# Bis-enaminone Based Parallel Solution-Phase Synthesis of 1,4-Dihydropyridine Derivatives

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Two variations of a parallel solution-phase synthesis of *N*-substituted dimethyl 4-oxo-1,4-dihydropyridine-3,5-dicarboxylates **4** and methyl 3-oxo-3,5-dihydro-2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylates **9** from dimethyl acetone-1,3-dicarboxylate (**1**) were developed. The first synthetic method comprises preparation of the bis-enaminone reagents **2** and **8** and their cyclization with primary amines **3** via double substitution of both dimethylamino groups to give dihydropyridines (DHPs) **4** and **9**, respectively. Another variation consists of preparation of the monoenaminone reagents **5** and **10**, followed by substitution of the dimethylamino group with primary amines **3**, and cyclization of the so formed intermediates **6** with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA). In this manner, a library of 46 analytically pure compounds, 24 intermediates **6**, **11**, and **13**, and 22 final dihydropyridines **4** and **9** was obtained employing just a simple filtration workup.



## Introduction

Numerous heterocyclic compounds have the ability to mimic structures of peptides and to bind reversibly to proteins. Consequently, heterocyclic compounds represent important scaffolds for the preparton of compound libraries for medicinal and pharmaceutical applications.[1−6] A nice example of a simple and useful scaffold is a 1,4-dihydropyridine (DHP) system, due to its ability to act as NAD(P)H analogue of 1,4-dihydronicotinamide.[7] Although 1,4-dihydropyridines (DHPs) are known at most as calcium channel blockers such as nifedipine and amlodipine, they also exhibit other pharmacological activities (Figure 1).[8] Therefore, the preparation of their novel DHP derivatives seems like a reasonable target in medicinal and synthetic organic chemistry. Within this context, efficient access to combinatorial libraries of dihydropyridines and fused analogues is of particular interest.[1,3]

In the literature, numerous methods for the preparation of DHPs are described. However, the most frequently used method for the preparation of dihydropyridines is a *Hantzsch*-type three-component cyclocondensation between 1,3-dicarbonyl compound, aldehyde, and ammonia including various modifications of this method.[8] It is not surprising, that Hantzch-type reactions have also found use in the solid-phase synthesis of combinatorial libraries of DHPs.[1,3,4,9−11] For example, combinatorial libraries of DHPs have been synthesized (a) from resin-bound enamino esters by treatment with α-benzylidene-β-keto esters or with β-keto esters and aldehydes,[9] (b) from resin-bound α-alkylidene-β-keto esters and β-aminocrotonate,[10] and (c) from resin-bound β-aminocrotonate and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (cyclic acetonide of acetoacetic acid).[11]

2-Substituted alkyl 3-(dimethylamino)prop-2-enoates and related enaminones are enamino masked analogues of β-keto aldehydes, and like their parent 1,3-dicarbonyl compounds, they are versatile reagents in the preparation of heterocyclic systems.[12] In addition to this, enaminones have also been widely used as the key-intermediates in the synthesis of functionalized heterocycles and natural product analogues[12−14] and in combinatorial applications as well.[15−20] Enaminone chemistry also offers an easy access to 4-oxo-1,4-dihydropyridines via the "bis-enaminone" route. Treatment of 1,3-disubstituted acetone (or its analogue) with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) gives the corresponding

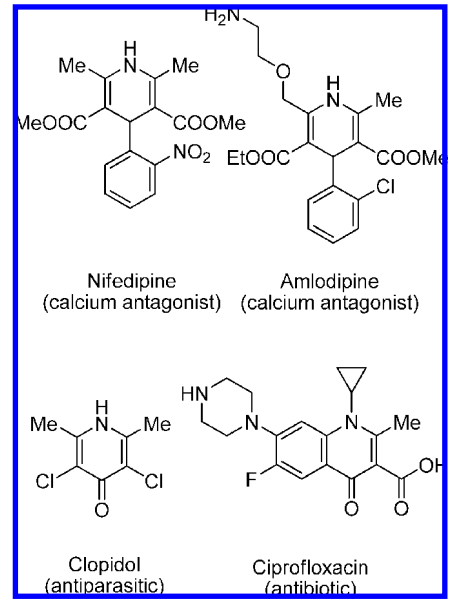


**Figure 1.** Some examples of important 1,4-dihydropyridines.

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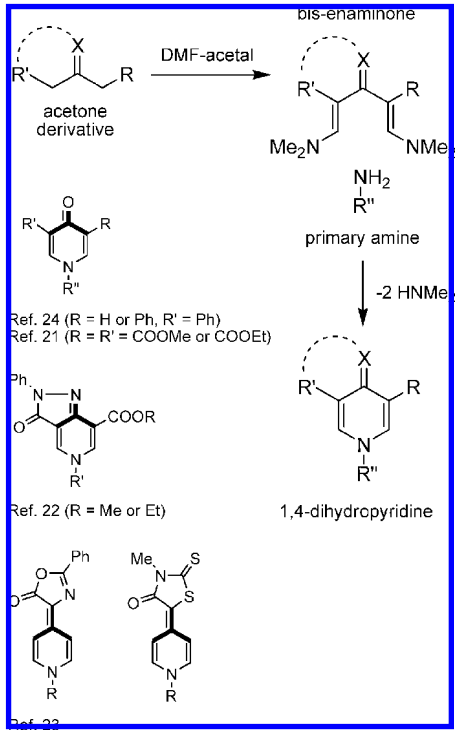



**Figure 2.** Bis-enamonine route to DHPs.[21−24]

bis-enaminone, which reacts with primary amines to furnish the corresponding DHP derivative (Figure 2).[21−24] Within this context, we have previously reported syntheses of 1-substituted 1,4-dihydropyridines and their fused analogues by treatment of primary amines with bis-enaminones, derived from dialkyl acetone-1,3-dicarboxylates,[21] ethyl 2-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)acetates,[22] 2-phenyl-4-(isopropylidene)oxazol-5(4*H*)-one, and 3-methyl-5-(propan-2-ylidene)-2-thioxothiazolidin-4-one.[23] In extension, we were interested in combinatorial application of the above method as well. Herein, we report the results of our study, i.e. utilization of the bis-enaminone approach in the parallel solution-phase synthesis of the title compounds.

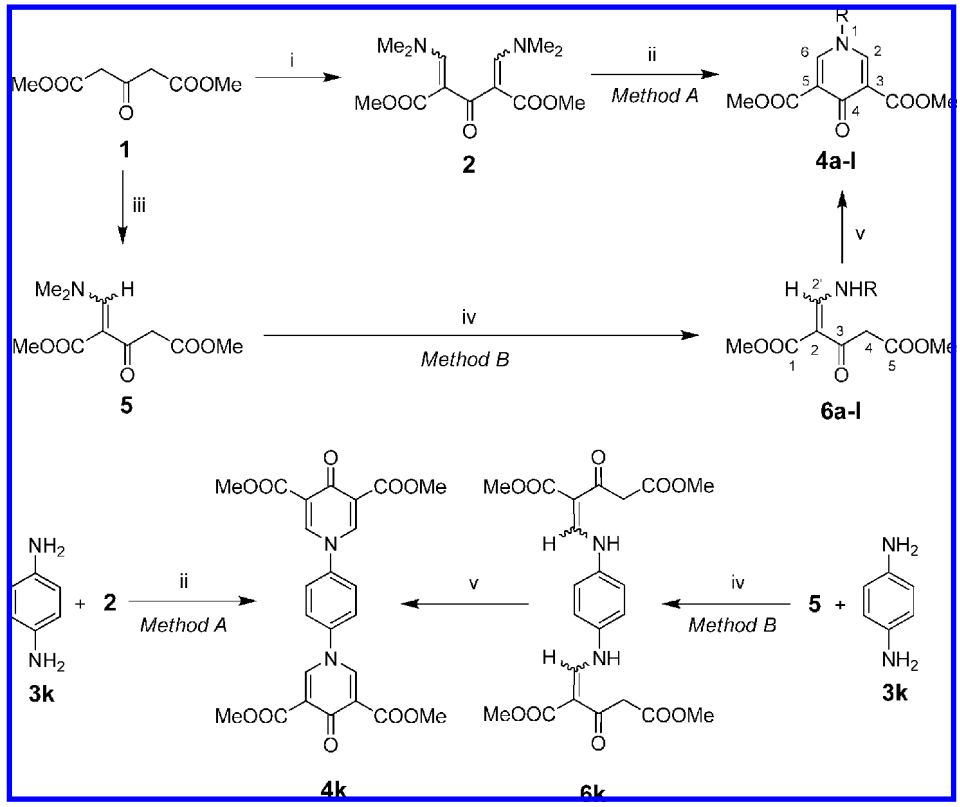
## Results and Discussion

**Solution-Phase Synthesis of 1-Substituted Dimethyl 4-Oxo-1,4-dihydropyridine-3,5-dicarboxylates 4.** First a one-step parallel solution phase synthesis of dimethyl 4-oxo-1,4-dihydropyridine-3,5-dicarboxylates **4a**−**l** was carried out. The key-intermediate, dimethyl 2,4-bis[(dimethylamino)-methylidene]-3-oxopentanedioate (**2**), was prepared in situ by treatment of dimethyl 3-oxopentanedioate (**1**) with 2 equiv of DMFDMA in toluene at 110 °C for 2 h. Further reaction of the crude bis-enaminone **2** with amines **3a**−**l** in 1-propanol at 90 °C for 2 h gave the corresponding DHPs **4a**−**l**. Upon cooling, the products **4a**−**l** precipitated from the reaction mixtures and were isolated simply by filtration to afford 12 dihydropyridines **4a**−**l** in 39−86% yields. Quite expectedly,[21] reaction of **2** with *p*-phenylenediamine (**3k**) was exceptional and furnished tetramethyl 1,1′-(1,4-phenylene)bis(4-oxo-1,4-dihydropyridine-3,5-dicarboxylate) (**4k**) as the only product. In terms of purity, seven compounds (**4a**−**g**) were analytically pure and five compounds (**4h**−**l**) were >80% pure according to $^1$H NMR (method A, Scheme 1, Table 1). Although a one-pot method was simple and efficient, its minor disadvantage was the average purity of the library, since almost one-half of the library members were not analytically pure. In order to improve this, we focused our attention on a stepwise preparation of the title compounds **4**. First, reaction of dimethyl 3-oxopentanedioate (**1**) with 1 equiv of DMFDMA in methanol at room temperature led selectively to the monoenaminone **5**. Acid-catalyzed treatment of the in situ formed **5** with (hetero)aromatic amines **3a**−**l** in methanol at room temperature afforded the corresponding dimethylamine substitution products **6a**−**l** as precipitates, which were isolated by filtration in 43−100% yields and in analytical purity. Finally, reaction of the intermediates **6a**−**l** with DMFDMA in methanol under reflux followed by filtration workup furnished dihydropyridines **4a**−**l** in moderate yields. Eleven products (**4a**−**j**,**l**) were analytically pure, while compound **4k** was ≥80% pure according to $^1$H NMR (method B, Scheme 1, Table 1).

**Solution-Phase Synthesis of Methyl 5-(Hetero)aryl-3-oxo-3,5-dihydro-2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylates 9.** Next, a parallel solution-phase synthesis of 5-substituted 3-oxo-3,5-dihydro-2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylates **9** was studied. The starting compound, methyl 2-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)acetate (**7**), was obtained from dimethyl 3-oxopentanedioate (**1**) and hydrazine hydrate in methanol following the literature procedure.[25] Reaction of **7** with 2 equiv of DMFDMA in refluxing DMF afforded the bis-enaminone **8** in 80% yield. Cyclization into pyrazolo[4,3-*c*]pyridines **9g**,**j**,**l**−**s** was then achieved by parallel acid-catalyzed treatment of **8** with (hetero)arylamines **3g**,**j**,**l**−**s** in methanol at room temperature. Again, all products precipitated from the reaction mixtures and were isolated by filtration to give a library of 10 analytically pure compounds **9g**,**j**,**l**−**s** in 30−82% yields. Also in this case, we were interested in exploring a two-step procedure as well. Treatment of the starting pyrazole **7** with 1 equiv of DMFDMA in toluene at room temperature proceeded regioselectively at the ring methylene group to give the monoenaminone **10** in 85% yield. Reagent **10** was the treated with (hetero)arylamines **3a**,**g**,**l**,**r**−**v** and *C*-nucleophiles **12a**−**d** in methanol at room temperature to produce the dimethylamine substitution products **11a**,**g**,**l**,**r**−**v** and **13a**−**d**, respectively, as precipitates, which were isolated by filtration. In this manner, 12 substitution products **11** and **13** were obtained in 38−94% yields and in analytical purity. Unfortunately, attempts to perform cyclization of compounds **11** into pyrazolo[4,3-*c*]pyridines **9** with DMFDMA were not successful (Scheme 2, Table 2).

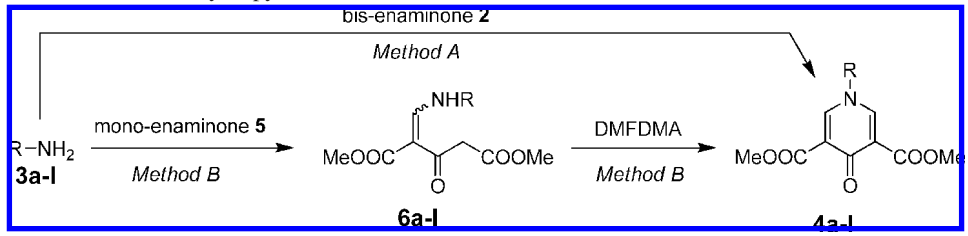
A one-pot formation of 1,4-dihydropyridines **4** and **9** from the bis-enaminone reagents **2** and **8** can be explained by substitution of both dimethylamino groups in the bis-enaminones **2** and **8** with primary amines **3** according to the previously established addition−elimination mechanism.[12,21−24] Reaction of the symmetrical reagent **2** with a primary amine **3** most probably proceeds by substitution of the first dimethylamino group to give the intermediate **14**, which then undergoes substitution of the second dimethylamino group to afford a DHP derivative **4**. On the other hand, reaction of the nonsymmetrical bis-enaminone **8** with a primary amine

**Scheme 1**[a]




[a] Reaction conditions: (i) DMFDMA, toluene, reflux; (ii) R−$NH_2$ **3a**−**l**, *n*-PrOH, 95 °C; (iii) DMFDMA, MeOH, rt; (iv) R−$NH_2$ **3a**−**l**, MeOH, rt; (v) DMFDMA, MeOH, reflux.

**Table 1.** Experimental Data on 1,4-Dihydropyridines **4** and Intermediates **6**[a]



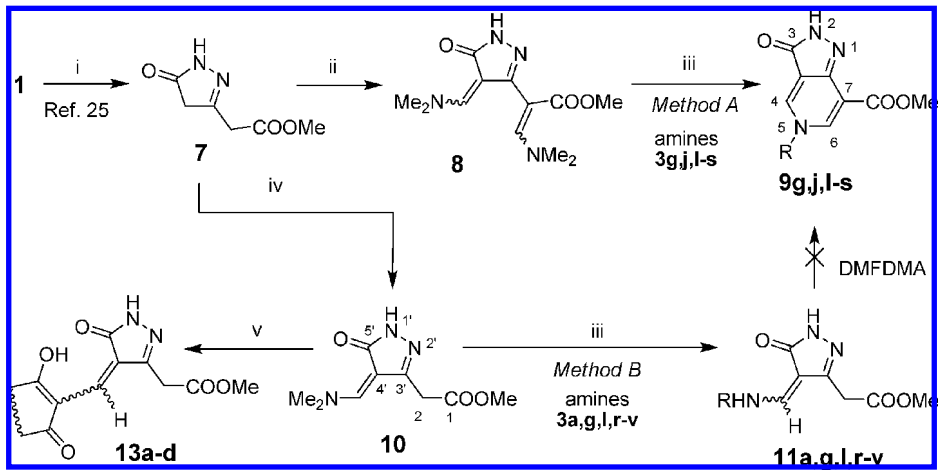

| | | yield (%) | | |
|---|---|---|---|---|
| | | method A | method B | |
| compound | R | **3** → **4** | **5** → **6** | **6** → **4** |
| **3a**, **4a**, **6a** | pyrazinyl | 50 | 60 | 25 |
| **3b**, **4b**, **6b** | pyridin-2-yl | 84 | 86 | 33 |
| **3c**, **4c**, **6c** | 4-methylpyridin-2-yl | 54 | 79 | 30 |
| **3d**, **4d**, **6d** | 5-methylpyridin-2-yl | 45 | 73 | 28 |
| **3e**, **4e**, **6e** | 3-hydroxypyridin-2-yl | 56 | 48 | 35 |
| **3f**, **4f**, **6f** | 5-chloropyridin-2-yl | 39 | 70 | 28 |
| **3g**, **4g**, **6g** | 4-nitrophenyl | 45 | 100 | 38 |
| **3h**, **4h**, **6h** | 4-fluorophenyl | 68[b] | 96 | 22 |
| **3i**, **4i**, **6i** | 2-iodophenyl | 86[b] | 100 | 30 |
| **3j**, **4j**, **6j** | 4-hydroxyphenyl | 69[b] | 74 | 26 |
| **3k**, **4k**, **6k** | 1,2-phenylene | 85[b] | 100 | 30[b] |
| **3l**, **4l**, **6l** | 4-methylphenyl | 54[b] | 70 | 66 |

[a] All products were obtained in >95% purity according to $^1$H NMR and elemental analyses. Unless otherwise stated, the found values for C, H, and N were within a ±0.4% range with respect to the theoretical values. [b] ≥80% purity according to $^1$H NMR. [c] Cyclization of 1,4-benzenediamine (**3k**) with enaminones **2** and **5** gave the bis-substitution products **4k** and **6k**, respectively (cf. Scheme 1).

**3** can furnish two regioisomeric intermediates, **15** and/or **16**, which cyclize into the same pyrazolo[4,3-*c*]pyridine **9** upon substitution of the second dimethylamino group. Similarly, substitution of the dimethylamino group in the reactions of monoenaminones **5** and **10** with amines **3** gave the corresponding substitution products **6** and **11**. Finally, cyclization of the intermediates **6** into dihydropyridines **4** is explainable as a 5 + 1 cyclocondensation between 1,5-dinucleophile **6** and DMFDMA as a $C_1$-electrophile (Scheme 3).

The structures and purity of all compounds **4a**−**l**, **5**, **6a**−**l**, **8**, **9g**,**j**,**l**−**s**, **10**, **11a**,**g**,**l**,**r**−**v**, and **13a**−**d** were determined by spectroscopic methods (IR, NMR, MS, HRMS) and by

**Scheme 2**[a]




[a] Reaction conditions: (i) $N_2H_4 \cdot H_2O$, MeOH, rt; (ii) DMFDMA, DMF, reflux; (iii) R−$NH_2$ **3a**,**g**,**j**,**l**−**v**, HCl (1 equiv), $H_2O$, rt; (iv) DMFDMA, toluene, rt; (v) *C*-nucleophile **12a**−**d**, HCl (1 equiv), MeOH, rt.



elemental analyses for C, H, and N. Compound **5** was not prepared in analytically pure form and was used for further tansformations without purification. The identity of **5** was confirmed by HRMS. Physical and spectral data for the known compounds **2**,[21] **7**,[25] and **4j**,**k**[21] were in agreement with the literature data.

## Conclusion

Reactions of bis-enaminones **2** and **8** with primary (hetero)arylamines **3** were employed in a parallel solution-phase synthesis of a library of 22 1,4-dihydropyridine derivatives **4** and **9**, while reactions of monoenaminones **5** and **10** with amines **3** and *C*-nucleophiles **12** produced 24 dimethylamine substitution products **6**, **11**, and **13**. Two methods for the preparation of the title compounds **4** and **9** were developed: (a) a one-step synthesis of DHPs **4** and **9** from bis-enaminones **2** and **8** (method A) and (b) a two-step synthesis of DHPs **4** from the monoenaminone **5** (method B). Generally, method A can be regarded as better and more convenient, since it afforded title compounds **4** and **9** in fair yields and in >80% average purity. In terms of purity, on the other hand, method B was more suited; within a library of 12 dihydropyridines **4**, 11 compounds were analytically pure. Surprisingly, method B could not be applied for the synthesis of the fused analogues **9**, since cyclization of the intermediates **11** with DMFDMA failed. In summary, a simple and efficient enaminone-based parallel solution-phase synthesis of 1,4-dihydropyridine derivatives **4** and **9** and intermediates **6** and **11** was developed. All products were obtained upon simple filtration workup, in most cases the isolated compounds were also analytically pure. To the best of our knowledge, this work represents the first example of utilization of the bis-enaminone methodology in the parallel synthesis of DHPs.

## Experimental Section

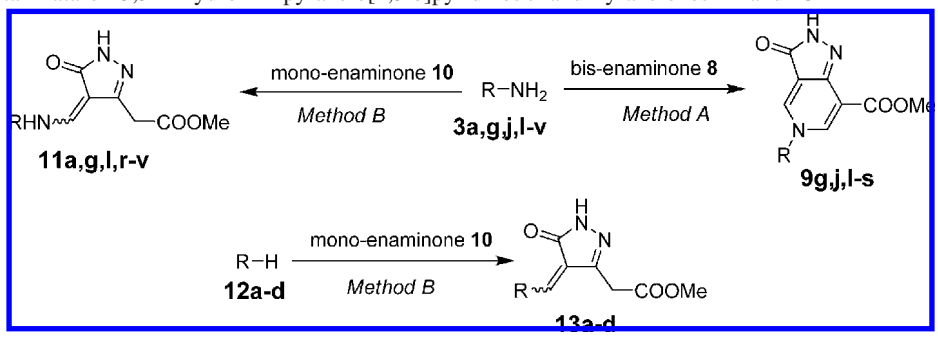
Melting points were determined on a Kofler micro hot stage. The NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for $^1$H and 75.5 MHz for $^{13}$C nucleus, using DMSO-$d_6$ and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an AutoSpecQ and on a Q-Tof Premier spectrometers, and IR spectra, on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400 II. Column chromatography (CC) was performed on silica gel (Fluka, silica gel 60, 0.04−0.06 mm).

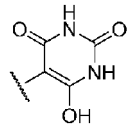
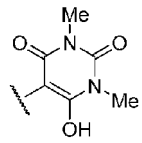
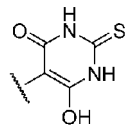
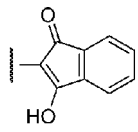
Dimethyl 3-oxopentanedioate (**1**), *N*,*N*-dimethylformamide dimethylacetal (DMFDMA), amines **3a**−**v**, and *C*-nucleophiles **12a**−**d** are commercially available (Sigma-Aldrich). Methyl 2-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)acetate (**7**) was prepared according to the literature procedure.[25]

Conventional and parallel stirring and heating were carried out on (a) a Mettler-Toledo Bohdan MiniBlock compact shaking and washing station and vacuum collection base (12 positions, vortex stirring, 400 rpm in all cases) and (b) a Büchi Syncore Polyvap parallel reactor equipped with a reflux module (24 positions, vortex stirring, 400 rpm in all cases). Parallel filtrations were performed on a Mettler-Toledo Bohdan MiniBlock compact shaking and washing station and vacuum collection base (12 positions). One-pot parallel synthesis of 1-substituted dimethyl 4-oxo-1,4-dihydropyridine-3,5-dicarboxylates **4a**−**l** from bis-enaminone **2** was carried out on a Mettler-Toledo Bohdan MiniBlock compact shaking and washing station and vacuum collection base (12 positions, vortex stirring, 400 rpm in all cases). Parallel evaportons and drying were carried out on (a) a Büchi Syncore Polyvap parallel evaporator (24 positions, vortex stirring, 400 rpm in all cases) and (b) a Hettlab IR-Dancer infrared vortex-evaporator (42 positions, vortex stirring, 400 rpm in all cases).

**Synthesis of Enaminones 2, 5, 8, and 10. Dimethyl 2,4-Bis[(dimethylamino)methylidene]-3-oxopentanedioate (2).** This compound was prepared following a slightly modified literature procedure.[21] A mixture of dimethyl 3-oxopentanedioate (**1**) (2.86 mL, 20 mmol), anhydrous toluene (30 mL), and DMFDMA (3 mL, 20 mmol) was refluxed for 3 h. Volatile components were evaporated in vacuo to give the crude bis-enaminone **2**, which was used for further transformations without purification. Yield: 5.7 g

**Table 2.** Experimental Data on 3,5-Dihydro-2*H*-pyrazolo[4,3-*c*]pyridines **9** and Pyrazolones **11** and **13**[a]




| Compound | R | Yield (%) | | |
|---|---|---|---|---|
| | | **9** | **11** | **13** |
| **3a**, **11a** | pyrazinyl | | 38 | |
| **3g**, **9g**, **11g** | 4-nitrophenyl | 63 | 78 | |
| **3j**, **9j** | 4-hydroxyphenyl | 82 | | |
| **3l**, **9l**, **11l** | 4-methylphenyl | 75 | 63 | |
| **3m**, **9m** | 3-methylphenyl | 80 | | |
| **3n**, **9n** | 2-aminophenyl | 75 | | |
| **3o**, **9o** | 3-chloro-4-fluorophenyl | 51 | | |
| **3p**, **9p** | 2-bromophenyl | 30 | | |
| **3q**, **9q** | 4-methoxyphenyl | 79 | | |
| **3r**, **9r** | phenyl | 58 | 57 | |
| **3s**, **9s**, **11s** | 3-nitrophenyl | 70 | 77 | |
| **3t**, **9t**, **11t** | 4-bromophenyl | | 69 | |
| **3u**, **11u** | 5-methylisoxazol-3-yl | | 52 | |
| **3v**, **11v** | quinolin-3-yl | | 69 | |
| **12a**, **13a** |  | | | 80 |
| **12b**, **13b** |  | | | 91 |
| **12c**, **13c** |  | | | 94 |
| **12d**, **13d** |  | | | 91 |

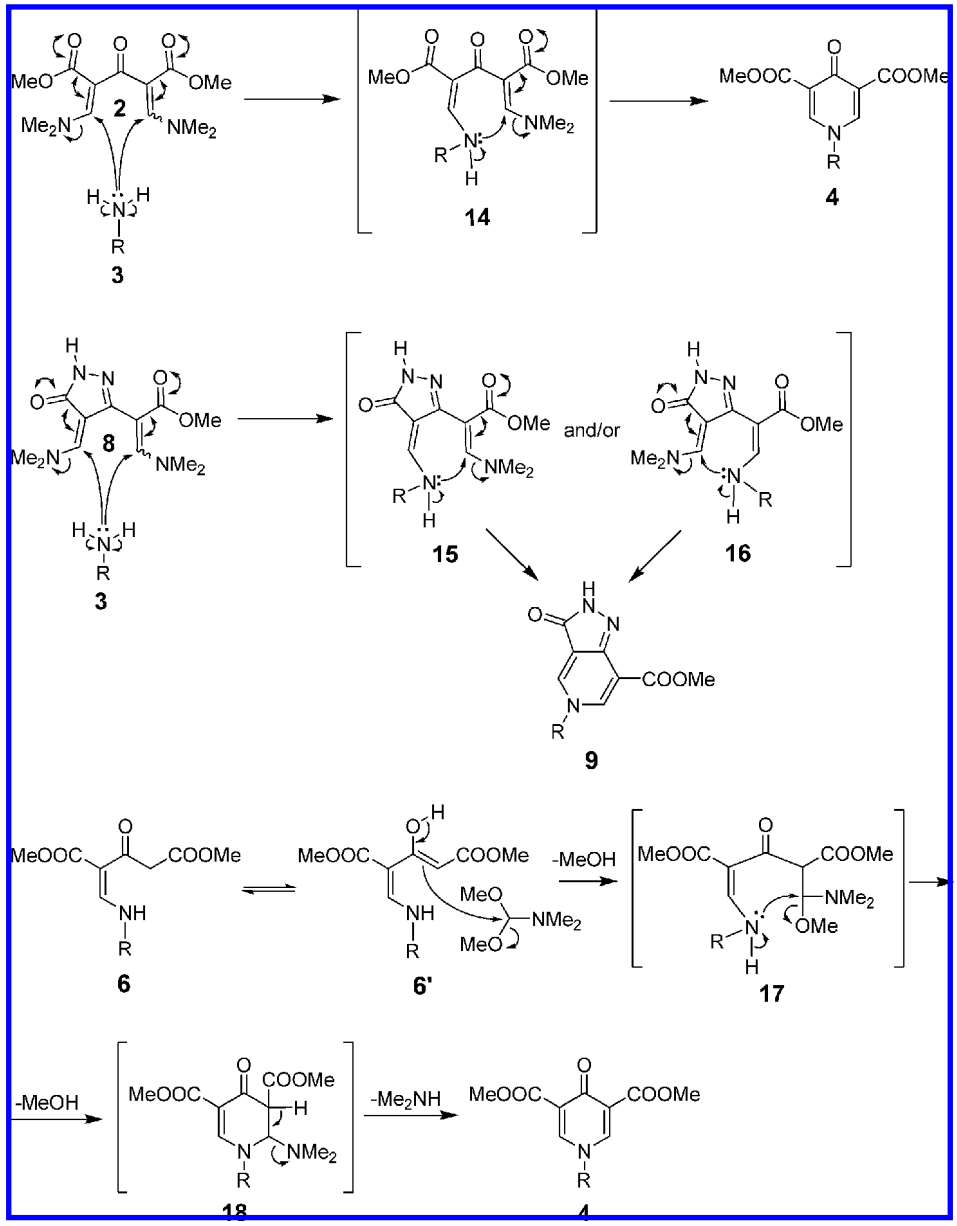
[a] All products were obtained in >95% purity according to $^1$H NMR and elemental analyses; the found values for C, H, and N were within a ±0.4% range with respect to the theoretical values.



(100%) of a yellow oil. Spectral data of **2** were consistent with the literature data.[21]

**Dimethyl 2-[(dimethylamino)methylidene]-3-oxopentanedioate (5).** A mixture of dimethyl 3-oxopentanedioate

**Scheme 3**






(**1**) (0.143 mL, 1 mmol), anhydrous methanol (3 mL), and DMFDMA (0.15 mL, 1 mmol) was stirred at rt for 16 h. Volatile components were evaporated in vacuo, and the yellow oily residue was purified by CC ($CHCl_3$−MeOH, 30:1). Fractions containing the product were combined and evaporated in vacuo to give **5** as a yellow oil, which was used for further tansformations without purification. Yield: 0.119 g (65%) of a yellow oil. ESI-MS: $m/z = 230$ ($MH^+$). IR (KBr): $\nu_{max}$ 2953 (NH), 1735 (C═O), 1692 (C═O), 1646 (C═O), 1579, 1432, 1259, 1120, 999, 769 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 2.91 and 3.29 (6H, 2br s, 1:1, $NMe_2$); 3.71 and 3.72 (6H, 2s, 1:1, 2 × OMe); 3.80 (2H, s, $CH_2$); 7.84 (1H, s, CH). ESI-HRMS Calcd. for $C_{10}H_{16}NO_5$: $m/z = 230.1028$ ($MH^+$). Found: $m/z = 230.1038$ ($MH^+$).

**Methyl (*E*)-3-(Dimethylamino)-2-[(*Z*)-4-(dimethylamino)methylidene]-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)propenoate (8).** A mixture of methyl 2-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)acetate (**8**) (2.11 g, 10 mmol), anhydrous DMF (20 mL), and DMFDMA (5 mL, 33 mmol) was heated under reflux for 2 h, and volatile components were evaporated in vacuo. The residue was triturated with methanol (30 mL) and then left in a refrigerator at −30 °C for 12 h. The precipitate was collected by filtration to give **9**. Yield: 2.12 g (80%) of a yellow solid. mp 236−239 °C (from MeOH). IR (KBr): $\nu_{max}$ 3137 (NH), 3098 (NH), 2966, 2944, 2813, 1668 (C═O), 1593, 1531, 1434, 1395, 1314, 1261, 1216, 1132, 1084, 1062, 987, 935, 807, 769, 696, 537 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): $\delta$ 3.21, 3.31, and 3.49 (12H, 3s, 1:2:1, 2 × $NMe_2$); 3.78 (3H, s, OMe); 6.86 and 7.53 (2H, 2s, 1:1, 2 × CH); 10.56 (1H, s, NH). Anal. Calcd. for $C_{12}H_{18}N_4O_3$ (266.30): C, 54.12; H, 6.81; N, 21.04. Found: C, 54.12; H, 6.98; N, 21.30.

**Methyl 2-{4-[(*Z*)-(Dimethylamino)methylidene]-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl}acetate (10).** A mixture of methyl 2-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)acetate (**7**)[25] (15.13 g, 97 mmol), anhydrous toluene (140 mL), and DMFDMA (18 mL, 116 mmol) was stirred at rt for 1 h and then at −15 °C for 1 h. The precipitate was collected by

filtration and crystallized from methanol−toluene to give **10**. Yield: 17.40 g (85%) of a yellow solid. mp 151−154 °C (from MeOH). IR (KBr): $\nu_{max}$ 3434 (NH), 3159 (NH), 1730 (C═O), 1672 (C═O), 1589, 1556, 1427, 1410, 1215, 1140, 824, 733, 669, 547 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): $\delta$ 3.26 and 3.61 (6H, 2s, 1:1, $NMe_2$); 3.50 (2H, s, $CH_2$); 3.77 (3H, s, OMe); 7.36 (1H, s, CH); 10.58 (1H, s, NH). Anal. Calcd. for $C_9H_{13}N_3O_3$ (211.22): C, 51.18; H, 6.20; N, 19.89. Found: C, 51.10; H, 6.39; N, 19.70.

**General Procedures for the Synthesis of Dimethyl 1-[(Hetero)aryl]-4-oxo-1,4-dihydropyridine-3,5-dicarboxylates 4a−l. One-Pot Procedure.** The MiniBlock was equipped with 12 fritted vessels and charged with 1-propanol (12 × 4 mL) and dimethyl 3-oxopentanedioate (**1**) (12 × 0.143 mL, 12 × 1 mmol). The mixtures were vortexed at 95 °C for 2 h and then cooled to 20 °C. Then, amines hydrochlorides **3a**−**l**[26] were added (12 × 1 mmol) to the in situ formed bis-enaminone **2**, the reaction mixtures were vortexed at 95 °C for 4 h, cooled to 0 °C, and vortexed at 0 °C for 1 h. The precipitates were collected by filtration, washed with methanol (12 × 3 mL), and dried in vacuo at rt over NaOH pellets for 12 h to give **4**. Compounds **4a**−**l** were prepared in this manner.

**Two-Step Procedure. Step 1: Synthesis of Dimethyl 2-[(Hetero)arylaminomethylidene]-3-oxopentanedioates 6a−l.** The MiniBlock was equipped with 12 fritted vessels, charged with anhydrous methanol (12 × 3 mL) and DMFDMA (12 × 0.143 mL, 12 × 1 mmol), and the mixtures were vortexed at 20 °C for 16 h. Then, amines hydrochlorides **3a**−**l**[26] were added (12 × 1 mmol), and the reaction mixtures were vortexed at 20 °C for 24 h. Water (12 × 2 mL) was added, and the mixtures were vortexed at −15 °C for 1 h. The precipitates were collected by filtration, washed with water (12 × 3 mL), and dried in vacuo at rt over NaOH pellets for 12 h to give **6**. Compounds **6a**−**l** were prepared in this manner.

**Step 2: Transformations of Dimethyl 2-[(Hetero)arylaminomethylidene]-3-oxopentanedioates 6a−l into Dihydropyridones 4a−l.** The Syncore Polyvap parallel reactor was equipped with 12 test tubes and a reflux module. Test tubes were charged with compounds **6a**−**l** (12 × 0.5 mmol), anhydrous methanol (12 × 3.5 mL), and DMFDMA (12 × 0.5 mL, 12 × 3.5 mmol). The temperature of the heating block was set to 100 °C, and the mixtures were vortexed under reflux for 16 h. Upon cooling to 0 °C, 10 precipitates were formed. The precipitates were collected by filtration on a MiniBlock parallel filtration module and dried in a Hettlab evaporator at 100 mbar/40 °C for 5 h to give **4**. Compounds **4a**−**l** were prepared in this manner. In two instances, the precipitates were not formed. These two reaction mixtures were evaporated in vacuo and the solid residues were crystallized from EtOAc−hexanes to give **4**. Compounds **4g** and **4k** were prepared in this manner.

Experimental data for compounds **4a**−**l** and **6a**−**l** are given in Table 1. Analytical and spectral data for compounds **4a**−**l** and **6a**−**l** are given in the Supporting Information (Tables 1 and 2).

**General Procedure for the Synthesis of Methyl 5-[(Hetero)aryl]-3-oxo-3,5-dihydro-2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylates 9g,j,l−s.** The MiniBlock was equipped with 12 fritted vessels and charged with bis-enaminone **8** (10 × 213 mg, 12 × 0.8 mmol), water (10 × 5 mL), and amines hydrochlorides **3g**,**j**,**l**−**s**[26,27] (10 × 0.8 mmol). The reaction mixtures were vortexed at 20 °C for 24 h. The precipitates were collected by filtration, washed with water (10 × 3 mL), and dried in vacuo at rt over NaOH pellets for 12 h to give **9**. Compounds **9g**,**j**,**l**−**s** were prepared in this manner.

Experimental data for compounds **9g**,**j**,**l**−**s** are given in Table 2. Analytical and spectral data for compounds **9g**,**j**,**l**−**s** are given in the Supporting Information (Tables 3 and 4).

**General Procedure for the Synthesis of (*Z*)-Methyl 2-[5-Oxo-4-(arylaminomethylidene)-4,5-dihydro-1*H*-pyrazol-3-yl]acetates 11a,g,l,r−v.** The MiniBlock was equipped with 12 fritted vessels and charged with monoenaminone **10** (12 × 411 mg, 12 × 2 mmol), water (12 × 3 mL), and amines hydrochlorides **3a**,**g**,**l**,**r**−**v**[26] (12 × 2 mmol). The reaction mixtures were vortexed at 20 °C for 24 h. The precipitates were collected by filtration, washed with water (10 × 1 mL), and dried in vacuo at rt over NaOH pellets for 12 h to give **11**. Compounds **11a**,**g**,**l**,**r**−**v** were prepared in this manner.

Experimental data for compounds **11a**,**g**,**l**,**r**−**v** are given in Table 2. Analytical and spectral data for compounds **11a**,**g**,**l**,**r**−**v** are given in the Supporting Information (Tables 3 and 4).

**General Procedure for the Synthesis of (*Z*)-Methyl 2-[5-Oxo-4-(heteroarylmethylidene)-4,5-dihydro-1*H*-pyrazol-3-yl]acetates 13a−d.** The MiniBlock was equipped with 12 fritted vessels and charged with monoenaminone **10** (4 × 103 mg, 4 × 0.5 mmol), methanol (4 × 3 mL), *C*-nucleophiles **12a**−**d** (4 × 0.5 mmol), and 1 M hydrochloric acid (4 × 0.5 mL, 4 × 0.5 mmol). The reaction mixtures were vortexed at 20 °C for 24 h. The precipitates were collected by filtration, washed with water (10 × 1 mL), and dried in vacuo at rt over NaOH pellets for 12 h to give **13**. Compounds **13a**−**d** were prepared in this manner.

Experimental data for compounds **13a**−**d** are given in Table 2. Analytical and spectral data for compounds **13a**−**d** are given in the Supporting Information (Tables 3 and 4).

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**Supporting Information Available.** Analytical and spectral data for compounds **4a**−**l**, **6a**−**l**, **9g**,**j**,**l**−**s**, **11a**,**g**,**l**,**r**−**v**, and **13a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) In the case of the free amine derivative **3**, 1 equiv of 37% hydrochloric acid (0.1 mL = 1 mmol) was added.

(27) In the case of the 4-nitroaniline (**3g**), chloroform (3 mL) was also added.


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