Aqueous One-Pot Synthesis of Pyrazoles, Pyrimidines and Isoxazoles Promoted by Microwave Irradiation

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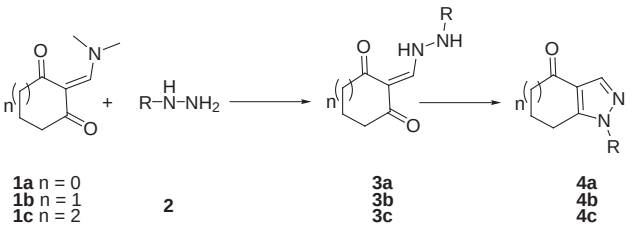
Abstract: Microwave irradiation promotes the conversion of enaminoketones formed in situ into a variety of heterocycles by reaction with the appropriate bidentate nucleophile. The advantages of the method over previous approaches are short reaction times and facile purification by precipitation of the products in aqueous media. Moreover the convenient one-pot procedure makes these syntheses particularly suitable for library production. Organic reactions in aqueous media have become of great interest as water is not only more environmentally friendly, but also because organic reactions in water often display unique reactivity and selectivity.

Key words: bidentate nucleophiles, tandem addition-elimination/cyclodehydration, enaminoketones, microwave irradiation



Scheme 1

It is well established that formamide acetals react with active methylene ketones to produce enaminoketones,[1] which can subsequently yield a vast array of heterocyclic compounds. Reaction of enaminoketones with the appropriate bidentate nucleophiles give pyrazoles,[2] pyrimidines,[3] pyrimidones,[4] isoxazoles,[5] pyrroles,[6] and pyridones.[7] During an ongoing project we became interested in the synthesis of compounds **4**, generally prepared from the corresponding enaminoketones **1** by reaction with substituted hydrazines **2** (Scheme 1).[8,1a] The reaction is a tandem addition-elimination/cyclodehydration, which takes place via a Michael addition of the terminal amino group of hydrazines **2** to form the acyclic intermediate **3**, followed by intramolecular cyclodehydration to pyrazole derivative **4**. Conditions have been reported that afford high yields of the products,[1a] but very limited variations in the substituent R are precedented (R = Ph, Me).[1] Furthermore, the known procedures require complex purification of the final product by distillation or crystallization and also proved to be unsatisfactory for the synthesis of analogs different from the one already known. Being interested in the parallel synthesis of many derivatives of **4**, we sought to develop an experimentally more straightforward and broadly applicable approach.

The synthesis of compound **4b-1** (R = 2, 4-dimethylphenyl) was chosen as a model reaction to investigate the reaction conditions. Typically, the tandem Michael addition-elimination/cyclodehydration requires refluxing in high boiling solvent (such as *n*-butanol) under acid catalysis (AcOH), therefore we decided to explore whether microwave irradiation could be used to enhance the utility of this sequence.[9] In the presence of AcOH, equimolar mixtures of the enaminoketone **1b** and 2,4-dimethylphenylhydrazine hydrochloride were subjected to microwave heating in a varitey of solvents (Table 1). Using *n*-butanol (0.2 M) and 2.6 equivalents of AcOH, the reaction was complete in 120 seconds at 170 °C, giving **4b-1** in an isolated yield of 67% (entry 1). Increasing the reaction concentration to 0.5 M was beneficial, resulting in conversion in 60 seconds at 190 °C with an isolated yield of 76% (entry 2). Further increase in the concentration with a reduction in AcOH resulted in a poorer yield (entry 3). Using the stoichiometry from entry 2, different reaction solvents were explored. Very short reaction times (entries 4, 5, 6 and 8) and very good isolated yields (usually >80%) were obtained with DMF, THF, MeOH and water. Longer times were required for MeOH (360 seconds), as pressure limitations (20 bar) precluded temperatures beyond 160 °C. Alternatively, the reaction in MeOH was faster (180 seconds) when the amount of AcOH was doubled however a slight decrease in yield was observed (entry 7). Interestingly, the reaction in water (entry 8) gave an isolated yield of 84% when the reaction was irradiated to 200 °C for 120 seconds. An appealing aspect of the reaction in water was that the product could be isolated by simple filtration from the reaction mixture (entry 9). The product appeared as an oil after microwave irradiation, but subsequent agitation caused precipitation of the desired compound. The yield and purity of **4b-1** obtained by filtration was analogous to reactions involving chromatographic purification (entry 8 vs entry 9). It was possible to reduce the reaction time to 60 seconds (entry 10), and increasing the temperature to 220 °C afforded a slighter higher yield (88%, entry 11).

To expand the scope of the reaction, various hydrazines were investigated under the same conditions (Scheme 1, Table 2). A slight modification in the purification step

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Table 1 Study of the Reaction Conditions for the Model Reaction (**1b** + 2,4-Dimethylphenylhydrazine)[a]

Entry	Solvent (M)	AcOH (equiv)	Microwave Conditions	Yield of **4b-1** (%)
1	*n*-BuOH (0.2)	2.6	170 °C, 120 s	67[b]
2	*n*-BuOH (0.5)	2.6	180 °C, 60 s	76[b]
3	*n*-BuOH (1.1)	0.5	190 °C, 120 s	39[b]
4	DMF (0.5)	2.6	200 °C, 60 s	83[b]
5	THF (0.5)	2.6	170 °C, 180 s	79[b]
6	MeOH (0.5)	2.6	150 °C, 360 s	83[b]
7	MeOH (0.5)	5.2	150 °C, 180 s	79[b]
8	H_2O (0.5)	2.6	200 °C, 120 s	84[b]
9	H_2O (0.5)	2.6	200 °C, 120 s	83[c]
10	H_2O (0.5)	2.6	200 °C, 60 s	84[c]
11	H_2O (0.5)	2.6	220 °C, 60 s	88[c]

[a] Observed pressures were between 15–18 bar.
[b] Yield after column chromatography.
[c] Yield obtained on the filtrated product after washings with water and hexane.

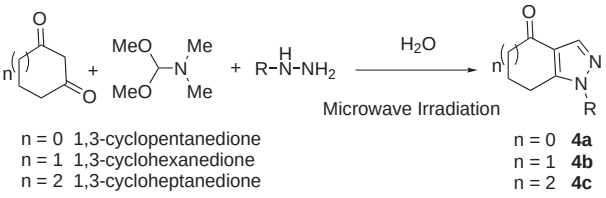
Table 2 Reaction of **1b** with Substituted Hydrazines

Product	R[a]	Yield %
4b-1	2,4-$Me_2C_6H_3$	92[b]
4b-2	Ph	86[b]
4b-3	2,4-F_2-C_6H_3	83[b]
4b-4	3,5-$Me_2C_6H_3$	78[b]
4b-5	4-CF_3,6-Me-2-pyridyl	65[b]
4b-6	2-pyridyl	85[b]
4b-7	cyclohexyl	79[c]
4b-8	*t*-Bu	99[d]
4b-9	H	80[c,e]

[a] Hydrazine substituent, Scheme 2.
[b] Yield of product isolated by filtration followed by washing only with water.
[c] Yield of product isolated by column chromatography.
[d] Yield of product isolated by extraction with CH_2Cl_2.
[e] Product isolated is the N-unsubstituted pyrazole (R = H).

(the filtered product was washed only with water, not with hexanes) afforded a better yield and more convenient procedure for **4b-1** (92%), without affecting the purity of the product. Excellent yields were obtained for all aryl substituted (**4b-2** to **4b-6**) and alkyl substututed hydrazines (**4b-7**, **4b-8**) attempted. An unusual reaction was observed using 4,5-dihydroimidazol-2-ylhydrazine, which afforded the N-unsubstituted pyrazole **4b-9** in 80% yield. Loss of the imidazoline fragment occurred in the cyclization step, as evidenced by gas chromatography (GC/MS). Conversely, the direct reaction with hydrazine hydrochloride did not afford compound **4b-9**, rather generating a symmetrical dimer via hydrazine addition to two molecules of enaminoketone, as demonstrated by MS and NMR data.

The overall process was simplified via a one-pot reaction in which the enaminoketone was generated in situ from the corresponding diketone (Scheme 2). Equimolar amounts of dimethylformamide dimethyl acetal (DMFDMA) and 1,3-cyclohexanedione were mixed, followed by the addition of *N*-phenylhydrazine, water (to 0.5 M), and 2.6 equivalents of AcOH. The heterogeneous mixture was then heated in the microwave for 120 seconds at 200 °C. Product **4b-1** (Table 3) was obtained by simple filtration with a yield and purity comparable to the two step reaction (Table 2). Chromatographic analyses (GC/MS and LC/MS) of the reaction indicated: 1) thorough agitation of the diketone/DMFDMA mixture was required prior to the addition of water; 2) reaction between the diketone and DMFDMA was complete by the time an initial GC/MS sample was obtained (less than one minute); 3) the order of addition of the hydrazine, water, and acetic acid to the diketone/DMFDMA mixture was unimportant; 4) prior to microwave irradiation the intermediate **3b-1** was detected by LC/MS, with only trace enaminoketone **1b** remaining; and 5) after microwave irradiation the intermediate **3b-1** was completely converted to the pyrazole **4b-1**. The reaction also proceeded without addition of AcOH, but in general led to formation of more side products. For comparison, the reaction under conventional heating required 4 hours at reflux for completion, and the product obtained was less pure (67% vs 94% by HPLC). The microwave reaction was also run in other solvents, but water proved optimal (H_2O 87%, THF 75%, DMF 78%, MeCN 67%, CH_2Cl_2 79%). The process was scalable to higher concentrations (up to 4 fold with the same type of reactor) without affecting yield or purity. This was especially valuable given that neither the reaction nor purification required any organic solvents.



Scheme 2

To demonstrate the generality of the one-pot reaction, the substrate scope of the sequence was explored. Several substituted hydrazines were used successfully, as shown in Table 3 (Scheme 2). The yields of the compounds resynthesized with the one-pot procedure were comparable to those obtained starting with the isolated enaminoketone (Table 2), hence making the isolation of the enaminoke-

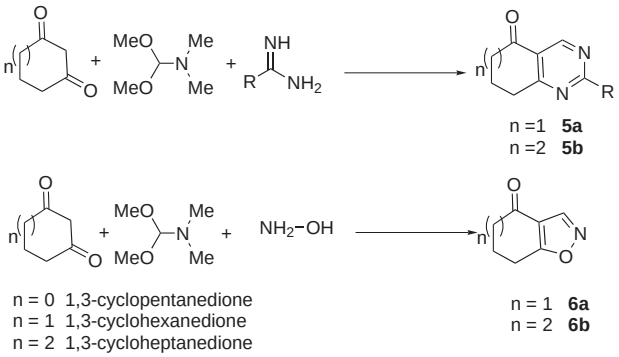
tone generally unnecessary. The reaction was also extended to other cyclic diketones. When 1,3-cycloheptanedione and phenylhydrazine were used, the reaction was complete in 120 seconds at 200 °C, giving **4c-2** in 79% yield. In contrast, 1,3-cyclopentanedione was less successful. While the formation of the intermediate **3a** (R = Ph) proceeded smoothly at room temperature, the cyclodehydration step was problematic (as previously described),[1a] even with microwave heating. After only 60 seconds at 200 °C, several compounds were detectable by LC/MS, along with a still significant amount of intermediate **3a**. Lower temperatures did not improve the outcome of the reaction. Optimal conversion to **4a-2**[1a] was obtained by heating for 600 seconds at 120 °C using *p*-toluenesulfonic acid instead of AcOH, giving a 27% yield after column chromatography. The reaction was also successful, with moderate yields, with acyclic symmetrical and asymmetrical ketones and with acyclic β-keto esters, β-keto sulfones, β-keto nitriles and β-keto amides.[10]

Table 3 One-Pot Procedure for the Preparation of Pyrazoles **4b**

Product	R[a]	Yield %
4b-1	2,4-$Me_2C_6H_3$	83[b]
4b-2	Ph	87
4b-6	2-pyridyl	69[b]
4b-7	cyclohexyl	66[b]
4b-8	*t*-Bu	78[c]
4b-9	H	76[d]

[a] Hydrazine substituent, Scheme 2.
[b] Yield of product isolated by filtration followed by washing only with water.
[c] Yield of product isolated by extraction with CH_2Cl_2.
[d] Product isolated by column chromatography is the N-unsubstituted pyrazole (R = H).

Having established the utility and aqueous stability of the enaminoketones prepared 'in situ', we wanted to identify more aqueous, microwave-induced heterocycle syntheses via enaminoketones. It was well known that enaminoketones react with amidines or hydroxylamine to give pyrimidines and isoxazoles, respectively, therefore we attempted the synthesis of these molecules with our one-pot method (Scheme 3). A preliminary investigation indicated that the reaction of 1,3-diketones with benzamidine hydrochloride afforded pyrimidines **5a-1** (54%)[3b] and **5b-1** (60%)[11] and reaction with 4-amidinopyridinium chloride afforded **5a-2** (68%).[12] Reaction with *tert*-butylcarbamidine hydrochloride afforded pyrimidine **5a-3** in poor yield (21%), while reaction with acetamidine hydrochloride was unsuccessful, giving rise to a complex mixture of products with only traces of the desired compound. Reaction of 1,-3-cycloheptanedione with hydroxylamine hydrochloride afforded the isoxazole **6b** (34%) whereas reaction with 1,3-cyclohexanedione afforded **6a**[5a] with low purity.



Scheme 3

The outcome of these reactions in water is counter intuitive considering that the reactions are cyclodehydrations and as such proceed with elimination of water. However, water has been recently demonstrated to be the solvent of choice for several reactions which previously were run only in organic solvents.[13] One of the reasons why many reactions were never attempted in water was because of the insolubility of many organic compounds in this media. The insolubility of reactants in water can definitely be an obstacle for reactions performed at room temperature but at higher temperature these reactions become more accessible.[14] If in addition to high temperature, higher pressures are also applied, the solubility becomes less of a concern. Therefore, the use of the microwave synthesizer, which allows for both high temperatures and higher pressures, may be very beneficial for running reactions when poor solubility is a limiting factor.

In summary, we have developed an extremely simple one-pot reaction for transforming diketones into the corresponding pyrazoles, pyrimidines and isoxazoles. In addition the use of microwave heating dramatically shortens reaction times, and the use of aqueous reaction conditions results in simple, environmentally friendly workup procedures. The outcome of these reactions demonstrates that reactions that are historically performed in organic solvents can have facile and more convenient aqueous counterparts. Our continued efforts in this area shall be reported in due course.

Solvents and reagents were obtained from commercial sources and used without further purification. Microwave assisted syntheses were carried out using the Smith Synthesizer from Personal Chemistry and Smith process vials™ (2–5 mL), with septum caps and magnetic stirring bars. Flash chromatography was performed using the ISCO CombiFlash system with Biotage columns and EtOAc–hexane gradients as indicated. EM Science precoated silca gel 60 F254 plates were used for TLC analyses using EtOAc–hexane mixtures as eluents. Analytical HPLC experiments were performed with a PE Sciex LC/MS system with Shimadzu SCL-10A system controller, Shimadzu SPD-10A UV-VIS detector, Shimadzu LC-8A pumps, Gilson 215 autosampler, API 150 EX mass spectrometer, and PE Sciex Sample Control 1.5 software running on a Macintosh G3 (OS 8.6). Analytical HPLC columns were YMC CombiScreen ODS-A (50 × 4.6 mm) and a gradient of MeCN 10% to 90% (MeCN with 0.035% TFA/H_2O with 0.05% TFA) was used

as eluent with run time of 6 min unless otherwise specified. Analytical GC experiments utilized an Agilent 6890, Agilent 7673 injector, and Agilent 6890 MSD detector. Analytical GC columns were J & W Scientific (5% diphenyl, 95% dimethyl polysiloxane; length: 29 m; diameter: 250.00 μm, film thickness: 0.25 μm). The column used was 8.17 min long with a flow rate of 19.2 mL/min. Temperature profile was: initial temp 70 °C for 1 min, 115 °C @ 45 °C/min for 1 min, 175 °C @ 40 °C/min for 1.5 min, 300 °C @ 30 °C/min for 4.17 min, the oven remained at 300 °C for 0.5 min. Retention times for both LC/MS and GC/MS are reported with the % area of the peak. NMR spectra were obtained using either Varian 300 MHz or 400 MHz instruments. Chemical shifts are reported in ppm relative to internal solvent signals. Coupling constants are reported in Hertz (Hz). Carbon spectra are proton spin decoupled and observed multiplicities are indicated for fluorine containing molecules.

Bicyclic 4-Acylpyrazoles 4b from Enaminoketones; General Procedure (Table 2)

In a Smith process vial, the enaminoketone[1] **1a–c** (1.25 mmol) was dissolved in H_2O (2.5 mL) and the corresponding hydrazine monochloride was added (1.25 mmol), followed by AcOH (3.25 mmol). The vial was sealed and submitted to microwave irradiation for 120 s at 200 °C using the Smith Synthesizer. Upon cooling and stirring with a spatula, the product precipitated from the reaction mixture. It was filtered, washed with water and hexane, and dried.

1-(2,4-Dimethylphenyl)-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4b-1)

Yield: 92% (276 mg); mp 127–128 °C; HPLC t_R 3.05 min (95%); GC/MS t_R 6.3 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (s, 1 H, CH), 7.06 (s, 1 H, Ar), 7.01 (s, 2 H, Ar), 2.53 (t, 2 H, *J* = 6.3 Hz, CH_2CO), 2.42 (t, 2 H, *J* = 6.3 Hz, CH_2C=), 2.28 (s, 3 H, CH_3), 2.03 (m, 2 H, $CH_2CH_2CH_2$), 1.95 (s, 3 H, CH_3).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 193.44, 150.79, 140.09, 138.08, 135.24, 134.73, 132.15, 127.59, 127.01, 119.29, 38.19, 23.66, 21.99, 21.40, 17.52.

MS (ESI): *m*/*z* = 241.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}N_2O$, 241.1341; found, 241.1335.

1-Phenyl-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4b-2)

Yield: 86% (228 mg); mp 139–140 °C (Lit.[1a] mp 140 °C); HPLC t_R 2.66 min (94%); GC/MS t_R 6.0 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (s, 1 H, CH), 7.43 (m, 5 H, Ar), 2.90 (t, 2 H, *J* = 6.3 Hz, CH_2CO), 2.48 (t, 2 H, *J* = 6.3 Hz, CH_2C=), 2.09 (m, 2 H, $CH_2CH_2CH_2$).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 193.45, 149.25, 138.69, 138.67, 129.63, 128.47, 123.80, 120.54, 38.10, 23.83, 23.46.

MS (ESI): *m*/*z* = 213.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{12}N_2O$, 213.1028; found, 213.1029.

1-(2,4-Difluorophenyl)-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4b-3)

Yield: 83% (257 mg); mp 121–122 °C; HPLC t_R 2.74 min (93%); GC/MS t_R 5.6 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.01 (s, 1 H, CH), 7.46 (m, 1 H, Ar), 6.96 (m, 2 H, Ar), 2.70 (t, 2 H, *J* = 5.4 Hz, CH_2CO), 2.47 (t, 2 H, *J* = 6 Hz, CH_2C=), 2.10 (m, 2 H, $CH_2CH_2CH_2$).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 193.42, 164.79 (d), 161.43 (d), 158.28 (d), 154.91 (d), 151.86, 139.30, 129.76 (d), 122.93 (d), 120.34, 112.57 (d), 105.41 (t), 38.07, 23.54, 21.99.

MS (ESI): *m*/*z* = 249.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{10}F_2N_2O$, 249.0839; found, 249.0842.

1-(3,5-Dimethylphenyl)-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4b-4)

Yield: 71% (213 mg); mp 120–121 °C; HPLC t_R 3.27 min (100%); GC/MS t_R 6.62 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (s, 1 H, CH), 7.03 (s, 2 H, Ar), 6.98 (s, 1 H, Ar), 2.89 (t, 2 H, *J* = 5.7 Hz, CH_2CO), 2.47 (t, 2 H, *J* = 5.7 Hz, CH_2C=), 2.31 (s, 6 H, 2 × CH_3), 2.09 (m, 2 H, $CH_2CH_2CH_2$).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 193.50, 149.19, 139.53, 138.53, 138.43, 130.15, 121.59, 120.33, 38.13, 23.84, 23.48, 21.51.

MS (ESI): *m*/*z* = 241.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}N_2O$, 241.1341; found, 241.1341.

1-(6-Methyl-4-trifluoromethylpyridin-2-yl)-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4b-5)

Yield: 65% (239 mg); mp 121–122 °C; HPLC t_R 3.63 min (82%); GC/MS t_R 5.83 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (s, 1 H, CH), 7.94 (s, 1 H, Ar), 7.21 (s, 1 H, Ar), 3.40 (t, 2 H, *J* = 6.3 Hz, CH_2CO), 2.56 (s, 3 H, CH_3), 2.46 (t, 2 H, *J* = 6.0 Hz, CH_2C=), 2.12 (m, 2 H, $CH_2CH_2CH_2$).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 193.96, 159.20, 153.06, 151.49, 141.5 (q), 139.43, 124.52, 122.03, 120.89, 117.06 (d), 108.8 (q), 38.14, 25.46, 24.48, 23.60.

MS (ESI): *m*/*z* = 296.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{12}F_3N_3O$, 296.1011; found, 296.1008.

1-Pyridin-2-yl-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4b-6)

Yield: 85% (226 mg); mp 125–126 °C; HPLC t_R 2.60 min (92%); GC/MS t_R 6.0 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.38 (m, 1 H, CH), 7.97 (s, 1 H, Ar), 7.89 (m, 1 H, Ar), 7.78 (m, 1 H, Ar), 7.18 (m, 1 H, Ar), 3.40 (t, 2 H, *J* = 6.3 Hz, CH_2CO), 2.46 (t, 2 H, *J* = 5.7 Hz, CH_2C=), 2.11 (m, 2 H, $CH_2CH_2CH_2$).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 194,15, 152.89, 151.14, 147.97, 139.02, 138.98, 122.32, 121.65, 115.85, 38.24, 25.25, 23.69.

MS (ESI): *m*/*z* = 214.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{11}N_3O$, 214.098; found, 214.0984.

1-Cyclohexyl-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4b-7)

Yield: 79% (215 mg); mp 87–88 °C; HPLC t_R 2.77 min (100%); GC/MS t_R 5.98 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (s, 1 H, CH=N), 3.87 (m, 1 H, CHN), 2.75 (t, 2 H, *J* = 6.0 Hz, CH_2CO), 2.40 (t, 2 H, *J* = 6.0 Hz, CH_2C=), 2.10 (m, 2 H, $CH_2CH_2CH_2$), 1.86 (m, 6 H, CH_2 cyclohexyl), 1.64 (m, 2 H, CH_2 cyclohexyl), 1.29 (m, 2 H, CH_2 cyclohexyl).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 193.42, 148.09, 137.04, 118.91, 58.75, 38.26, 32.74, 25.69, 25.26, 23.48, 21.49.

MS (ESI): *m*/*z* = 219.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{18}N_2O$, 219.1497; found, 219.1494.

1-(*tert*-Butyl)-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4b-8)
Yield: 99% (238 mg); mp 80–81 °C; HPLC t_R 2.57 min (100%); GC/MS t_R 4.77 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (s, 1 H, CH), 2.98 (t, 2 H, *J* = 6.0 Hz, CH_2CO), 2.40 (t, 2 H, *J* = 6.0 Hz, CH_2C=), 2.10 (m, 2 H, $CH_2CH_2CH_2$), 1.57 (s, 9 H, 3 × CH_3).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 193.82, 148.21, 135.72, 120.81, 60.92, 37.76, 30.02, 24.93, 24.01.

MS (ESI): *m*/*z* = 193.4 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{16}N_2O$, 193.1341; found, 193.1344.

1,5,6,7-Tetrahydro-4*H*-indazol-4-one (4b-9)
Yield: 80% (136 mg); mp 164–165 °C; HPLC t_R 0.56 min (100%); GC/MS t_R 4.53 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (s, 1 H, CH), 2.83 (t, 2 H, *J* = 5.7 Hz, CH_2CO), 2.44 (t, 2 H, *J* = 5.4 Hz, CH_2C=), 2.10 (m, 2 H, $CH_2CH_2CH_2$).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 194.66, 153.17, 134.55, 118.95, 38.66, 23.77, 22.03.

MS (ESI): *m*/*z* = 137.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_7H_8N_2O$, 137.0715; found, 137.0709.

One-Pot Preparation of Bicyclic 4-Acylpyrazoles 4b and 4c from 1,3-Diketones via Enaminoketones; General Procedure
In a Smith process vial, the 1,3-diketone **1b** (140 mg, 1.25 mmol) and DMFDMA (1.5 mmol) were mixed and the substituted hydrazine monochloride **2** was added (1.25 mmol) followed by addition of distilled H_2O (3 mL) and AcOH (3.25 mmol). The vial was sealed with the appropriate cap with septa and submitted to microwave irradiation for 120 s at 200 °C using the Smith Synthesizer. Upon cooling and stirring with a spatula, the product precipitated down from the reaction mixture. It was filtered, washed with H_2O and dried.

4b-1
Yield: 83% (249 mg); mp 123–124 °C; HPLC t_R 3.09 min (94%); GC/MS t_R 6.3 min (100%).

MS (ESI): *m*/*z* = 241.2 $[M + H]^+$.

4b-2
Yield: 87% (230 mg); mp 137–138 °C; HPLC t_R 2.72 min (94%); GC/MS t_R 6.1 min (100%).

MS (ESI): *m*/*z* = 213.2 $[M + H]^+$.

4b-6
Yield: 69% (183 mg); mp 126–127 °C; HPLC t_R 2.63 min (92%); GC/MS t_R 6.0 min (100%).

MS (ESI): *m*/*z* = 214.2 $[M+H]^+$.

4b-7
Yield: 66% (180 mg); mp 90–91 °C; HPLC t_R 2.90 min (100%); GC/MS t_R 5.95 min (100%).

MS (ESI): *m*/*z* = 219.2 $[M + H]^+$.

4b-8
Yield: 78% (187 mg); HPLC t_R 2.56 min (100%); GC/MS t_R 4.76min (100%).

MS (ESI): *m*/*z* = 193.2 $[M + H]^+$.

4b-9
Yield: 76% (129 mg); mp 164–165 °C; HPLC t_R 0.69 min (100%); GC/MS t_R 4.53 min (100%).

MS (ESI): *m*/*z* = 137.2 $[M + H]^+$.

1-Phenyl-5,6,7,8-tetrahydrocyclohepta[*c*]pyrazol-4(1*H*)-one (4c-2)
Yield: 79% (223 mg); mp 106–108 °C; HPLC 4.62 t_R min (93%); GC/MS t_R 6.37 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (s, 1 H, CH), 7.41–7.30 (m, 5 H, Ar), 2.84 (br, 2 H, CH_2CO), 2.67 (br, 2 H, CH_2C=), 1.87 (br, 4 H, $CH_2CH_2CH_2CH_2$).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 196.63, 146.09, 141.88, 139.07, 129.53, 129.04, 125.94, 123.61, 43.62, 27.54, 25.64, 22.80.

MS (ESI): *m*/*z* = 227.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{14}N_2O$, 226.1106; found, 227.1185.

One-Pot Preparation of Bicyclic 4-Acylpyrimidines 5 from 1,3-Diketones via Enaminoketones; General Procedure
In a Smith process vial, the 1,3-diketone **1a** or **1b** (1.25 mmol) and DMFDMA (1.25 mmol) were mixed and the substituted amidine monochloride was added (1.25 mmol) followed by addition of distilled H_2O (3 mL). The vial was sealed with the appropriate cap with septa and submitted to microwave irradiation for 120 s at 200 °C using the Smith Synthesizer. Upon cooling and stirring with a spatula the product precipitated down from the reaction mixture. It was filtered, washed with H_2O and dried.

2-Phenyl-7,8-dihydroquinazolin-5(6*H*)-one (5a-1)
Yield: 54% (151 mg); mp 123–124 °C (Lit.[3a] mp 126–127 °C); HPLC t_R 4.96 min (100%); GC/MS t_R 6.17 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.18 (s, 1 H, CH), 8.45 (m, 2 H, Ar), 7.44 (m, 3 H, Ar), 3.08 (t, 2 H, *J* = 6.0 Hz, CH_2CO), 2.66 (t, 2 H, *J* = 6.0 Hz, CH_2C=), 2.17 (m, 2 H, $CH_2CH_2CH_2$).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 196.87, 172.13, 166.68, 157.14, 137.01, 132.05, 129.30, 128.95, 123.41 38.80, 32.34, 21.46.

MS (ESI): *m*/*z* = 225.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{12}N_2O$, 225.1028; found, 225.1027.

2-Pyridin-4-yl-7,8-dihydroquinazolin-5(6*H*)-one (5a-2)
Yield: 68% (191 mg); mp 162–163 °C (Lit.[10] mp 140–141 °C); HPLC t_R 3.19 min (100%); GC/MS t_R 6.34 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.21 (s, 1 H, CH), 8.71 (m, 2 H, Ar), 8.26 (m, 2 H, Ar), 3.10 (t, 2 H, *J* = 6.3 Hz, CH_2CO), 2.67 (t, 2 H, *J* = 6.0 Hz, CH_2C=), 2.18 (m, 2 H, $CH_2CH_2CH_2$).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 196.55, 172.45, 164.85, 157.26, 150.77, 144.13, 124.57, 122.70, 38.74, 32.21, 21.32.

MS (ESI): *m*/*z* = 226.4 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{11}N_3O$, 226.098; found, 226.0977.

2-*tert*-Butyl-7,8-dihydroquinazolin-5(6*H*)-one (5a-3)
Yield: 21% (53 mg); mp 66–67 °C; HPLC t_R 3.54 min; GC/MS t_R 4.38 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.03 (s, 1 H, CH), 2.96 (t, 2 H, *J* = 6. 0 Hz, CH_2CO), 2.58 (t, 2 H, *J* = 6.0 Hz, CH_2C=), 2.10 (m, 2 H, $CH_2CH_2CH_2$), 1.30 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 197.08, 171.32, 156.30, 122.88, 38.78, 32.22, 29.90, 29.63, 21.51.

MS (ESI): *m*/*z* = 205.2 (100%) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{16}N_2O$, 205.1341; found, 205.1322.

2-Phenyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*d*]pyrimidin-5-one (5b-1)

Yield 60% (143 mg); mp 65–66 °C (Lit.[11] mp 64–65 °C); HPLC t_R 3.58 min (100%); GC/MS t_R 6.49 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.97 (s, 1 H, CH), 8.43 (m, 2 H, Ar), 7.32 (m, 3 H, Ar), 3.15 (t, 2 H, *J* = 5.7 Hz, CH_2CO), 2.77 (t, 2 H, 6.6 Hz, CH_2C=), 1.92 (m, 4 H, $CH_2CH_2CH_2CH_2$).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 202.41, 170.04, 165.78, 158.10, 137.04, 131.76, 129.10, 128.90, 41.59, 36.27, 23.95, 21.86.

MS (ESI): *m*/*z* = 239.0 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{14}N_2O$, 239.1184; found, 239.1186.

One-Pot Preparation of 5,6,7,8-Tetrahydro-4*H*-cyclohepta[*d*]isoxazol-4-one (6b) from 1,3-Diketone 1b via Enaminoketones; Typical Procedure

The diketone **1b** (1.25 mmol) and DMFDMA (1.25 mmol) were mixed and hydroxylamine hydrochloride was added (87 mg, 1.25 mmol) followed by addition of distilled H_2O (0.5 mL). The compound was purified by column chromatography upon evaporation of H_2O; yield: 34% (64 mg); mp 61–62 °C; GC/MS t_R 3.75 min (100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42 (s, 1 H, CH), 3.04 (t, 2 H, *J* = 6.3 Hz, CH_2CO), 2.66 (t, 2 H, *J* = 5.7 Hz, CH_2C=), 2.04–1.84 (m, 4 H, $CH_2CH_2CH_2CH_2$).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 194.72, 175.32, 150.61, 119.48, 44.71, 28.42, 24.65, 22.77.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_9NO_2$, 151.0711; found, 152.0707.

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