}NO$: 139.0997, found 139.0960.

#### 6.2.2. 2-Cyclohexyl-2,3-dihydropyridin-4(1*H*)-one (6b).[22]

Pale-yellow oil, $R_f$ = 0.16 (EtOAc); yield: 37.5 mg (63%); purity > 99% (GC); UV: $\lambda_{max}$ = 316 nm; IR (neat): 3297 (br, –N–H), 3045 (w, –C=*C*–*H*), 2926 (s, –C–H), 2854 (m, –C–H), 1680 (s, amide I), 1559 (s, amide II), 1210 (s)/1185 (s)/1136 $cm^{-1}$ (s, characteristic dihydropyridone fingerprint); $^1H$ NMR (DMSO-$d_6$): δ 7.47 (s broad, 1H, NH), 7.22 (t, *J* = 6.7 Hz, 1H, 6-H), 4.61 (d, *J* = 7.0 Hz, 1H, 5-H), 3.28 (dt, *J* = 12.5, 5.9 Hz, 1H, 2-H), 2.16 (dd, *J* = 16.0, 12.5 Hz, 1H, 3-H), 2.08 (dd, *J* = 16.0, 5.9 Hz, 1H, 3-H), 1.74–1.56 (m, 5H, –cyclohexyl), 1.52–1.42 (m, 1H, –C*H*($CH_2$)$_5$), 1.23–0.91 (m, 5H, –cyclohexyl); $^{13}C$ NMR (DMSO-$d_6$): δ 189.8 (C-4), 150.9 (C-6), 95.0 (C-5), 55.9 (C-2), 39.0 (–*C*H($CH_2$)$_5$), 37.3 (C-3), 27.1, 26.8, 24.8 (3C, –cyclohexyl), 24.6 (2C, –cyclohexyl); MS (70 eV) *m/e* (rel.int.): 179 (M, 33), 136 (M − *i*Pr, 27), 121 (M − butyl, 43), 96 (M − cyclohexyl, 100), 68 (M − cyclohexyl–CO, 52); HRMS (70 eV) *m/e* calcd for $C_{11}H_{17}NO$: 179.1310, found 179.1290.

#### 6.2.3. 2-*tert*-Butyl-2,3-dihydropyridin-4(1*H*)-one (6c).[7]

Yellow oil, $R_f$ = 0.23 (EtOAc); yield: 23.6 mg (47%); purity > 99% (GC); IR (neat): 3447 (broad, –N–H), 2968 (m, –C–H), 1684 (s, amide I), 1559 (s, amide II), 1253 (s)/1206 (s)/1146 $cm^{-1}$ (s, characteristic dihydropyridone fingerprint); $^1H$ NMR (DMSO-$d_6$): δ 7.36 (s broad, 1H, NH), 7.26 (t, *J* = 6.8 Hz, 1H, 6-H), 4.65 (d, *J* = 7.1 Hz, 1H, 5-H), 3.19 (dd, *J* = 14.0, 5.5 Hz, 1H, 2-H), 2.17 (dd, *J* = 16.0, 14.3 Hz, 1H, 3-H), 2.08 (dd, *J* = 16.0, 5.4 Hz, 1H, 3-H), 0.89 (s, 9H, –C(C*H*$_3$)$_3$); $^{13}C$ NMR (DMSO-$d_6$): δ 191.7 (C-4), 153.3 (C-6), 96.6 (C-5), 61.9 (C-2), 37.8 (C-3), 33.6 (–*C*($CH_3$)$_3$), 26.4 (3C, –$CH_3$); MS (70 eV) *m/e* (rel.int.): 153 (M, 24), 96 (M − *t*Bu, 100), 68 (M − *t*Bu–CO, 34); HRMS (70 eV) *m/e* calcd for $C_9H_{15}NO$: 153.1154, found 153.1137.

#### 6.2.4. 2-Phenyl-2,3-dihydropyridin-4(1*H*)-one (6d).[7,22]

Yellow oil, $R_f$ = 0.23 (EtOAc); yield: 29.8 mg (52%); purity > 99% (GC); UV: $\lambda_{max}$ = 302 nm; IR (neat): 3234 (broad, –N–H), 3031 (w, –C=*C*–*H*), 2924 (w, –C–H), 1685 (s, amide I), 1556 (s, amide II), 1231 (s)/1203 (s)/1165 (s)/1134 (s, characteristic dihydropyridone fingerprint), 697 $cm^{-1}$ (s, out-of-plane); $^1H$ NMR (DMSO-$d_6$): δ 7.84 (d broad, *J* = 5.5 Hz, 1H, NH), 7.41–7.28 (m, 6H, –Ph + 6-H), 4.76 (d, *J* = 7.4 Hz, 1H, 5-H), 4.71 (dd, *J* = 12.5, 5.9 Hz, 1H, 2-H), 2.49 (dd, *J* = 16.0, 12.5 Hz, 1H, 3-H), 2.38 (dd, *J* = 16.0, 5.9 Hz, 1H, 3-H); $^{13}C$ NMR (DMSO-$d_6$): δ 190.6 (C-4), 152.8 (C-6), 141.5 (C-1′), 129.2 (2C, –Ph, *ortho*), 128.4 (–Ph, *para*), 127.3 (2C, –Ph, *meta*), 97.7 (5-C), 57.0 (2-C), 44.6 (3-C); MS (70 eV) *m/e* (rel.int.): 173 (M, 100), 145 (M − CO, 55), 104 (M − NHCH=CHC(=O), styrene = Retro-Diels–Alder-fragment, 73), 78 (–Ph, 43); HRMS (70 eV) *m/e* calcd for $C_{11}H_{11}NO$: 173.0841, found 173.0856.

#### 6.2.5. 2-Butyl-2,3-dihydropyridin-4(1*H*)-one (6e).

Pale-yellow oil, $R_f$ = 0.13 (EtOAc); yield: 17.0 mg (34%); purity ~98% (GC); IR (neat): 3296 (broad, –N–H), 3046 (w, –C=*C*–*H*), 2959 (m, –C–H), 2930 (m, –C–H), 2861 (m, –C–H), 1676 (s, amide I), 1559 (s, amide II), 1241 (m)/1205 (s)/1186 (s)/1137 $cm^{-1}$ (s, characteristic dihydropyridone fingerprint); $^1H$ NMR (DMSO-$d_6$): δ 7.47 (s broad, 1H, NH), 7.21 (t, *J* = 6.8 Hz, 1H, 6-H), 4.62 (d, *J* = 7.0 Hz, 1H, 5-H), 3.46 (tt, *J* = 12.2, 6.1 Hz, 1H, 2-H), 2.19 (dd, *J* = 16.0, 5.3 Hz, 1H, 3-H), 2.07 (dd, *J* = 16.0, 12.2 Hz, 1H, 3-H), 1.62–1.48 (m, 1H, –C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.48–1.36 (m, 1H, –C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.34–1.16 (m, 4H, –CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 0.91–0.76 (m, 3H, –CH$_2$CH$_2$CH$_2$C*H*$_3$); $^{13}C$ NMR (DMSO-$d_6$): δ 191.3 (C-4), 152.4 (C-6), 97.0 (C-5), 52.8 (C-2), 42.2 (C-3), 33.5 (–*C*H$_2$CH$_2$CH$_2$CH$_3$′), 27.6 (–CH$_2$*C*H$_2$CH$_2$CH$_3$), 22.8 (–CH$_2$CH$_2$*C*H$_2$CH$_3$′), 14.6 (–CH$_2$CH$_2$CH$_2$*C*H$_3$); MS (70 eV) *m/e* (rel.int.): 153 (M, 13), 138 (M − $CH_3$, 20), 110 (M − $C_3H_7$, 21), 96 (M − Bu, 100), 68 (M − Bu–CO, 60); HRMS (70 eV) *m/e* calcd for $C_9H_{15}NO$: 153.1154, found 153.1134.

#### 6.2.6. 2-(2-Methylpropyl)-2,3-dihydropyridin-4(1*H*)-one (6f).

Yellow oil, $R_f$ = 0.14 (EtOAc); yield: 29.7 mg (59%); purity > 99% (GC); IR (neat): 3298 (broad, –N–H), 3052 (w, –C=*C*–*H*), 2960 (m, –C–H), 2928 (m, –C–H), 2874 (m,

–C–H), 1676 (s, amide I), 1559 (s, amide II), 1186 (s)/1137 $cm^{-1}$ (s, characteristic dihydropyridone-fingerprint); $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.49 (s broad, 1H, NH), 7.21 (t, $J$=6.8 Hz, 1H, 6-H), 4.63 (d, $J$=7.1 Hz, 1H, 5-H), 3.59–3.49 (m, 1H, 2-H), 2.21 (dd, $J$=16.0, 5.1 Hz, 1H, 3-H), 2.04 (dd, $J$=16.0, 12.1 Hz, 1H, 3-H), 1.73–1.60 (m, 1H, $-CH_2CH(CH_3)_2$), 1.55–1.46 (m, 1H, $-CH_2CH(CH_3)_2$), 1.29–1.19 (m, 1H, $-CH_2CH(CH_3)_2$), 0.85 (d, $J$=6.7 Hz, 3H, $-CH_3$), 0.84 (d, $J$=6.7 Hz, 3H, $-CH_3$); $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 189.5 (C-4), 150.5 (C-6), 95.1 (C-5), 48.9 (C-2), 41.1 ($-CH_2CH(CH_3)_2$), 40.7 (C-3), 22.5 ($-CH_2CH(CH_3)_2$), 21.5, 21.1 (2C, $-CH_3$); MS (70 eV) *m/e* (rel.int.): 153 (M, 44), 138 (M−$CH_3$, 23), 110 (M−$C_3H_7$, 11), 96 (M−(2-methylpropyl), 100), 68 (M−(2-Methylpropyl)–CO, 100); HRMS (70 eV) *m/e* calcd for $C_9H_{15}NO$: 153.1154, found 153.1111.

**6.2.7. 2-(4-Nitrophenyl)-2,3-dihydropyridin-4(1*H*)-one (6g).** Yellow oil, $R_f$=0.12 (EtOAc); yield: 48.1 mg (67%); purity>99% (GC); IR (neat): 3274 (broad, –N–H), 3045 (w, –C=*C–H*), 2926 (w, –C–H), 1680 (s, amide I), 1561 (s, amide II), 1518 (s, $-NO_2$ asym.), 1347 (s, $-NO_2$ sym.), 1235 (m)/1204 (s)/1137 (s, characteristic dihydropyridone fingerprint), 698 $cm^{-1}$ (m, out-of-plane); $^1H$ NMR (DMSO-$d_6$): $\delta$ 8.22 (d, $J$=9.0 Hz, 2H, 3′-H), 8.02 (d broad, $J$=5.9 Hz, 1H, NH), 7.67 (d, $J$=8.2 Hz, 2H, 2′-H), 7.44 (t, $J$=6.9 Hz, 1H, 6-H), 4.95–4.88 (m, 1H, 2-H), 4.78 (d, $J$=6.7 Hz, 1H, 5-H), 2.53 (dd, $J$=16.1, 6.4 Hz, 1H, 3-H), 2.46 (dd, $J$=16.1, 10.6 Hz, 1H, 3-H); $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 189.9 (C-4), 152.8 (C-6), 149.3 (C-4′), 147.6 (C-1′), 128.6 (2C, C-2′), 124.4 (2C, C-3′), 98.1 (C-5), 56.1 (C-2), 43.9 (C-3); MS (70 eV) *m/e* (rel.int.): 218 (M, 100), 190 (M−CO, 55), 172 (M−$NO_2$, 7), 149 (M−NHCH=CHC(=O), 4-nitrostyrene=Retro-Diels–Alder-fragment, 17), 119 (Retro-Diels–Alder-fragment-NO, 23), 96 (M−(4-nitrophenyl), 11), 91 ($C_7H_7$, 38); HRMS (70 eV) *m/e* calcd for $C_{11}H_{10}N_2O_3$: 218.0691, found 218.0667.

**6.2.8. 2-(2-Bromophenyl)-2,3-dihydropyridin-4(1*H*)-one (6h).** Pale-yellow oil, $R_f$=0.18 (EtOAc/petroleum ether=75:25); yield: 52.0 mg (63%); purity>99% (GC); IR (neat): 3252 (broad, –N–H), 3036 (m, –C=*C–H*), 1676 (s, amide I), 1559 (s, amide II), 1236 (m)/1202 (s)/1187 (s)/1136 (s, characteristic dihydropyridone fingerprint), 720 $cm^{-1}$ (m, out-of-plane); $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.90 (d broad, $J$=5.5 Hz, 1H, NH), 7.63 (dd, $J$=8.0, 1.4 Hz, 1H, 3′-H), 7.56 (dd, $J$=7.6, 1.8 Hz, 1H, 6′-H), 7.48–7.39 (m, 2H, 6-H+5′-H), 7.25 (td, $J$=7.6, 2.0 Hz, 1H, 4′-H), 5.01–4.94 (m, 1H, 2-H), 4.80 (d, $J$=7.4 Hz, 1H, 5-H), 2.49 (dd, $J$=16.0, 6.3 Hz, 1H, 3-H), 2.39 (dd, $J$=16.0, 11.7 Hz, 1H-3-H); $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 190.0 (C-4), 153.3 (C-6), 139.8 (C-1′), 133.7 (C-3′), 130.5 (C-4′), 128.9 (2C, C-5′+C-6′), 122.6 (C-2′), 97.8 (C-5), 56.5 (C-2), 42.6 (C-3); MS (70 eV) *m/e* (rel.int.): 253 ($^{81}$BrM, 78), 251 ($^{79}$BrM, 81), 225 ($^{81}$BrM−CO, 12), 223 ($^{79}$BrM−CO, 15), 184 (2-$^{81}$bromostyrene=Retro-Diels–Alder-fragment, 62), 182 (2-$^{79}$bromostyrene=Retro-Diels–Alder-fragment, 58), 172 (M−Br, 56), 144 (M−Br–CO, 55), 130 (isoquinolinium, 100), 103 (styrene, 91), 77 (–Ph, 12); HRMS (70 eV) *m/e* calcd for $C_{11}H_{10}BrNO$: 252.9925 ($^{81}$Br)/250.9946 ($^{79}$Br), found 252.9909 ($^{81}$Br)/250.9924 ($^{79}$Br).

**6.2.9. 2-(Furan-2-yl)-2,3-dihydropyridin-4(1*H*)-one (6i).** Yellow oil, $R_f$=0.22 (EtOAc); yield: 14.0 mg (26%); purity>99% (GC); IR (neat): 3247 (broad, –N–H), 3034 (m, –C=*C–H*), 2927 (w, –C–H), 1675 (w, amide I), 1560 (s, amide II), 1404 (m), 1281 (s)/1227 (s)/1205 (s)/1167 (s, characteristic dihydropyridone-fingerprint), 740 $cm^{-1}$ (m, out-of-plane); $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.89 (d broad, $J$=5.1 Hz, 1H, NH), 7.63 (dd, $J$=1.6, 0.8 Hz, 1H, 5′-H), 7.25 (dd, $J$=7.0, 0.8 Hz, 1H, 6-H), 6.41 (dd, $J$=3.1, 1.6 Hz, 1H, 4′-H), 6.30 (d, $J$=3.1 Hz, 1H, 3′-H), 4.78 (dt, $J$=7.0, 1.6 Hz, 1H, 2-H), 4.71 (dd, $J$=7.0, 0.8 Hz, 1H, 5-H), 2.53–2.47 (m, 2H, 3-H); $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 190.1 (C-4), 153.7 (C-2′), 151.9 (C-6), 143.3 (C-5′), 111.1 (C-4′), 107.4 (C-3′), 97.6 (C-5), 49.9 (C-2), 40.5 (C-3); MS (70 eV) *m/e* (rel.int.): 163 (M, 39), 135 (M−CO, 93), 106 (Furo[2,3-c]pyrrole, 100), 94 (Retro-Diels–Alder-fragment, 61), 66 (pyrrole, 74); HRMS (70 eV) *m/e* calcd for $C_9H_9NO_2$: 163.0633, found 163.0590.

**6.2.10. 2-(Thiophen-2-yl)-2,3-dihydropyridin-4(1*H*)-one (6k).** Yellow oil, $R_f$=0.24 (EtOAc); yield: 14.6 mg (30%); purity>99% (GC); IR (neat): 3235 (broad, –N–H), 3025 (w, –C=*C–H*), 2924 (w, –C–H), 2852 (w, –C–H), 1684 (m, amide I), 1558 (s, amide II), 1232 (s), 1204 (s), 1179 (s), 1135 (s, characteristic dihydropyridone fingerprint), 702 $cm^{-1}$ (m, out-of-plane); $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.96 (d broad, $J$=5.1 Hz, 1H, NH), 7.44 (dd, $J$=5.1, 1.6 Hz, 1H, 3′-H), 7.29 (dd, $J$=7.4, 0.8 Hz, 1H, 6-H), 7.08–7.07 (m, 1H, 5′-H), 6.98 (dd, $J$=5.1, 3.1 Hz, 1H, 4′-H), 5.00 (ddd, $J$=9.8, 6.3, 1.6 Hz, 1H, 2-H), 4.76 (dd, $J$=7.4, 1.2 Hz, 1H, 5-H), 2.55 (dd, $J$=16.0, 6.3 Hz, 1H, 3-H), 2.48 (dd, $J$=15.7, 10.2 Hz, 1H, 3-H); $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 190.1 (C-4), 152.0 (C-6), 145.0 (C-2′), 127.4 (C-4′), 126.0 (2C, C-3′+C-5′), 98.1 (C-5), 52.2 (C-2), 44.8 (C-3); MS (70 eV) *m/e* (rel.int.): 179 (M, 31), 162 (thiophen-2-ylpyridine·$H^+$, 61), 151 (M−CO, 72), 110 (Retro-Diels–Alder-fragment, 100), 106 (2-allylpyridine·$H^+$, 21), 96 (M−thiophenyl, 13), 84 (thiophen, 27), 66 (pyrrole, 53); HRMS (70 eV) *m/e* calcd for $C_9H_9NOS$: 179.0405, found 179.0381.

**6.2.11. 2,3-Dihydro-2,2′-bipyridin-4(1*H*)-one (6l).** Yellow oil, $R_f$=0.36 (EtOAc/MeOH/$Me_2NEt$=87.5:10:2.5); yield: 23.2 mg (40%); purity>99% (GC); IR (neat): 3226 (broad, –N–H), 3022 (m, –C=*C–H*), 2929 (w, –C–H), 1619 (m, amide I), 1562 (s, amide II), 1275 (w)/1236 (m)/1207 (s)/1166 (m, characteristic dihydropyridone fingerprint), 782, 748 $cm^{-1}$ (m, out-of-plane); $^1H$ NMR (DMSO-$d_6$): $\delta$ 8.57–8.54 (m, 1H, 3′-H), 7.96 (d broad, $J$=5.5 Hz, 1H, NH), 7.80 (td, $J$=7.8, 2.0 Hz, 1H, 5′-H), 7.44 (d, $J$=7.8 Hz, 1H, 6′-H), 7.39 (t, $J$=6.9 Hz, 1H, 6-H), 7.33–7.29 (m, 1H, 4′-H), 4.78 (ddd, $J$=10.2, 6.3, 2.0 Hz, 1H, 2-H), 4.73 (d, $J$=7.4 Hz, 1H, 5-H), 2.64 (dd, $J$=16.0, 10.2 Hz, 1H, 3-H), 2.55 (dd, $J$=16.0, 6.3 Hz, 1H, 3-H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 190.3 (C-4), 159.8 (C-1′), 152.4 (C-6), 149.8 (C-3′), 137.7 (C-5′), 123.5 (C-4′), 121.4 (C-6′), 97.8 (C-5), 57.5 (C-2), 42.0 (C-3); MS (70 eV) *m/e* (rel.int.): 174 (M, 14), 146 (M−CO, 63), 130 ([1,7]naphthyridine, 100), 106 (Retro-Diels–Alder-fragment, 18), 96 (M−pyridine, 18), 78 (pyridine, 15); HRMS (70 eV) *m/e* calcd for $C_{10}H_{10}N_2O$: 174.0793, found 174.0790.

**6.2.12. Ethyl 2-methyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate (6m).** Yellow oil, $R_f$=0.23 (EtOAc); yield: 20.1 mg (33%); purity>99% (GC); IR (neat): 3291 (broad,

–N–H), 2985 (w, –C–H), 1732 (m, –(*C*═*O*)–O–), 1680 (s, amide I), 1624 (s), 1566 (s, amide II), 1294 (m, –*C*–*O*–(C═O)–), 1242 (s)/1186 (s)/1137 (s)/1106 $cm^{-1}$ (s, characteristic dihydropyridone fingerprint); $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.97 (d broad, $J=5.1$ Hz, 1H, NH), 7.26 (t, $J=6.9$ Hz, 1H, 6-H), 4.66 (d, $J=7.4$ Hz, 1H, 5-H), 4.08 (quart, $J=7.0$ Hz, 2H, –OC$H_2$CH$_3$), 2.58 (d, $J=16.0$ Hz, 1H, 3-H), 2.38 (d, $J=16.0$ Hz, 1H, 3-H), 1.38 (s, 3H, –C$H_3$), 1.14 (t, $J=7.0$ Hz, 3H, –OCH$_2$C$H_3$); $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 189.8 (C-4), 174.3 (–*C*O$_2$Et), 152.0 (C-6), 97.6 (C-5), 61.9 (–O*C*H$_2$CH$_3$), 60.4 (C-2), 45.8 (C-3), 24.4 (–CH$_3$), 14.6 (–OCH$_2$*C*H$_3$); MS (70 eV) *m/e* (rel.int.): 183 (M, 16), 110 (M−ethoxycarbonyl, 100), 82 (M−ethoxycarbonyl–CO, 22); HRMS (70 eV) *m/e* calcd for $C_9H_{13}NO_3$: 183.0895, found 183.0879.

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