Facile and Straightforward Method Leading to Substituted 4-Amino-1-arylpyrazoles

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Abstract: A new method for the synthesis of substituted 4-amino-1-arylpyrazoles is described, starting from β-enaminones and variously substituted benzenediazonium tetrafluoroborates. The reaction proceeds under mild conditions, is very simple to perform, and is applicable to a relatively wide range of substituents, both at the β-enaminone and diazonium salt starting materials.

Key words: diketones, enaminones, diazonium salts, pyrazoles, heterocycles

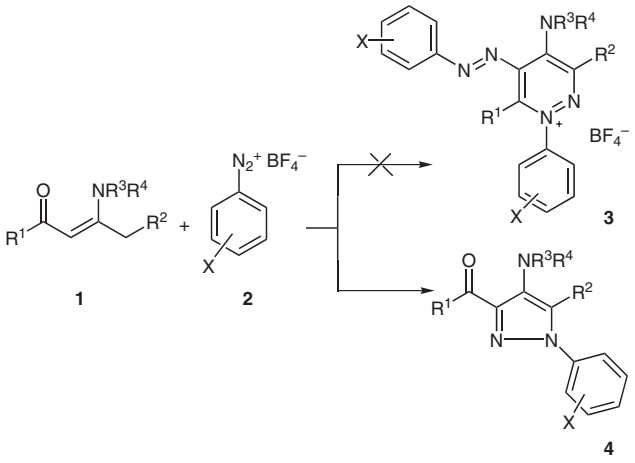
β-Enaminones are, thanks to their ability to react with wide variety of both electrophilic and nucleophilic agents,[1] versatile intermediates in many synthetic transformations, especially in heterocyclic syntheses.[2–8] β-Enaminones are also important precursors and building blocks for syntheses of many biologically active compounds, such as dopamine agonists,[9] acetylcholinesterase inhibitors,[10] anticonvulsants,[11] alkaloids,[12] and anti-inflammatory[13] and antitumor[14] drugs. Chiral enaminones are useful ligands for diastereoselective syntheses.[15]

The combination of β-enaminones with benzenediazonium salts has shown to be a powerful tool for the synthesis of some heterocyclic systems. We have previously described the utilisation of β-enaminones in the syntheses of pyridazinium salts,[16,17] oxazaborines, and triazaborines.[18]

A small modification in the structure of the starting enaminone **1** (introduction of a methylene group next to the enamino group) does not lead to the formation of 3-substituted pyridazinium salts **3**, as expected in analogy with literature procedures[16,17] (Scheme 1). On the basis of the analysis of ^{1}H and ^{13}C NMR spectra, we concluded that the reaction products are pyrazole derivatives **4** (Scheme 1). The pyrazole structure **4** was finally proved also by ^{15}N NMR spectra and by X-ray diffraction analyses (Figure 1 and Figure 2).

The scope and limitation of the reaction was tested with regard to the structure of the starting enaminone **1**, the type of amino group and the substitution on the diazonium salt **2** (Scheme 1).

The starting β-diketones **5** were prepared by reaction of the corresponding methyl ketones with methyl esters



Scheme 1

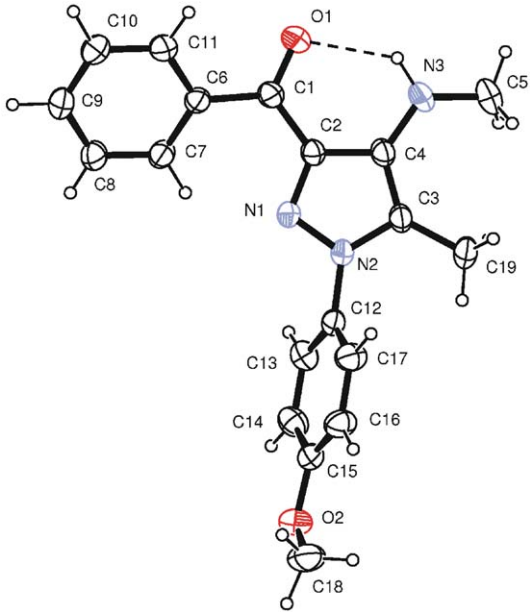


Figure 1 ORTEP[19] view of compound **4b** (thermal ellipsoids at 30% probability)

(Scheme 2). We successfully used potassium *tert*-pentyloxide (*t*-PentOK) as the base instead of sodium hydride or amide (Scheme 2). The resulting β-diketones **5** were (except for **5c**) purified via the corresponding copper(II) β-diketonates.

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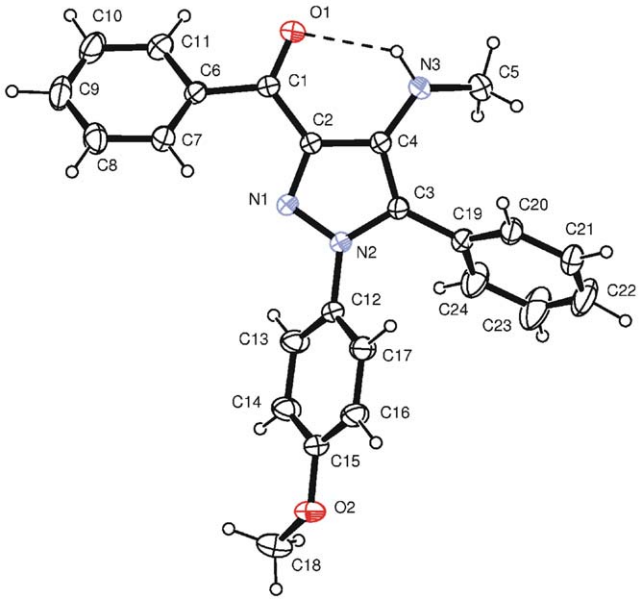
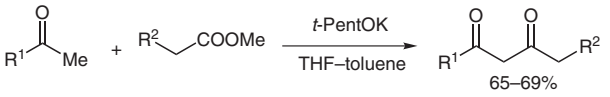


Figure 2 ORTEP[19] view of compound **4h** (thermal ellipsoids at 30% probability)

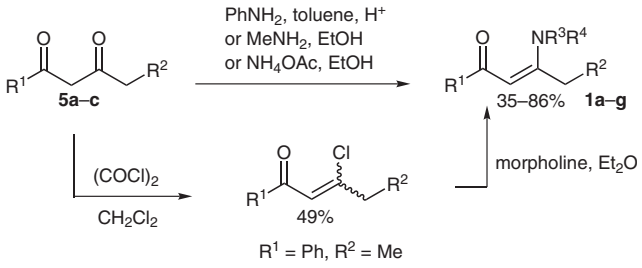


5a: R^1 = Ph, R^2 = Me
5b: R^1 = Ph, R^2 = Ph
5c: R^1 = *c*-Pr, R^2 = Et

Scheme 2

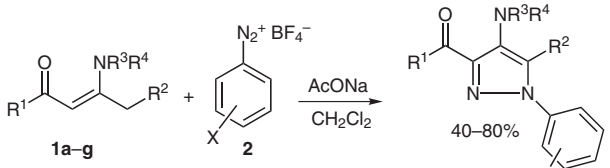
β-Enaminones **1** with *N*-methyl and *N*-phenyl groups were prepared by condensation of β-diketones **5** with methylamine or aniline (Scheme 3). Preparation of **1c** by reaction of **5a** with morpholine was not successful. Instead, product **1c** was prepared by transformation of **5a** into 3-chloro-1-phenylpent-2-en-1-one by reaction with oxalyl chloride. Subsequent reaction of 3-chloro-1-phenylpent-2-en-1-one with morpholine led to nucleophilic substitution of the chloro group to give **1c** (Scheme 3). Enaminone **1d** with a primary amino group was prepared by heating **5c** with ammonium acetate (Scheme 3).

The scope of the described procedure for the synthesis of pyrazoles **4** (Scheme 4) is significantly broader than that described for pyridazinium salts **3**.[16,17] The method is applicable to β-enaminones **1** with aromatic, alicyclic, and aliphatic scaffolds, with primary, *N*-methyl, *N*-phenyl, and tertiary amino groups as well (Scheme 4). The requirement for pyrazole formation is the presence of the methylene group in the enamino group neighbourhood, i.e., the arrangement $=C(NR^3R^4)–CH_2–R^2$ ($R^2 \neq H$). Regarding the substitution on the diazonium salt **2**, pyrazoles **4** were formed from diazonium salts **2** with both electron-donating and electron-withdrawing substituents (Scheme 4). A diazonium salt **2**/enaminone **1** ratio of 2:1 appeared to be optimal in terms of yield. The presence of sodium acetate is necessary to avoid the formation of byproducts.



1a: R^1 = Ph, R^2 = Me, R^3 = Ph, R^4 = H
1b: R^1 = Ph, R^2 = Me, R^3 = Me, R^4 = H
1c: R^1 = Ph, R^2 = Me, R^3 ,R^4 = morpholin-4-yl
1d: R^1 = *c*-Pr, R^2 = Et, R^3 = R^4 = H
1e: R^1 = Ph, R^2 = Ph, R^3 = Me, R^4 = H
1f: R^1 = Ph, R^2 = Ph, R^3 = Ph, R^4 = H
1g: R^1 = Et, R^2 = Me, R^3 = Me, R^4 = H

Scheme 3



4a: R^1 = Ph, R^2 = Me, R^3 = Me, R^4 = H, X = 4-Me
4b: R^1 = Ph, R^2 = Me, R^3 = Me, R^4 = H, X = 4-OMe
4c: R^1 = Ph, R^2 = Me, R^3 = Ph, R^4 = H, X = 4-Me
4d: R^1 = Ph, R^2 = Me, R^3 = Ph, R^4 = H, X = 3-Me
4e: R^1 = Ph, R^2 = Me, R^3 = Ph, R^4 = H, X = 4-Cl
4f: R^1 = Ph, R^2 = Me, R^3 = Ph, R^4 = H, X = 2-Me
4g: R^1 = Ph, R^2 = Me, R^3,R^4 = morpholin-4-yl, X = 4-Me
4h: R^1 = Ph, R^2 = Ph, R^3 = Me, R^4 = H, X = 4-OMe
4i: R^1 = Ph, R^2 = Ph, R^3 = Me, R^4 = H, X = 4-Me
4j: R^1 = Ph, R^2 = Ph, R^3 = Ph, R^4 = H, X = 3-CF_3
4k: R^1 = Ph, R^2 = Ph, R^3 = Ph, R^4 = H, X = 3-CO_2Et
4l: R^1 = *c*-Pr, R^2 = Et, R^3 = R^4 = H, X = 4-Me
4m: R^1 = Et, R^2 = Me, R^3 = Me, R^4 = H, X = 4-OMe

Scheme 4

Pyrazoles are potentially biologically active molecules. Many of them have found use as agrochemicals.[20] Some pyrazole derivatives are used as ligands for homogeneous catalysis – so-called scorpionates.[21–23]

Therefore, much attention has been given to the syntheses of pyrazoles. Recently, a survey of the methods leading to pyrazoles has been published.[24] However, the large majority of the methods uses toxic and dangerous hydrazine or phenylhydrazine derivatives. The method reported here replaces the phenylhydrazine derivatives with considerably safer benzenediazonium tetrafluoroborates. The reaction proceeds under mild conditions, and the procedure is very simple and applicable to a relatively wide range of substituents both at the starting β-enaminone **1** and diazonium salt **2**. Further extension of the applicability of the method is the subject of future research.

THF was dried by refluxing over Na in the presence of benzophenone under an inert atmosphere until a blue-violet coloration appeared; it was freshly distilled under an inert atmosphere before use. Commercially available (Fluka) CH_2Cl_2 was dried over MS and stored in a bottle with a Sure Seal cap. Diazonium tetrafluoroborates

2 were prepared shortly before use by a previously described method,[25] and dried in vacuo. Commercially available (Fluka) potassium *tert*-pentoxide (*t*-PentOK) was used as ca. 1.7 M solns in toluene. Commercially available (Aldrich) heptane-3,5-dione (**5d**) was used. Commercially available anhyd NaOAc was used without further purification. $MeNH_2$ was used as a 33 wt% soln in EtOH (Aldrich). NMR spectra of samples in $CDCl_3$ were recorded on Bruker AVANCE 500 (^1H, 500 MHz; ^{13}C, 125 MHz) and Bruker AMX 360 (^1H, 360 MHz; ^{13}C, 90 MHz) spectrometers. Hexamethyldisiloxane was used as internal standard for ^1H NMR spectroscopy ($\delta = 0.05$). The ^{13}C NMR spectra were standardised by means of the middle signal of the solvent multiplet ($\delta = 76.9$). The ^{13}C NMR spectra were recorded by the standard method with broadband decoupling of protons or by means of the APT pulse sequence.

X-ray Crystallography of 4b and 4h

X-ray diffraction data for compounds **4b** and **4h** were collected at r.t. (295 K) on a Nonius Kappa CCD diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.7107$ Å). The structures were solved by direct methods (SIR97)[26] and refined (SHELXL-97)[27] by full-matrix least squares with anisotropic non-hydrogen atoms and isotropic hydrogens.

Compound 4b

$C_{24}H_{21}N_3O_2$; triclinic, space group $P\bar{1}$, $a = 9.8447(3)$, $b = 9.8237(3)$, $c = 11.9725(3)$ Å, $\alpha = 108.070(2)$, $\beta = 99.118(2)$, $\gamma = 105.685(1)°$, $V = 1021.96(5)$ Å^3, $Z = 2$, $Dc = 1.246$ g cm^{-3}. Intensity data collected with $\theta \leq 28°$; 4880 independent reflections measured; 3559 observed [$I > 2\sigma(I)$]. Final R index = 0.0465 (observed reflections), $Rw = 0.1274$ (all reflections), $S = 1.020$. CCDC 670161. The molecule (Figure 1) displays an intramolecular N3–H···O1 hydrogen bond [N3···O1, 2.850(2) Å; H···O1, 2.16(2) Å; N3–H···O3, 133(2)°] and forms dimers, in the crystal packing, by means of intermolecular N3–H···O3(1 – x,–y,1 – z) hydrogen bonds [N3···O1, 3.120(2) Å; H···O1, 2.35(2) Å; N3–H···O3, 144(2)°].

Compound 4h

$C_{19}H_{19}N_3O_2$; monoclinic, space group $C2/c$, $a = 18.5976(3)$, $b = 8.2831(1)$, $c = 21.6594(5)$ Å, $\beta = 91.5999(8)°$, $V = 3335.2(1)$ Å^3, $Z = 8$, $Dc = 1.280$ g cm^{-3}. Intensity data collected with $\theta \leq 28°$; 3985 independent reflections measured; 2873 observed [$I > 2\sigma(I)$]. Final R index = 0.0454 (observed reflections), $Rw = 0.1316$ (all reflections), $S = 1.027$. CCDC 670162. The molecule (Figure 2) exhibits an intramolecular N3–H···O1 hydrogen bond [N3···O1, 2.808(2) Å; H···O1, 2.09(2) Å; N3–H···O3, 132(2)°].

β-Diketones 5; General Procedure

The reaction was carried out under an inert atmosphere. A 500-mL four-necked round-bottomed flask was charged with *t*-PentOK (26.51 g, 0.21 mol) and freshly distilled THF (150 mL). The ketone (0.2 mol) was added from a dropping funnel over 15 min to the stirred and cooled reaction mixture. The temperature was maintained at <10 °C. After addition of the ketone, the mixture was stirred for 5 min, and then the ester (0.2 mol) was added dropwise, over 15 min, to the stirred and cooled reaction mixture. The cooling bath was then removed and the mixture was allowed to warm to 25 °C and subsequently stirred overnight. Then 10% aq HCl (120 mL) was added, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (1 × 150 mL), H_2O (1 × 150 mL), and brine (1 × 150 mL). The organic phase was dried (Na_2SO_4) and evaporated in vacuo. Except for **5c**, the crude diketones **5** were purified by their conversion into the corresponding copper(II) β-diketonates (see below).

Copper(II) β-Diketonates from Diketones 5: Preparation and Decomposition

A soln of $CuCl_2 \cdot 2\,H_2O$ (11.59 g, 0.068 mol) in EtOH (115 mL) was added to a soln of crude β-diketone **5** (0.137 mol) in EtOH (55 mL). Aq NaOH (0.137 mol in 30 mL) was added portionwise to the mixture. At the end of the addition, the pH of the mixture was 6–7. The mixture was left to cool and a dense precipitate was collected by suction, washed with EtOH (50 mL) and Et_2O (50 mL) and dried in air; yield: almost quantitative. The dried complex was decomposed by the addition of 10% aq H_2SO_4 (100 mL) under stirring and mild heating (ca. 50 °C). After the whole complex had dissolved, the mixture was cooled, and extracted with CH_2Cl_2 (3 × 50 mL). The extract was dried (Na_2SO_4) and the solvent was evaporated in vacuo. According to NMR analysis, the thus obtained β-diketone **5** was sufficiently pure for the next reaction step.

1-Phenylpentane-1,3-dione (5a)

Yield: 21.50 g (61%); bp 101–106 °C/1 kPa (Lit.[28] 151 °C/2.5 kPa).

^1H NMR (500 MHz, $CDCl_3$): δ (enol form) = 1.20 (t, $J = 7.6$ Hz, 3 H, CH_3), 2.46 (q, $J = 7.6$ Hz, 2 H, CH_2), 6.16 (s, 1 H, =CH), 7.42–7.47 (m, 2 H), 7.48–7.52 (m, 1 H), 7.86–7.87 (m, 2 H), 16.11 (br s, 1 H, OH); δ (keto form) = 1.07 (t, 0.4 H, $J = 7.2$ Hz, CH_3), 2.60 (t, 0.24 H, $J = 7.2$ Hz, CH_2), 4.08 (s, 0.2 H, CH_2), 7.57–7.59 (m, 0.18 H), 7.92–7.94 (m, 0.27 H) (the rest of the signals are overlapped by the signals of the major form).

^{13}C NMR (125 MHz, $CDCl_3$): δ (enol form) = 9.2, 31.9, 126.5, 128.1, 131.7, 134.4, 182.4, 197.7; δ (keto form) = 7.1, 36.3, 52.8, 128.3, 133.2, 135.9, 193.7, 204.5.

1,4-Diphenylbutane-1,3-dione (5b)

Yield: 32.88 g (69%); mp 44–48 °C (Lit.[29] 50–51 °C).

^1H NMR (360 MHz, $CDCl_3$): δ = 3.71 (s, 2 H, CH_2), 6.11 (s, 1 H, =CH), 7.24–7.50 (m, 8 H), 7.78–7.81 (m, 2 H), 16.03 (br s, 1 H, OH).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 45.8, 96.0, 126.8, 126.9, 128.3, 128.5, 129.2, 132.1, 134.4, 134.9, 183.1, 194.6.

1-Cyclopropylhexane-1,3-dione (5c)

Yield: 20.05 g (65%); bp 80–87 °C/0.7 kPa.

^1H NMR (500 MHz, $CDCl_3$): δ (enol form) = 0.88–0.96 (m, 6 H), 1.07–1.11 (m, 2 H), 1.58–1.65 (m, 4 H), 2.21 (t, $J = 7.5$ Hz, 2 H), 5.59 (s, 1 H, =CH), 15.64 (br s, 1 H, OH); δ (keto form) = 1.99–2.02 (m, 0.25 H), 2.49 (t, 0.45 H, $J = 7.0$ Hz), 3.66 (s, 0.55 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (enol form) = 10.1, 13.6, 18.5, 19.3, 38.6, 98.8, 187.6, 199.1; δ (keto form) = 11.6, 13.4, 16.8, 21.2, 45.4, 57.9, 204.1, 204.2.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.22; H, 8.96.

Enaminones 1a and 1f with Anilino Groups; General Procedure

Compounds **1a** and **1f** were prepared by heating of equimolar amounts of the corresponding β-diketone **5** and $PhNH_2$ in the presence of cat. PTSA. The H_2O formed during the reaction was removed by azeotropic distillation until only clear toluene distilled (7 h for **1a**, 4.5 h for **1f**). The toluene distilled off was continuously replaced by fresh toluene. After completion of the reaction, the solvent was evaporated in vacuo and the residue was purified by vacuum distillation or crystallisation.

3-Anilino-1-phenylpent-2-en-1-one (1a)

Yield: 59%; bp 197–200 °C/0.3 kPa; mp 43–47 °C (Lit.[28] 48–49 °C).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.14 (t, $J = 7.5$ Hz, 3 H, CH_3), 2.44 (q, $J = 7.5$ Hz, 2 H, CH_2), 5.91 (s, 1 H, =CH), 7.17–7.18 (m, 2

H), 7.21–7.24 (m, 1 H), 7.34–7.37 (m, 2 H), 7.40–7.44 (m, 3 H), 7.90–7.92 (m, 2 H), 13.08 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.5, 25.5, 91.9, 125.2, 125.9, 126.9, 128.1, 129.1, 130.7, 138.3, 140.1, 167.9, 188.9.

3-Anilino-1,4-diphenylbut-2-en-1-one (1f)
Yield: 75%; crystallisation (EtOH); mp 97–101.5 °C (Lit.[30] 100–102 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.74 (s, 2 H, CH_2), 5.83 (s, 1 H, =CH), 7.08–7.10 (m, 4 H), 7.18–7.25 (m, 4 H), 7.27–7.30 (m, 2 H), 7.37–7.44 (m, 3 H), 7.83–7.84 (m, 2 H), 13.10 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.6, 94.6, 125.5, 126.1, 126.7, 127.0, 128.2, 128.5, 128.7, 129.0, 130.9, 136.6, 138.2, 139.9, 164.2, 188.9.

Enaminones 1b,e,g with Methylamino Groups; General Procedure
A mixture of the appropriate β-diketone **5** (0.025 mol) and a soln of $MeNH_2$ (3.10 g, 0.1 mol) in EtOH (12.5 mL) was refluxed for 5 h or stirred at 25 °C for 2 h (**1g**). The volatile components were evaporated in vacuo. Products **1b** and **1e** were sufficiently pure for further use, and product **1g** was purified by vacuum distillation.

3-(Methylamino)-1-phenylpent-2-en-1-one (1b)
Yield: 2.94 g (62%); mp 62–64 °C (Lit.[31] 59–60 °C).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.5 Hz, 3 H, CH_3), 2.33 (q, *J* = 7.5 Hz, 2 H, CH_2), 3.01 (d, *J* = 5.3 Hz, 3 H, NCH_3), 5.68 (br s, 1 H, =CH), 7.35–7.42 (m, 3 H), 7.83–7.85 (m, 2 H), 11.40 (br s, 1 H, NH).

3-(Methylamino)-1,4-diphenylbut-2-en-1-one (1e)
Yield: 2.34 g (37%); mp 55–60 °C (Lit.[18] 51–55 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.86 (d, *J* = 5.5 Hz, 3 H), 3.65 (s, 2 H, CH_2), 5.69 (s, 1 H, =CH), 7.21–7.24 (m, 3 H), 7.28–7.31 (m, 2 H), 7.33–7.39 (m, 3 H), 7.81–7.82 (m, 2 H), 11.36 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.7, 38.7, 93.0, 126.8, 126.9, 128.1, 128.5, 128.8, 130.4, 135.6, 140.3, 166.7, 187.9.

5-(Methylamino)hept-4-en-3-one (1g)
Yield: 3.05 g (86%); bp 85 °C/0.7 kPa.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (t, *J* = 8.0 Hz, 3 H, CH_3), 1.15 (t, *J* = 7.5 Hz, 3 H, CH_3), 2.21–2.28 (m, 4 H, 2 × CH_2), 2.94 (d, *J* = 5.5 Hz, 3 H, NCH_3), 4.99 (s, 1 H, =CH), 10.82 (br s, 1 H, NH).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 9.9, 11.4, 24.4, 28.6, 34.5, 91.6, 168.8, 198.5.

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.17; H, 10.59; N 9.92.

3-Amino-1-cyclopropylhex-2-en-1-one (1d)
A mixture of β-diketone **5c** (6.94 g, 45 mmol) and NH_4OAc (13.80 g, 179 mmol) in EtOH (50 mL) was heated to ca. 50 °C for 24 h. Concd aq NH_3 (20 mL) and H_2O (20 mL) were then added to the cooled mixture. The mixture was extracted with CH_2Cl_2 (40 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was subjected to vacuum distillation. Although according to the NMR spectrum the product contained about 10% of isomeric 1-amino-1-cyclopropylhex-1-en-3-one, it was used for the pyrazole synthesis without further purification. The minor isomer is not able to form the pyrazole derivative, due to the absence of the methylene group next to the enamino group.

Yield: 1.83 g (48%); bp 105 °C/1 kPa.

^{1}H NMR (500 MHz, $CDCl_3$): δ (major isomer) = 0.70–0.74 (m, 2 H), 0.93–0.97 (m, 5 H), 1.59 (sext, *J* = 7.4 Hz, 2 H, CH_2), 1.65–1.70 (m, 1 H), 2.10 (t, *J* = 7.5 Hz, 2 H, CH_2), 4.94 (br s, 1 H, NH), 5.18 (s, 1 H, =CH), 9.68 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ (major isomer) = 8.9, 13.8, 20.1, 21.1, 38.2, 94.6, 163.8, 198.6.

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.28; H, 9.81; N, 9.11.

3-Morpholin-4-yl-1-phenylpent-2-en-1-one (1c)
3-Chloro-1-phenylpent-2-en-1-one: Oxalyl chloride (16.00 g, 0.126 mol) was added to a soln of **5a** (8.81 g, 0.05 mol) in $CHCl_3$ (40 mL). The mixture was stirred at 25 °C for 2 h, and then the volatile components were distilled off in vacuo and the residue was subjected to vacuum distillation. The product was immediately used for the next reaction step.

Yield: 4.77 g (49%); bp 120–125 °C/0.9 kPa.

3-Morpholin-4-yl-1-phenylpent-2-en-1-one (1c): A soln of morpholine (4.36 g, 0.05 mol) in CH_2Cl_2 (10 mL) was slowly added dropwise to a soln of 3-chloro-1-phenylpent-2-en-1-one (4.87 g, 0.025 mol) in CH_2Cl_2 (10 mL). The mixture was stirred at 25 °C for 14 h. The volatile components were evaporated in vacuo, the residue was extracted with Et_2O (30 mL) and dried (Na_2SO_4), and the solvent was removed by distillation. The evaporation residue was crystallised from *n*-hexane. The product exists in $CDCl_3$ soln as a mixture of *E*/*Z* isomers (ca. 10:1). The enaminones with tertiary amino groups occur predominantly in the *E*-form.[32]

Yield: 2.15 g (35%); mp 70–74 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ (*E*) = 1.18 (t, *J* = 7.5 Hz, 3 H, CH_3), 3.12 (q, *J* = 7.5 Hz, 2 H, CH_2), 3.40–3.42 (m, 4 H, 2 × CH_2–N), 3.75–3.77 (m, 4 H, 2 × CH_2–O), 5.80 (s, 1 H, =CH), 7.36–7.43 (m, 3 H), 7.83–7.84 (m, 2 H); δ (*Z*) = 2.45 (q, 0.2 H, *J* = 7.5 Hz, CH_2), 2.88–2.90 (m, 0.4 H, 2 × CH_2–N), 3.68–3.70 (m, 0.4 H, 2 × CH_2–N), 6.16 (s, 0.1 H, =CH), 7.85–7.87 (m, 0.2 H) (the other signals are overlapped by the signals of the major form).

^{13}C NMR (125 MHz, $CDCl_3$): δ (*E*) = 12.6, 21.7, 46.3, 66.3, 93.3, 127.2, 127.9, 130.5, 142.3, 168.1, 188.5; δ (*Z*) = 45.9, 67.5, 95.3, 126.8, 128.4, 132.0 (owing to the low abundance of the minor form, only some of the carbons were detected).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C,73.23; H, 7.76; N, 5.89.

Pyrazoles 4a–m; General Procedure
The apparatus (Erlenmeyer flask and magnetic stirrer) used for the procedure were dried in an oven before use. The appropriate β-enaminone **1** (5 mmol) was dissolved in CH_2Cl_2 (30 mL). The soln was treated with anhyd NaOAc (2.46 g, 30 mmol) followed by the appropriate diazonium tetrafluoroborate **2** (10 mmol). The mixture was stirred at r.t. for 24 h. The solid was removed by suction, the filter cake was washed with a small amount of CH_2Cl_2, and the filtrate was evaporated in vacuo. The evaporation residue was subjected to column chromatography (silica gel). (The yields given below are for isolated compounds purified by chromatography.)

3-Benzoyl-5-methyl-4-(methylamino)-1-(4-tolyl)-1*H*-pyrazole (4a)
Column chromatography (silica gel, CH_2Cl_2–EtOAc, 4:1); yield: 0.67 g (44%); crystallisation (EtOH); mp 114–117 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 2.94 (s, 3 H, NCH_3), 5.06 (br s, 1 H, NH), 7.24–7.26 (m, 2 H), 7.32–7.34 (m, 2 H), 7.39–7.42 (m, 2 H), 7.46–7.49 (m, 1 H), 8.28–8.30 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.6, 21.0, 34.2, 124.9, 125.2, 127.8, 129.5, 130.3, 131.9, 137.0, 137.9, 137.9, 138.2, 138.5, 189.8.

Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.87; H, 6.41; N, 13.96.

3-Benzoyl-1-(4-methoxyphenyl)-5-methyl-4-(methylamino)-1*H*-pyrazole (4b)

Column chromatography (silica gel, CH_2Cl_2–EtOAc, 4:1); yield: 0.83 g (52%); mp 117–121 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, CH_3), 2.95 (s, 3 H, NCH_3), 3.83 (s, 3 H, OCH_3), 5.47 (br s, 1 H, NH), 6.95–6.98 (m, 2 H), 7.34–7.38 (m, 2 H), 7.40–7.43 (m, 2 H), 7.47–7.50 (m, 1 H), 8.27–8.29 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.5, 34.2, 55.4, 114.1, 125.4, 126.5, 127.8, 130.3, 131.9, 132.5, 137.9, 138.0, 138.4, 159.4, 189.9.

Anal. Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C, 71.26; H, 5.97; N, 12.81.

4-Anilino-3-benzoyl-5-methyl-1-(4-tolyl)-1*H*-pyrazole (4c)

Column chromatography (silica gel, CH_2Cl_2); yield: 1.03 g (56%); mp 132–134 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_3), 2.42 (s, 3 H, CH_3), 6.81–6.84 (m, 3 H), 7.20–7.23 (m, 3 H), 7.29–7.31 (m, 2 H), 7.41–7.44 (m, 4 H), 7.50–7.53 (m, 1 H), 8.31–8.33 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.1, 21.0, 115.5, 119.5, 124.6, 128.0, 128.3, 129.0, 129.7, 130.6, 131.5, 132.5, 137.0, 137.1, 138.4, 141.8, 144.7, 189.4.

Anal. Calcd for $C_{24}H_{21}N_3O$: C, 78.45; H, 5.76; N, 11.44. Found: C, 78.34; H, 5.86; N, 11.45.

4-Anilino-3-benzoyl-5-methyl-1-(3-tolyl)-1*H*-pyrazole (4d)

Column chromatography (silica gel, CH_2Cl_2); yield: 1.03 g (56%); crystallisation (*n*-hexane); mp 90–93 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.19 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 6.82–6.85 (m, 3 H), 7.21–7.27 (m, 4 H), 7.34–7.42 (m, 3 H), 7.43–7.46 (m, 2 H), 7.52–7.55 (m, 1 H), 8.32–8.34 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.1, 21.3, 115.5, 119.5, 121.9, 125.5, 128.0, 128.3, 128.9, 129.0, 129.1, 130.6, 131.6, 132.5, 137.1, 139.3, 139.4, 141.9, 144.7, 189.4.

Anal. Calcd for $C_{24}H_{21}N_3O$: C, 78.45; H, 5.76; N, 11.44. Found: C, 78.29; H, 5.94; N, 11.40.

4-Anilino-3-benzoyl-1-(4-chlorophenyl)-5-methyl-1*H*-pyrazole (4e)

Column chromatography (silica gel, CH_2Cl_2); yield: 1.44 g (74%); mp 51–53 °C; crystallisation (aq EtOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.19 (s, 3 H, CH_3), 6.80–6.86 (m, 3 H), 7.21–7.24 (m, 2 H), 7.42–7.46 (m, 2 H), 7.47–7.54 (m, 5 H), 8.29–8.31 (m, 2 H) (signal of NH proton is missing).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.2, 115.6, 119.7, 125.8, 128.0, 128.7, 129.0, 129.4, 130.5, 131.4, 132.7, 134.1, 137.0, 137.9, 142.2, 144.4, 189.3.

Anal. Calcd for $C_{23}H_{18}ClN_3O$: C, 71.22; H, 4.68; N, 10.83. Found: C, 71.29; H, 4.87; N, 10.84.

4-Anilino-3-benzoyl-5-methyl-1-(2-tolyl)-1*H*-pyrazole (4f)

Column chromatography (silica gel, CH_2Cl_2); yield: 1.07 g (58%); crystallisation (*n*-hexane); mp 127–128 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.96 (s, 3 H), 2.16 (s, 3 H), 6.78–6.83 (m, 3 H), 7.19–7.23 (m, 3 H), 7.32–7.33 (m, 2 H), 7.35–7.42 (m, 4 H), 7.48–7.51 (m, 1 H), 8.26–8.28 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.0, 17.3, 115.5, 119.5, 126.6, 127.2, 127.4, 128.0, 129.0, 129.6, 130.4, 131.1, 132.5, 132.6, 135.7, 137.1, 138.1, 141.8, 144.7, 189.5.

Anal. Calcd for $C_{24}H_{21}N_3O$: C, 78.45; H, 5.76; N, 11.44. Found: C, 78.29; H, 5.95; N, 11.33.

3-Benzoyl-5-methyl-4-(morpholin-4-yl)-1-(4-tolyl)-1*H*-pyrazole (4g)

Column chromatography (silica gel, $CHCl_3$); yield: 1.28 g (71%); mp 127–130 °C.

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 3.09–3.10 (m, 4 H, $2 \times CH_2$–N), 3.76–3.78 (m, 4 H, $2 \times CH_2$–O), 7.24–7.26 (m, 2 H), 7.33–7.34 (m, 2 H), 7.41–7.44 (m, 2 H), 7.49–7.52 (m, 1 H), 8.12–8.14 (m, 2 H).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 10.4, 20.9, 51.5, 67.7, 124.5, 127.8, 129.5, 130.5, 132.3, 135.1, 135.6, 137.0, 137.9, 138.1, 145.1, 189.5.

Anal. Calcd for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63. Found: C, 72.84; H, 6.33; N, 11.49.

3-Benzoyl-1-(4-methoxyphenyl)-4-(methylamino)-5-phenyl-1*H*-pyrazole (4h)

Column chromatography (silica gel, CH_2Cl_2–EtOAc 4:1); yield: 1.42 g (74%); crystallisation (EtOH); mp 159–162.5 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, OCH_3), 6.00 (br s, 1 H, NH), 6.74–6.77 (m, 2 H), 7.12–7.15 (m, 2 H), 7.28–7.31 (m, 5 H), 7.44–7.47 (m, 2 H), 7.50–7.53 (m, 1 H), 8.33–8.34 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 33.4, 55.3, 113.7, 126.4, 127.4, 127.9, 128.0, 128.1, 130.3, 130.4, 131.0, 131.9, 133.0, 137.7, 138.1, 138.6, 158.8, 189.7.

Anal. Calcd for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52; N, 10.96. Found: C, 75.06; H, 5.60; N, 10.93.

3-Benzoyl-4-(methylamino)-5-phenyl-1-(4-tolyl)-1*H*-pyrazole (4i)

Column chromatography (silica gel, CH_2Cl_2); crystallisation (EtOH); yield: 1.19 g (65%); mp 138–141 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3), 2.51 (s, 3 H, CH_3), 6.00 (br s, 1 H, NH), 7.04–7.05 (m, 2 H), 7.09–7.10 (m, 2 H), 7.29–7.32 (m, 5 H), 7.44–7.47 (m, 2 H), 7.51–7.54 (m, 1 H), 8.33–8.35 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.9, 33.4, 124.9, 127.3, 127.9, 127.9, 128.1, 129.1, 130.3, 130.5, 131.0, 131.9, 137.4, 137.5, 137.9, 138.1, 138.7, 189.8.

Anal. Calcd for $C_{24}H_{21}N_3O$: C, 78.45; H, 5.76; N, 11.44. Found: C, 78.24; H, 5.92; N, 11.42.

4-Anilino-3-benzoyl-5-phenyl-1-[3-(trifluoromethyl)phenyl]-1*H*-pyrazole (4j)

Column chromatography (silica gel, CH_2Cl_2); crystallisation (EtOH); yield: 1.93 g (80%); mp 145–147 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.60–6.62 (m, 2 H), 6.63–6.66 (m, 1 H), 6.90–6.93 (m, 2 H), 7.12–7.14 (m, 2 H), 7.15–7.20 (m, 3 H), 7.42–7.52 (m, 5 H), 7.57–7.60 (m, 2 H), 7.63 (br s, 1 H), 8.34–8.36 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 116.6, 119.9, 122.3 (q, $J_{C,F}$ = 3.9 Hz), 123.2 (q, $J_{C,F}$ = 272.5 Hz), 124.6 (q, $J_{C,F}$ = 3.8 Hz), 128.2, 128.3, 128.5, 128.5, 128.7, 129.1, 129.3, 129.4, 130.4, 131.4 (q, $J_{C,F}$ = 33.1 Hz), 132.8, 133.1, 137.0, 140.2, 142.5, 142.8, 189.3.

Anal. Calcd for $C_{29}H_{20}F_3N_3O$: C, 72.04; H, 4.17; N, 8.69. Found: C, 72.04; H, 4.35; N, 8.83.

4-Anilino-3-benzoyl-1-[3-(ethoxycarbonyl)phenyl]-5-phenyl-1*H*-pyrazole (4k)

Column chromatography (silica gel, CH_2Cl_2); crystallisation (aq EtOH); yield: 0.98 g (40%); mp 129–132 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.0 Hz, 3 H, CH_3), 4.33 (q, *J* = 7.0 Hz, 2 H, CH_2), 6.60–6.66 (m, 3 H), 6.90–6.93 (m, 2 H), 7.15–7.17 (m, 5 H), 7.36–7.40 (m, 1 H), 7.43–7.44 (m, 1 H), 7.48–7.51 (m, 3 H), 7.56–7.59 (m, 1 H), 7.99–8.01 (m, 1 H), 8.08 (br s, 1 H), 8.35–8.37 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 61.2, 116.5, 119.8, 126.5, 128.1, 128.2, 128.3, 128.4, 128.8, 128.9, 129.0, 129.1, 129.5, 130.5, 131.5, 132.7, 133.2, 137.1, 140.0, 142.3, 143.0, 165.3, 189.4.

Anal. Calcd for $C_{31}H_{25}N_3O_3$: C, 76.37; H, 5.17; N, 8.62. Found: C, 76.22; H, 5.39; N, 8.74.

4-Amino-3-(cyclopropylcarbonyl)-5-ethyl-1-(4-tolyl)-1*H*-pyrazole (4l)

Column chromatography (silica gel, CH_2Cl_2–EtOAc, 4:1); yield: 0.70 g (52%); mp 108–111 °C.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.92–0.97 (m, 2 H), 1.06 (t, *J* = 7.6 Hz, 3 H, CH_3), 1.16–1.20 (m, 2 H), 2.40 (s, 3 H, CH_3), 2.59 (q, *J* = 7.6 Hz, 2 H, CH_2), 3.00–3.05 (m, 1 H), 3.99 (br s, 2 H, NH_2), 7.25–7.28 (m, 2 H), 7.30–7.32 (m, 2 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 10.9, 12.4, 16.7, 17.0, 21.0, 125.1, 129.7, 130.1, 130.4, 137.2, 138.5, 139.0, 198.2.

Anal. Calcd for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60. Found: C, 71.24; H, 7.04; N, 15.88.

1-[(4-Methoxy)phenyl]-5-methyl-4-(methylamino)-3-propanoyl-1*H*-pyrazole (4m)

Column chromatography (silica gel, CH_2Cl_2–EtOAc, 4:1); crystallisation (*n*-hexane); yield: 1.02 g (75%); mp 79–82 °C.

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.16 (t, *J* = 7.5 Hz, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 2.89 (s, 3 H, NCH_3), 3.00 (q, *J* = 7.5 Hz, 2 H, CH_2), 3.84 (s, 3 H, OCH_3), 4.95 (br s, 1 H, NH), 6.97–6.98 (m, 2 H), 7.31–7.33 (m, 2 H).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 8.0, 11.4, 31.5, 34.0, 55.4, 114.1, 125.6, 126.5, 132.4, 135.6, 138.3, 159.3, 199.7.

Anal. Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.75; H, 7.06; N, 15.27.

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