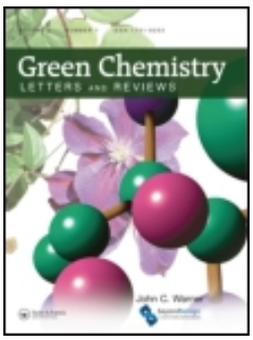

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High-yielding method for preparation of carbocyclic or *N*-containing heterocyclic β-keto esters using *in situ* activated sodium hydride in dimethyl sulphoxide

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High-yielding method for preparation of carbocyclic or *N*-containing heterocyclic β-keto esters using *in situ* activated sodium hydride in dimethyl sulphoxide

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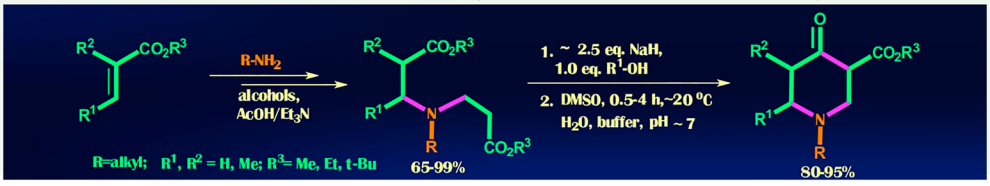
ABSTRACT

It was found that NaH suspension in DMSO was highly activated when reacted with an alcohol. The *in situ* generated NaH/alkoxide mixture permitted very rapid and complete deprotonation and acylation of various cyclic ketones with alkyl carbonates at ambient temperature. Activated NaH/alkoxide in DMSO is particularly effective in Dieckmann condensations, where it affords 5- and 6-membered carbocyclic or *N*-containing heterocyclic β-keto esters in high yields. A heterocyclic Dieckmann condensation was performed on a molar scale, demonstrating the scalability of the procedure. Besides, DMSO is non-toxic, relatively inexpensive and environmentally benign solvent.



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Keywords
Acylation; condensation reaction; environmentally benign solvent

1. Introduction

β-Keto esters are important synthetic precursors widely used in laboratory (1) and industrial syntheses (2,3). The compounds are very often prepared by the acylation of preformed ketone enolate anions using reagents such as Weinreb amides (4), alkyl-cyanoformates (5,6) or 1-Boc-imidazole (7), as well as alkyl carbonates at elevated temperature (8–11). Dieckmann condensation (12) of various diesters provides good yields of 5- and 6-membered carbocyclic (13–15) or heterocyclic β-keto esters (16–21) while acyclic analogues result from Claisen ester condensation (22) typically after prolonged heating in aromatic solvents with alkoxides. Alternatively, the acylation is promoted by Lewis acids (23,24). Several examples of deprotonation, acylation and/or cyclization of ketones (25) in DMSO, using NaH at elevated temperatures (50–90°C), have been reported previously. The use of DMSO as a solvent offers distinct advantages in nucleophilic substitutions, elimination and related reactions (26–28); however, it reacts rapidly with NaH at ~50°C, forming highly nucleophilic dimsyl anion (29). Certain ketones were acylated with alkyl carbonates in DMSO, using alkoxide base (30).

Therefore, this work was aimed to develop an efficient and general preparative method for both the ketone acylation and Dieckmann condensation, avoiding hazardous solvents and elevated temperatures.

2. Results and discussion

In connection with our research projects, we needed multigram quantities of various carbocyclic and heterocyclic β-keto esters (Tables 1 and 2). However, available literature procedures for ketone acylation with alkyl carbonates using NaH in benzene (8) or NaH/dry KH in THF (9) resulted, in our hands, in slow conversions, difficult to separate mixtures and low to moderate yields. In addition, benzene and dry KH are particularly hazardous chemicals. While Dieckmann condensation of various amino-diesters (Table 2) using alkoxide bases often afforded heterocyclic β-keto esters in 70–90% yields, it required 3–5 h of reflux in toluene or xylenes. More significantly, under the reaction conditions, a number of the starting amino-diesters (e.g. **2a**, **2d**, **2e**, Table 2) formed thick gels, greatly reducing the isolated yields and purity of the products. Therefore, we sought to develop a more efficient and general preparative method for both the ketone acylation and Dieckmann condensation.

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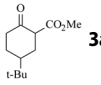
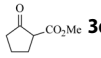
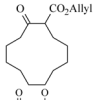
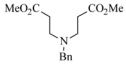
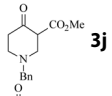
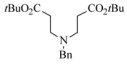
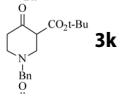
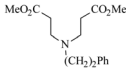
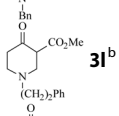
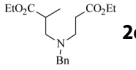
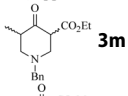
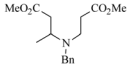
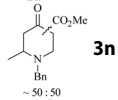
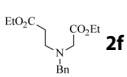
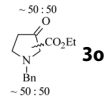
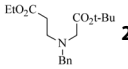
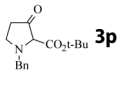
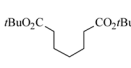
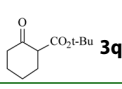
Table 1. Cyclic β-keto esters prepared by acylation of ketones **1a**–**1g** according to Scheme 1.

Cyclic ketone	β-Keto ester[a]	Time(min); Scale (mmol)	Yield (%)[b]
1a	 **3a**	30–45; 65–160	93
1b	 **3b**	30–45; 100	90
1c	 **3c**	30–45; 36	90
1d	 **3d**	30–45; 80	83
1e	 **3e**	30–45; 80	88
1f	 **3f**	30–45; 24	91
1g	 **3g**	30–45; 55	95
1g[c]	 **3h**	30–45; 27	85
1a[d]	 **3i**	30–45; 32	95

[a]Methyl β-keto esters obtained with 4 eq. of dimethylcarbonate.
[b]Isolated yields; ^{1}H NMR purity > 95%.
[c]Obtained with 1.5 eq. of diallyl carbonate in DMSO/THF mixture (75:25).
[d]Obtained with 4 eq. of ethyl formate.

Table 2. Cyclic β-keto esters prepared by Dieckmann condensation according to Scheme 2.

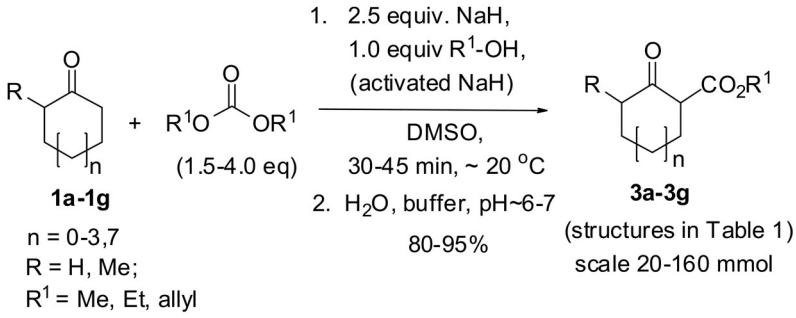
Diester	β-Keto ester	Time (min); Scale (mmol)	Yield (%)[a]
 **2a**	 **3j**	30–45; 50–500	85–95
 **2b**	 **3k**	180; 14	83
 **2c**	 **3l**[b]	30–60; 50–1000 30–45; 60	87–94
 **2d**	 **3m**		92
 **2e**	 **3n**	30–45; 30	88
 **2f**	~ 50 : 50  ~ 50 : 50 **3o**	30–45; 30	88–92
 **2g**	 **3p**	180; 30	80
 **2h**	 **3q**	180; 30	85

[a]Isolated yields; ^{1}H NMR purity > 95%.
[b]Reaction carried out in DMSO/THF (75:25) to prevent gel formation.

To that end, the acylation of carbocyclic ketones with alkyl carbonates in DMSO was reexamined, using NaH as a base. Initial attempts resulted in exceedingly slow deprotonation/acylation rate at ~20°C, while at ~40–50°C, the reaction proceed erratically and with delayed exotherm, often yielding numerous side products. Further experiments involved addition of various co-solvents, solid alkaline alkoxides (MeONa, EtONa, *t*-BuOK) and/or free alcohols. The activity of NaH suspension in DMSO was highly enhanced after treatment with certain amounts of the alcohol (MeOH, EtOH, allyl, *t*-BuOH). Except for *t*-BuOH, the alcohols were chosen according to the alkyl carbonate used, to prevent transesterification. Subsequent addition of ketone/alkyl carbonate mixture resulted in immediate deprotonation/acylation at ~20°C, as evidenced by vigorous H_2 evolution and aliquot analysis. Variations in molar amounts of NaH and alcohol relative to the ketone gave the optimal NaH/alcohol/ketone molar ratio of ~2.5:1.0:1.0, respectively. The relative amount of NaH can be reduced to ca. 2.0–2.1 equiv, without affecting the yields; however the overall reaction rate was decreased (by 20–50%). It appears that the alcohol has a dual role, providing alkoxide as the kinetically more active base as well as the activation of the NaH surface. However, the complete conversion of NaH to the alkoxide with stoichiometric quantity of alcohol greatly reduced the isolated yields and purity of β-keto esters. Hence, the mixture of NaH and *in situ* formed alkoxide in DMSO was found to be a particularly effective base system, providing both rapid and irreversible deprotonation of ketones, Scheme 1. Attempted use of LiH failed to effect any reaction.

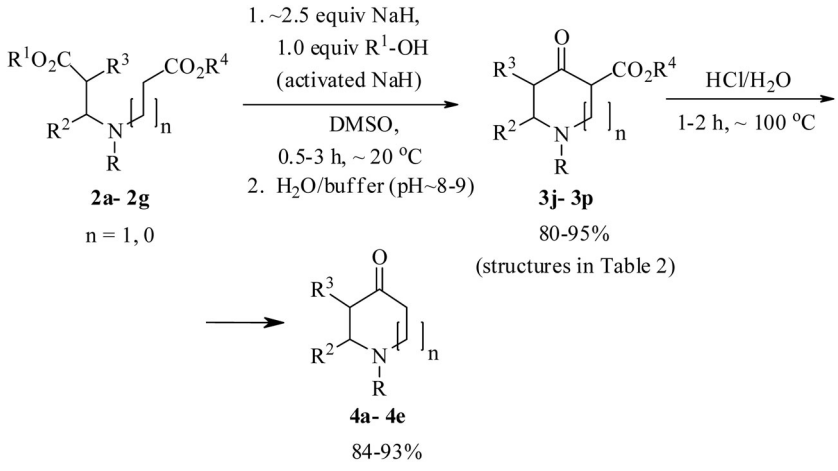
In experiments where a mixture of alcohol, ketone and alkyl carbonate was added to a stirred NaH/DMSO suspension, a significant reaction delay was observed, followed by the vigorous exotherm. The results confirm that the NaH suspension must be activated with alcohol, before the addition of reactants. Under these conditions, complete conversion of ketones was achieved and the corresponding β-keto esters were isolated in excellent yields, on a 20–160 mmol scale (Table 1). Side products of undetermined structures were detected only occasionally, when the internal temperature exceeded ~35°C. Use of ethyl formate instead of alkyl carbonate provided β-formyl derivative **3i**.

The activated NaH/alkoxide suspension was equally effective in Dieckmann condensation, providing high yields of 5 and 6-membered β-keto esters (Scheme 2 and Table 2). Compounds **3b** and **3d** (Table 1) were also prepared by Dieckmann condensation from the corresponding diesters.



1a: 4-t-Bu-cyclohexanone; **1b**: cyclohexanone; **1c**: 2-methylcyclohexanone;
1d: cyclopentanone; **1e**: cycloheptanone; **1f**: cyclooctanone;
1g: cyclododecanone

Scheme 1. Acylation of cyclic ketones with alkyl carbonates using activated NaH.



4a: 1-Benzyl-piperidin-4-one; **4b**:1-Phenethylpiperidin-4-one;
4c:1-Benzyl-3-methylpiperidin-4-one; **4d**: 1-Benzyl-2-methylpiperidin-4-one;
4e: 1-Benzylpyrrolidin-3-one.

Note: Carbocyclic β-keto esters **3b**, **3d** and **3q** were prepared analogously from the corresponding succinates and adipates.

Scheme 2. Dieckmann condensation of diesters using activated NaH/DMSO.

The requisite amino-diesters **2a**–**2h** were prepared by aza-Michael reaction, using modified literature procedures (31–34). Formation of 7-membered or larger rings failed, as mixtures were obtained. Regio-selectivity was observed in one case, affording single isomer **3p**. However, compounds **3n** and **3o** were obtained as regio-isomer mixtures.

Simple acid hydrolysis and decarboxylation of β-keto esters **3j**, **3l**, **3m**, **3n** and **3o** yielded heterocyclic ketones **4a**–**4e**, respectively (Scheme 2). Both the heterocyclic β-keto esters and the corresponding ketones present significant synthetic precursors (35–41). Concentrations of up to ~0.4 mol/L of the reactant were achieved, even when THF was used as a co-solvent to prevent gel formation. DMSO was quantitatively removed by simple aqueous extraction.

3. Conclusion

In conclusion, the use of *in situ* generated NaH/alkoxide mixture in DMSO allows for a high-yielding and efficient procedure for the Dieckmann condensation and alkoxycarbonylation of ketones. It is inexpensive and suitable method for large scale preparations of various β-keto esters. In comparison with previously reported procedures, advantages of the method described are numerous; expediency, high yields, the operational simplicity, and in addition, use of DMSO as non-toxic, non-flammable and environmentally benign solvent which could be quantitatively removed by simple aqueous extraction. Other solvents used (petroleum ether, PhMe, MeOAc or EtOAc) are also of low toxicity.

4. Experimental

4.1. General information

^{1}H NMR spectra were recorded at 200 MHz or 500 MHz and ^{13}C NMR/APT at 50 or 126 MHz as indicated in each case. Data are reported as chemical shifts in δ (ppm). The chemical shift references were as follows: ^{1}H NMR (7.26 δ, $CHCl_3$ or 0.00 δ, TMS) and ^{13}C NMR (77.00 δ, $CDCl_3$). ^{1}H and ^{13}C NMR spectra were Bruker Avance 500, or Varian Gemini 2000 instruments. All high-resolution mass spectra were obtained by ESI-ToF and recorded on Agilent Technologies 6210-1210 TOF-LC-ESI-HR/MS instrument in positive mode. All experiments were monitored by thin-layer chromatography on silica and/or by ^{1}H NMR. Reagent-grade solvents and commercial precursors (declared H_2O content <0.1%) were used without further purification. BHT refers to 3,5-di-*tert*-butyl-4-hydroxytoluene. NaH was used exclusively as a 60% mineral oil suspension. Typically, the mineral oil was washed with petroleum ether prior to the reaction, using the reverse filtration under positive pressure of Ar. In molar-scale experiments, the washing was omitted and the mineral oil was removed during the work-up. The reaction mixture was worked-up with an aqueous solution of tartaric acid, followed by pH adjustment to pH 9–10 with 20% K_2CO_3 solution. Low volatile compounds (amino-diesters, most β-keto esters and heterocyclic ketones were vacuum dried to remove H_2O and solvents (20–50°C, 0.1–0.5 mm Hg, 30–60 min) prior to the spectral analysis and determination of the yields.

4.2. Procedure

4.2.1. Typical procedure for the ketone acylation

The compounds **3a**–**3i** were prepared according to the typical procedure for **3a**.

*4.2.1.1. Methyl 5-(***tert***-butyl)-2-oxocyclohexanecarboxylate (3a, CAS No. 74851-58-4).* After purging the apparatus with Ar, MeOH (2.63 mL, 64.8 mmol) in DMSO (3.0 mL) was added dropwise to the magnetically stirred suspension of oil-washed NaH (60%, 6.48 g, 162 mmol) in DMSO (140 mL) at ~20°C (H_2 evolution!). Then, 4-(*tert*-butyl) cyclohexanone (10.0 g, 64.8 mmol) in dimethyl carbonate (21.8 mL, 259 mmol) was added over 20 min at ~20°C and stirring continued for 20 min. Excess NaH was destroyed with MeOH (5.25 mL, 0.130 mol). The reaction mixture was poured into a solution prepared from tartaric acid (12.2 g, 81 mmol), NaCl (10 g), H_2O (300 mL) and ice (100 g), and extracted with petroleum ether/MeOAc (7:3, 3 mL × 100 mL). The extracts were concentrated under reduced pressure (40°C) and the obtained yellow oil was vacuum dried. Yield: 12.8 g, 93%, yellow liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 12.13 (s, 1H), 3.76 (s, 3H), 2.43- 2.23 (m, 3H), 1.99–1.79 (m, 2H), 1.31–1.16 (m, 2H), 0.91 ppm (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.1, 172.0, 97.3, 51.2, 44.0, 32.1, 30.0, 27.2, 23.6, 23.0 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{12}H_{20}O_3$: ($[M + Na]^+$) 235.1304, found 235.1302.

4.2.1.2. Methyl 2-oxocyclohexanecarboxylate (3b, CAS No. 41302–34–5). Prepared from cyclohexanone (9.82 g, 100.0 mmol). Yield (distilled, colourless liquid): 14.1 g, 90%. Alternatively prepared according to the procedure **3.3** from dimethyl heptanedioate (15.1 g, 80 mmol). Yield: 10.7 g, 86%. ^{1}H NMR (keto-enol mixture = 35:65; 200 MHz, $CDCl_3$): δ = 12.15 (s), 3.74 (s), 3.74 (s), 3.40 (t, J = 7.8 Hz), 2.63–2.32 (m), 2.31–2.06 (m), 2.03–1.50 ppm (m). ^{13}C NMR (50 MHz, $CDCl_3$): δ= 205.6, 172.7, 171.8, 170.1, 97.1, 56.8, 51.6, 50.9, 41.1, 29.6, 28.7, 26.8, 23.0, 22.04, 22.01, 21.6 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_8H_{13}O_3$: ($[M + H]^+$) 157.0859, found 157.0862.

4.2.1.3. Methyl 3-methyl-2-oxocyclohexanecarboxylate (3c, CAS No. 59416-90-9). Prepared from 2-methylcyclohexanone (4.00 g, 36 mmol). Yield: (colourless liquid) 5.52 g, 90%. ^{1}H NMR (*cis*/*trans* keto-enol mixture = 50:50; 500 MHz, $CDCl_3$): δ = 12.29 (s), 3.75 (s), 3.74 (s), 3.73 (s), 3.45–3.41 (m), 3.39 (dd, J = 5.5, 1.1 Hz), 2.69–2.60 (m), 2.55–2.52 (m), 2.50–2.39 (m), 2.28–2.24 (m), 2.24–2.18 (m), 2.16–2.09 (m), 2.08–2.00 (m), 1.99 (d, J = 3.8 Hz), 1.93 (ddd, J = 7.0, 3.9, 3.2 Hz), 1.90 (td, J = 3.7, 1.8 Hz), 1.85–1.56 (m), 1.56–1.46 (m), 1.46 -1.36 (m), 1.18 (d, J = 7.1 Hz), 1.07 (d, J = 6.6 Hz), 1.04 ppm (d, J = 6.5 Hz). ^{13}C NMR/APT (126 MHz, $CDCl_3$): δ= 208.1, 207.5, 175.4, 173.2, 170.4, 96.9, 57.4, 55.6, 52.1, 51.7, 51.2, 45.5, 43.9, 36.2, 35.4, 33.3, 30.6, 30.4, 30.1, 24.0, 22.8, 21.5, 19.9, 17.9, 14.7, 14.2 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_9H_{15}O_3$: ($[M + H]^+$) 171.1015, found 171.1007.

4.2.1.4. Methyl 2-oxocyclopentanecarboxylate (3d, CAS No 10472-24-9). Prepared from cyclopentanone (6.73 g, 80.0 mmol). Yield (distilled, colourless liquid): 83%, 9.48 g. Alternatively prepared acc. to the procedure for **4.3**, from dimethyl adipate (13.9 g, 80 mmol). Yield: 9.21 g, 81%. ^{1}H NMR (keto-enol mixture = 95:5; 200 MHz, $CDCl_3$): δ = 10.34 (s), 3.75 (s), 3.74 (s, 3H), 3.18 (t, J = 9.0 Hz, 1H), 2.40–2.22 (m, 4H), 2.22–2.03 (m, 1H), 2.02 -1.77 ppm (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 212.1, 169.6, 54.3, 52.1, 37.7, 27.1, 20.6 ppm.

4.2.1.5. Methyl 2-oxocycloheptanecarboxylate (3e, CAS No. 52784-32-4). Prepared from cycloheptanone (8.97 g, 80.0 mmol). Yield (colourless liquid): 12.0 g,

88%. ^{1}H NMR (keto-enol mixture = 75:25; 200 MHz, $CDCl_3$): δ = 12.66 (s), 3.75 (s), 3.72 (s), 3.57 (dd, J = 10.1, 4.0 Hz), 2.67–2.53 (m), 2.49–2.35 (m), 2.20–2.03 (m), 2.03–1.81 (m), 1.80–1.55 (m), 1.55–1.37 ppm (m). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 208.6, 179.4, 170.7, 101.2, 58.5, 51.8, 51.1, 42.8, 35.0, 31.7, 29.3, 27.7, 27.3, 27.1, 24.3, 24.1 ppm.

4.2.1.6. Methyl 2-oxocyclooctanecarboxylate (3f, CAS No. 5452-73-3).

Prepared from cyclooctanone (3.00 g, 23.8 mmol). Yield (vacuum dried, yellow liquid): 3.97 g, 91%. ^{1}H NMR (keto-enol mixture = 43:57; 200 MHz, $CDCl_3$): δ= 12.51 (s), 3.75 (s), 3.69 (s), 3.65–3.54 (m), 2.69–2.46 (m), 2.46–2.28 (m), 2.18–2.03 (m), 1.98–1.81 (m), 1.81–1.62 (m), 1.62–1.33 ppm (m). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 211.9, 176.0, 173.2, 170.4, 98.9, 56.6, 52.0, 51.2, 41.6, 32.0, 29.7, 28.9, 28.5, 26.9, 26.3, 25.9, 25.2, 25.0, 24.4, 23.7 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{10}H_{16}O_3$: ($[M + H]^+$) 185.1172, found 185.1164.

4.2.1.7. Methyl 2-oxocyclododecanecarboxylate (3g, CAS No. 62939-87-1).

Prepared from cyclododecanone (10.0 g, 54.8 mmol). Yield (vacuum dried, yellow liquid): 12.5 g, 95% ^{1}H NMR: (keto:enol mixture = 90:10; 200 MHz, $CDCl_3$): δ = 12.84 (s), 3.76 (s), 3.70 (s), 3.64 (dd, J = 11.4, 3.5 Hz), 2.79–2.39 (m), 2.39–2.02 (m), 2.01–1.66 (m),1.65–1.47 (m), 1.45 -1.09 ppm (m). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 206.5, 175.6, 170.3, 57.0, 52.1, 51.3, 40.2, 38.4, 28.6, 27.6, 26.7, 25.4, 25.3, 25.0, 24.6, 24.5, 24.5, 24.2, 24.1, 24.0, 23.6, 23.1, 22.9, 22.4, 22.2, 21.9 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{14}H_{24}O_3$: ($[M + Na]^+$) 263.1617, found 263.1620.

4.2.1.8. Allyl 2-oxocyclododecanecarboxylate (3h, CAS No. 97416-37-0).

Prepared from cyclododecanone (4.92 g, 27 mmol), allyl alcohol and diallyl carbonate (5.70 g, 40 mmol) in DMSO/THF (8:2). Yield (vacuum dried, yellow liquid): 85–90% (over several runs). ^{1}H NMR (keto-enol mixture = 90:10; 500 MHz, $CDCl_3$): δ = 12.82 (s), 5.92–5.83 (m), 5.31 (dd, J = 2.9, 1.4 Hz), 5.28 (dd, J = 2.9, 1.4 Hz), 5.24 (dd, J = 2.4, 1.2 Hz), 5.22 (dd, J = 2.4, 1.2 Hz), 4.59 (dd, J = 2.6, 1.3 Hz), 4.58 (dd, J = 2.6, 1.3 Hz), 3.64 (dd, J = 11.5, 3.4 Hz), 2.67 (ddd, J = 16.2, 11.0, 3.4 Hz), 2.56 (dd, J = 6.8, 3.4 Hz), 2.53 (dd, J = 6.8, 3.4 Hz,), 2.48–2.42 (m), 2.32 (t, J = 7.6 Hz), 2.25 (t, J = 6.8 Hz), 2.21–2.10 (m), 1.95–1.82 (m), 1.82–1.65 (m), 1.61–1.50 (m), 1.44–1.17 ppm (m). APT (126 MHz, $CDCl_3$): δ = 206.5, 169.5, 132.3, 131.5, 118.8, 117.6, 65.8, 64.7, 57.3, 40.3, 38.5, 26.8, 25.4, 25.1, 24.6, 24.3, 24.2, 24.1, 24.1, 23.0, 22.5, 22.3, 22.0 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{16}H_{26}O_3$: ($[M + K]^+$) 305.1513, found 305.1509.

4.2.1.9. 5-(Tert-butyl)-2-oxocyclohexanecarbaldehyde (3i, CAS No. 22252-96-6).

Prepared from 4-(*tert*-butyl) cyclohexanone (5.00 g, 32.4 mmol), HCO_2Et (10.5 mL, 130 mmol) and MeOH. Yield (gelatinous reddish solid, vacuum dried): 95%, 5.61 g. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 14.35 (s, 1H), 8.68 (s, 1H), 2.52–2.24 (m, 3H), 2.16–1.76 (m, 2H), 1.41–1.15 (m, 2H), 0.93 ppm (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 188.1, 184.2, 108.5, 44.4, 32.2, 31.9, 27.1, 24.3, 22.3 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{11}H_{18}O_2$: ($[M + H]^+$) 183.1379, found 183.1373.

4.2.2. Typical procedure for the Dieckmann condensation

The compounds **3j**–**3q** were prepared according to the typical procedure for **3j**, using the appropriate alcohol (MeOH, EtOH or *t*-BuOH. The compound **3l** was prepared in DMSO/THF mixture (75:25) to prevent formation of a gel. In the case of di-*t*-butyl esters (**2b**, **2h**), the onset of H_2 evolution was delayed during *t*-BuOH addition (5–10min) and the reaction required 2–4h to complete.

4.2.2.1. Methyl 1-benzyl-4-oxopiperidine-3-carboxylate (3j, CAS No. 57611-47-9).

After purging the apparatus with Ar, MeOH (2.00 mL 50.0 mol,) in DMSO (3.0 mL) was added dropwise to the magntically stirred suspension of oil-washed NaH (60%, 5.00 g, 125 mmol) in DMSO (120 mL) at ~20°C (H_2 evolution!).Then, a solution of diester **2a** (14.00 g, 50.0 mmol) in DMSO (10 mL) was added over 15 min at ~20°C and stirring continued for 15 min. The reaction rate was monitored by hydrogen evolution. Excess NaH was destroyed with MeOH (2.00 mL, 50.0 mmol). The reaction mixture was poured into the buffer solution prepared from tartaric acid (9.40 g, 62.5 mmol), NaCl (10 g), H_2O (300 mL) and ice (100 g), followed by PhMe extraction (3 mL × 100 mL). The extracts were concentrated (rotatory evaporator), then vacuum dried. Yield (yellow oil): 11.35 g, 92%. The compound slowly decomposes at ~20°C and was storied at −20°C. Over several runs, on 20–100 mmol scale, isolated yields were 82–95%. ^{1}H NMR (keto-enol mixture = 30:70; 200 MHz, $CDCl_3$): δ = 11.95 (s), 7.43–7.16 (m), 3.71 (s), 3.70 (s), 3.62 (s), 3.54–3.43 (m), 3.17 (t, J = 1.5 Hz), 3.08–2.65 (m), 2.63–2.54 (m), 2.38 ppm (t, J = 5.9 Hz).^{13}C NMR (50 MHz, $CDCl_3$): δ=203.9, 171.2, 170.3, 169.1, 137.9, 137.6, 128.9, 128.7, 128.2, 127.3, 127.1, 96.6, 62.0, 61.4, 56.3, 54.8, 52.9, 52.0, 51.2, 49.7, 48.6, 40.6, 29.2 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{14}H_{17}NO_3$: ($[M + H]^+$) 248.1281, found 248.1275.

4.2.2.2. Tert-butyl 1-benzyl-4-oxopiperidine-3-carboxylate (3k, new compound).

Prepared from **2b** (5.00 g, 13.7 mmol). Yield (amorphous white mass): 3.29 g, 83%.

^{1}H NMR (500 MHz, $CDCl_3$), (keto-enol mixture = 10:90), enol form only: δ = 12.16 (s, 1H), 7.55–7.03 (m, 5H), 3.62 (s, 2H), 3.17 (t, J = 1.6 Hz, 2H), 2.56 (t, J = 5.9 Hz, 2H), 2.35 (tt, J = 5.9, 1.6 Hz, 2H), 1.48 ppm (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 204.6, 170.8, 169.6, 168.1, 138.1, 137.9, 129.0, 128.8, 128.3, 128.2, 127.3, 127.1, 97.8, 81.8, 81.1, 62.0, 61.6, 57.2, 55.4, 53.1, 50.5, 48.3, 40.6, 29.4, 28.1, 27.9 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{17}H_{23}NO_3$: ($[M + H]^+$) 290.1750, found 290.1753.

4.2.2.3. Methyl 4-oxo-1-phenethylpiperidine-3-carboxylate (3i, CAS No. 66670-11-9).

Prepared from **2c** (293.4 g, 1.00 mol), in DMSO/THF (75/25, 2L), using sealed mechanical stirrer. Yield (yellow oil): 247.9 g (95%). ^{1}H NMR (keto-enol mixture = 30:70; 500 MHz, $CDCl_3$): δ = 11.92 (s), 7.35–7.15 (m), 3.76 (s), 3.75 (s), 3.48 (ddd, J = 7.8, 4.9, 1.2 Hz), 3.23 (t, J = 1.6 Hz), 3.16 (ddd, J = 11.6, 7.8, 1.1 Hz), 3.01 (ddd, J = 11.7, 4.9, 1.7 Hz), 2.92–2.77 (m), 2.77–2.71 (m), 2.69 (t, J = 5.9 Hz), 2.63 (dd, J = 6.4, 4.9 Hz), 2.60 (dd, J = 6.4, 4.9 Hz), 2.57–2.49 (m), 2.44 ppm (tt, J = 5.8, 1.6 Hz).^{13}C NMR (126 MHz, $CDCl_3$): δ = 203.70, 171.18, 170.19, 169.11, 139.93, 139.71, 128.52, 128.25, 126.01, 125.94, 96.39, 59.50, 58.55, 56.16, 54.91, 53.07, 52.07, 51.20, 49.42, 49.19, 40.49, 33.85, 33.67, 29.21 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{15}H_{19}NO_3$: ($[M + H]^+$) 262.1437, found 262.1433.

4.2.2.4. Ethyl 1-benzyl-5-methyl-4-oxopiperidine-3-carboxylate (3m, CAS No. 93614-12-1).

Prepared from **2d** (60 mmol, 19.3 g). Yield (yellow oil): 15.1 g, 92% (Note: the obtained mixture [*cis/trans* stereoisomers and keto-enol tautomers] gave poorly resolved ^{1}H NMR [200 MHz, $CDCl_3$, in Supplementary information] and was further characterized by acidic hydrolysis/decarboxylation to ketone **4c**). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 206.4, 205.6, 173.9, 171.3, 168.6, 138.3, 137.9, 137.8, 128.8, 128.7, 128.4, 128.2, 127.4, 127.3, 127.1, 96.2, 62.0, 61.5, 61.3, 60.9, 60.9, 60.7, 60.2, 56.3, 56.2, 56.0, 55.7, 55.5, 50.7, 44.1, 43.5, 34.1, 15.8, 14.2, 14.0, 14.0, 12.0, 11.2 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{16}H_{21}NO_3$: ($[M + H]^+$) 276.1594, found 276.1583.

4.2.2.5. Compound 3n (equimolar mixture of methyl 1-benzyl-6-methyl-4-oxopiperidine-3-carboxylate [new compound] and methyl 1-benzyl-2-methyl-4-oxopiperidine-3-carboxylate [new compound]).

Prepared from **2e** (8.80 g, 30 mmol). Yield (yellow oil): 6.92 g, 88%. [Note: the obtained mixture (*cis/trans* stereoisomers and keto-enol tautomers) gave poorly resolved ^{1}H NMR (200 MHz, $CDCl_3$, in Supporting information) and was further characterized by acidic hydrolysis/decarboxylation to ketone **4d**. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 204.6, 204.0, 203.7, 171.8, 171.3, 170.5, 169.5, 169.4, 139.0, 138.9, 138.5, 138.5, 128.5, 128.4, 128.1, 127.1, 126.8, 102.0, 95.6, 63.0, 57.6, 57.5, 57.1, 56.6, 56.5, 56.1, 56.0, 56.0, 55.6, 51.9, 51.8, 51.4, 51.1, 51.0, 50.8, 50.5, 50.1, 48.1, 47.2, 47.1, 45.1, 40.7, 39.5, 35.3, 26.6, 17.9, 16.4, 16.3, 13.9, 13.7 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{15}H_{19}NO_3$: ($[M + H]^+$) 262.1437, found 262.1440.

4.2.2.6. Compound 3o (equimolar mixture of ethyl 1-benzyl-3-oxopyrrolidine-2-carboxylate, CAS No. 329956-59-4 and ethyl 1-benzyl-4-oxopyrrolidine-3-carboxylate, CAS No. 1027-35-6).

Prepared from **2f** (8.80.g, 30 mmol) and it was not separated. Yield (yellow oil): 6.69 g, 90%. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.34–7.02 (m), 4.26–4.04 (m), 3.95–3.59 (m), 3.55–3.19 (m), 3.07 (t, J = 8.9 Hz), 2.95–2.43 (m), 1.43–1.06 ppm (m). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 206.4, 167.3, 136.9, 129.3, 128.6, 128.4, 128.3, 127.5, 127.4, 72.2, 61.5, 61.4, 60.9, 60.0, 58.2, 54.4, 53.9, 48.2, 40.7, 37.1, 14.0 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{14}H_{17}NO_3$: ($[M + H]^+$) 248.1281, found 248.1283.

4.2.2.7. Tert-butyl 1-benzyl-3-oxopyrrolidine-2-carboxylate (3p, CAS No. 329956-61-8). Prepared from 2g (9.64 g, 30 mmol).

Yield (amorphous white mass): 7.25 g, ca. 85%, contaminated with a single impurity, ca. 5% acc. to ^{1}H NMR). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–7.14 (m, 5H), 3.95 (d, J = 13.0 Hz, 1H), 3.73 (d, J = 12.9 Hz, 1H), 3.46 (s, 1H), 3.31 (td, J = 8.6, 3.7 Hz, 1H), 2.72 (dd, J = 16.5, 8.3 Hz, 1H), 2.60–2.50 (m, 1H), 2.45 (dd, J = 7.4, 3.7 Hz, 1H), 2.41 (dd, J = 7.4, 3.7 Hz, 1H), 1.45 ppm (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 207.8, 166.4, 136.5, 129.1, 128.3, 127.4, 82.1, 72.6, 57.8, 48.0, 37.1, 27.8 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{16}H_{21}NO_3$: ($[M + H]^+$) 276.1594, found 276.1596.

4.2.2.8. Tert-butyl 2-oxocyclohexanecarboxylate (3q, CAS No. 55623-56-8).

Prepared from di-*tert*-butyl heptanedioate (8.00 g, 29.4 mmol). Yield (distilled colourless liquid): 4.95 g, 85%. ^{1}H NMR (keto-enol mixture = 30:70; 200 MHz, $CDCl_3$): δ = 12.40 (s), 3.33–3.20 (m), 2.58–2.31 (m), 2.30–2.10 (m), 1.94–1.75 (m), 1.74–1.53 (m), 1.50 (s), 1.48 ppm (s). ^{13}C NMR (50 MHz, $CDCl_3$): 206.7, 172.6, 171.2, 169.2, 98.8, 81.4, 80.5, 57.8, 41.4, 29.9, 29.0, 28.1, 27.9, 27.0, 23.0, 22.7, 22.4, 21.9 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{11}H_{18}O_3$: ($[M + K]^+$) 237.0887, found 237.0878.

4.2.3. Typical procedure for the preparation of heterocyclic ketones (piperidones and pyrrolidones)

The compounds **4a**–**4e** were prepared according to the typical procedure for **4a**.

4.2.3.1. 1-Benzyl-piperidin-4-one (4a, CAS No. 3612-20-2).

Compound **3j** (12.4 g, 50 mmol) was dissolved in

aqueous HCl (28–30%, 80 mL) and heated to reflux with magnetic stirring for 2–3 h (vigorous CO_2 and HCl evolution!). The reaction mixture was cooled to ~20°C, poured on the crashed ice (50 g) and alkalized to pH ~10 with 20% NaOH solution at 15–25°C (strongly exothermic!). The resulting biphasic mixture was extracted with toluene (2 mL × 50 mL), concentrated (rotatory evaporator) and vacuum dried (0.1–0.3 mmHg, ~20°C, 30 min). Yield: (yellow liquid): 8.75 g, 92%, ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.39–7.20$ (m, 5H), 3.60 (s, 2H), 2.72 (t, $J = 6.1$ Hz, 4H), 2.43 ppm (t, $J = 6.1$ Hz, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 209.0$, 138.0, 128.7, 128.2, 127.1, 61.7, 52.7, 41.1 ppm.

4.2.3.2. 1-Phenethylpiperidin-4-one (4b, CAS No. 39742-60-4). Prepared from **3l** (247.9 g, 0.95 mol). Estimated purity (^{1}H NMR): >95%. Yield (yellow solid): 184.2 g, 91%. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.58–6.94$ (m, 5H), 2.88–2.78 (m, 6H), 2.76–2.69 (m, 2H), 2.47 ppm (t, $J = 6.2$ Hz, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 208.69$, 139.78, 128.44, 128.21, 125.94, 58.99, 52.78, 40.96, 33.86 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{13}H_{17}NO$: ($[M + H]^+$) 204.1382, found 204.1385.

4.2.3.3. 1-Benzyl-3-methylpiperidin-4-one (4c, CAS No. 34737-89-8). Prepared from **3m** (30 mmol, 8.26 g) Yield: (yellow liquid) 5.35 g, 88%. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta =$ 7.38–7.22 (m, 5H), 3.60 (s, 2H), 3.20–2.95 (m, 2H), 2.74–2.24 (m, 4H), 2.09 (t, $J = 11.1$ Hz, 1H), 0.99 ppm (d, $J =$ 6.7 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 211.0$, 138.1, 128.8, 128.3, 127.2, 61.7, 60.6, 53.6, 44.2, 40.8, 11.8 ppm. HRMS-Tof-ESI: *m/z* calcd for $C_{13}H_{17}NO$: ($[M + H]^+$) 204.1382, found 204.1392.

4.2.3.4. 1-Benzyl-2-methylpiperidin-4-one (4d CAS No. 203661-73-8). Prepared from **3n** (7.84 g, 30 mmol) Yield (yellow liquid): 5.20 g, 85%. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.39–7.22$ (m, 5H), 3.94 (d, $J = 13.5$ Hz, 1H), 3.43 (d, $J = 13.4$ Hz, 1H), 3.09–2.79 (m, 2H), 2.66–2.42 (m, 2H), 2.39–2.20 (m, 3H), 1.15 ppm (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 209.3$, 138.8, 128.5, 128.2, 126.9, 56.8, 55.9, 48.5, 48.3, 40.6, 17.2 ppm. HRMS-ToF-ESI: *m/z* calcd for $C_{13}H_{17}NO$: ($[M + H]^+$) 204.1382, found 204.1384.

4.2.3.5. 1-Benzylpyrrolidin-3-one (4e, CAS No. 775-16-6). Prepared from **3o** (30 mmol, 7.42 g). Yield: (yellow liquid) 4.40 g, 84%. The compound was relatively unstable and was kept at −20°C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.55–7.08$ (m, 5H), 3.70 (s, 2H), 3.07–2.68 (m, 4H), 2.38 ppm (t, $J = 6.8$ Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 213.8$, 137.2, 128.6, 128.2, 127.2, 61.2, 60.4, 51.0, 37.7 ppm.

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