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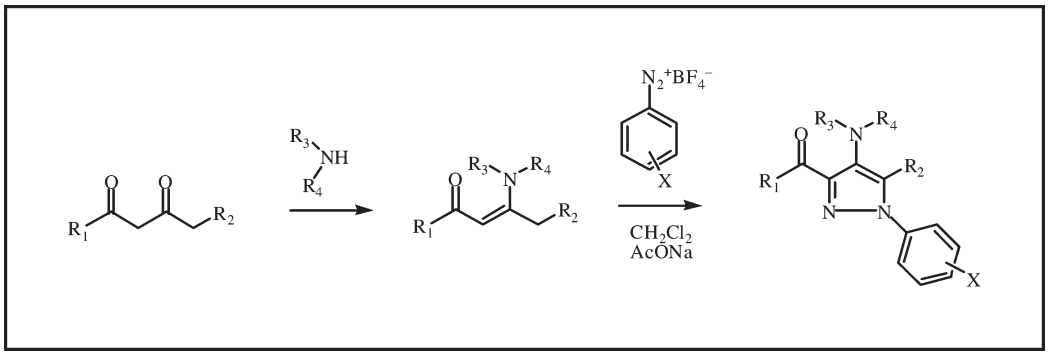

A series of 3-acyl-4-amino-1-aryl-1*H*-pyrazoles has been prepared by reaction of β-enaminones with benzenediazonium tetrafluoroborates substituted especially by fluorine-containing groups (F, CF_3, and OCF_3). The compounds prepared have been characterized by means of ^1H and ^{13}C NMR spectroscopy. In the case of reaction of 5-phenylaminohept-4-en-3-one with 2,6-dichloro-4-trifluoromethylbenzenediazonium tetrafluoroborate the product of azo coupling on phenylamino group of the corresponding pyrazole has been isolated and identified. The intermediate (4-(4-methoxyphenyldiazenyl)-5-methylaminohept-4-en-3-one) on the route from enaminone to pyrazole has been isolated.

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INTRODUCTION

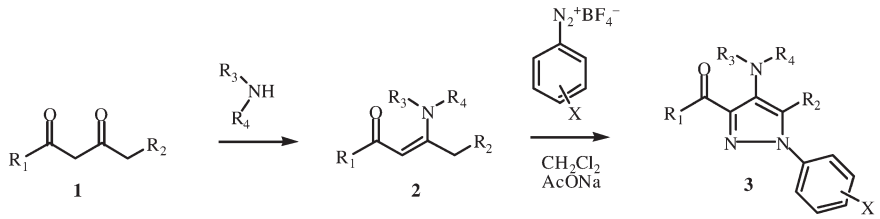
Fluorinated heterocycles represent an important class of compounds. These compounds are widely used as agrochemicals, pharmaceuticals, fluorinated polymers, and catalysts [1]. It has been proved that the introduction of a CF_3 group into heterocycle often leads to enhancement of biological effect compared with a parent compound, probably due to high lipophilicity of perfluoralkyl groups [2].

Compounds containing pyrazole moiety rank among the compounds having broad spectrum of biological activity [3]. A number of fluorine-containing pyrazoles found application as insecticides [4] (e.g., fiproles), herbicides [4] (e.g., pyrasulfotole, fluazolate, azimsulfurone), and fungicides [4] (e.g., penthiopyrad). Pyrazole ring is also an important pharmacophore. Celecoxib [5] (Celebrex) is an example of fluorinated pyrazole used in human medicine for treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms, and to reduce numbers of colon and rectum polyps in patients with familial adenomatous polyposis. Pyrazole derivatives so-called scorpionates work as metal ligands with promising perspective in homogeneous catalysis [6,7].

Great practical usability of pyrazole derivatives is reflected in interest in their syntheses. Stanovnik and Svete [8] published a review of the synthetic methods leading to pyrazoles. Probably, the most used method for synthesis of pyrazole skeleton is reaction of hydrazines with 1,3-difunctional compounds [8]. A drawback of the methods is the possibility of formation of regioisomers in the case of using of unsymmetrical 1,3-difunctional compounds. Kumar et al. [9] published a review dealing with a synthesis of trifluoromethylpyrazoles by reaction of corresponding trifluoromethyl-β-diketones with hydrazines. Pyrazoles are also obtainable from enaminones [10].

Combination of enaminones and diazonium salts is useful for preparation of some heterocyclic systems: pyridazinones [11], pyridazinium salts [12,13], and some boron-containing heterocycles [14,15]. We also developed a method for synthesis of substituted 3-acyl-4-amino-1-aryl-1*H*-pyrazoles using reaction of β-enaminones with substituted benzenediazonium tetrafluoroborates [16]. Advantages of the method are mild reaction conditions and easy performance. The method is applicable for diazonium salts substituted by both electron-donating and electron-withdrawing groups. The aim of this study was to prepare and characterize some

Scheme 1



1a: R_1 = Ph, R_2 = Me
1b: R_1 = R_2 = Ph
1c: R_1 = Et, R_2 = Me
1d: R_1 = cycloPr, R_2 = Et
1e: R_1 = CF_3, R_2 = *i*Pr

2a: R_1 = Ph, R_2 = Ph, R_3 = H, R_4 = Ph
2b: R_1 = Et, R_2 = Me, R_3 = H, R_4 = Ph
2c: R_1 = Et, R_2 = Me, R_3 = H, R_4 = antipyrine-4-yl
2d: R_1 = Ph, R_2 = Me, R_3 = H, R_4 = 3,4-diFPh
2e: R_1 = Ph, R_2 = Me, R_3 = H, R_4 = CH_2COOEt
2f: R_1 = Ph, R_2 = Me, R_3,R_4 = $(CH_2)_4$
2g: R_1 = CF_3, R_2 = *i*Pr, R_3 = H, R_4 = 3,4-diFPh
2h: R_1 = R_2 = Ph, R_3 = H, R_4 = Me
2i: R_1 = cycloPr, R_2 = Et, R_3 = H, R_4 = CH_2CH_2OH
2j: R_1 = Et, R_2 = Me, R_3 = H, R_4 = Me

3a: R_1 = Et, R_2 = Me, R_3 = H, R_4 = Ph, X = 4-F
3b: R_1 = Ph, R_2 = Me, R_3 = H, R_4 = 3,4-diFPh, X = 4-F
3c: R_1 = Ph, R_2 = Ph, R_3 = H, R_4 = Ph, X = 4-F
3d: R_1 = Et, R_2 = Me, R_3 = H, R_4 = antipyrine-4-yl, X = 4-F
3e: R_1 = Ph, R_2 = Ph, R_3 = H, R_4 = Me, X = 2-F
3f: R_1 = Ph, R_2 = Me, R_3 = H, R_4 = CH_2COOEt, X = 4-F
3g: R_1 = Ph, R_2 = Me, R_3,R_4 = $(CH_2)_4$, X = 3-CF_3
3h: R_1 = cycloPr, R_2 = Et, R_3 = H, R_4 = CH_2CH_2OH, X = 4-Me
3i: R_1 = Et, R_2 = Me, R_3 = H, R_4 = Me, X = 4-OMe
3j: R_1 = Et, R_2 = Me, R_3 = H, R_4 = Ph, X = 4-OCF_3

potentially biologically active pyrazoles with one or more fluorine atoms at various places of molecule and to explore extension of its applicability for other substituents at the amino group of the starting β-enaminones.

RESULTS AND DISCUSSION

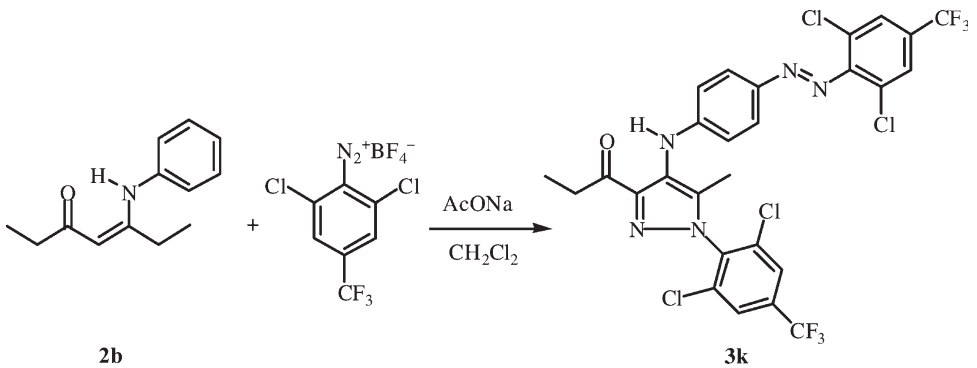
The pyrazoles have been synthesized according to the general Scheme 1. The starting components have been selected so that a series of the pyrazoles containing fluorine at various places of the molecule is prepared (fluorinated diazonium salts, diketones, and amines). For consideration of the applicability of the method some new amines for preparation of the β-enaminones have been used (aminoantipyrine, ethyl glycinate, 2-aminoethanol) and polysubstituted diazonium salt (from 2,6-dichloro-4-trifluoromethylaniline). For a review of the prepared pyrazoles see Scheme 1. Pyrazoles **3b,c,h** were prepared in relative good yields 65–79%. In the most cases, however, yields about 35% were obtained.

In the case of the reaction of 2,6-dichloro-4-trifluoromethylbenzenediazonium tetrafluoroborate with enaminone **2b**, a product of azo coupling on benzene ring of the group $=C-NHC_6H_5$ of pyrazole **3** has been isolated (Scheme 2). We have never observed formation of a product of this type for any previously used diazonium ions, including very reactive 4-nitrobenzenediazonium. Indeed 2,6-Dichloro-4-trifluoromethylbenzenediazonium is considerably more reactive than 4-nitrobenzenediazonium. For 2,6-dichloro-4-trifluoromethylbenzenediazonium was, from the kinetics of azo coupling with anion of pentane-2,4-dione, found the value [17] $\Sigma\sigma = 1.73$. Difference in the values of σ_p constants [18] between groups 4-NO_2 and 4-CF_3 is $\Delta\sigma = 0.24$, and the value of the reaction constant of azo coupling at position 4- of *N*,*N*-dimethylaniline is $\rho = 4.15$ [19] and at position 4- of *N*-methylaniline is $\rho = 3.98$ [20]. It results that, for azo coupling at position 4- of phenylamino group, 2,6-dichloro-4-trifluoromethylbenzenediazonium is about 10 times more reactive than 4-nitrobenzenediazonium.

Because of no intermediate of the reaction has been detected, the sequence of the reaction stages of formation of the compound **3k** is unclear.

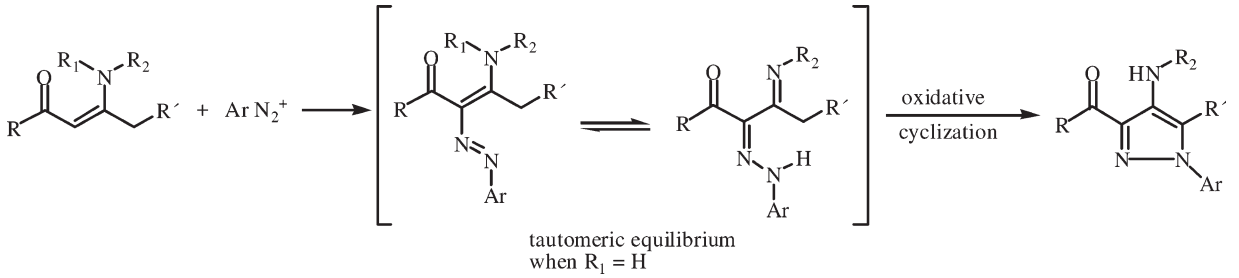
From the reaction mixture of enaminone **2g** and 4-methylbenzenediazonium tetrafluoroborate, only the

Scheme 2



2b **3k**

Scheme 3



starting enaminone has been isolated after 24 h and no pyrazole was formed.

The mechanisms of the pyrazole formation by reaction of diazonium salts with β-enaminones is so far not clear. A hypothesis assumes the primary attack of diazonium ion at α-carbon of enaminone to form a product of azo coupling undergoing subsequently oxidative cyclization to pyrazole (Scheme 3). The hypothesis is supported by the fact that by the reaction of 5-methylaminohept-4-en-3-one (**2j**) with 4-methoxybenzenediazonium tetrafluoroborate at a molar ratio 1:1 of 4-methoxyphenyldiazenyl-5-methylaminohept-4-en-3-one (**4**) (tautomeric form assigned based on results of the structural study [21] performed for similar compounds) was isolated as the main product. Compound **4** exists in $CDCl_3$ solution as *Z* isomer (in analogy with similar compounds [21]) with traces of *E* isomer. Corresponding pyrazole **3i** was isolated as a by-product. Oxidative cyclization of hydrazones to pyrazoles by number of oxidative agents ($Pb(OAc)_4$, hypervalent iodine compounds, MnO_2. . .) is described in the literature [22–24]. An oxidative agent in the case of formation of pyrazoles **3** is unclear; it could be the second molecule of diazonium salt.

To eliminate possibility of oxidation of primarily formed azo compound (Scheme 3) by air oxygen, the reaction of enaminone **2b** with 4-fluorobenzenediazonium tetrafluoroborate has been performed in an inert atmosphere. After finishing the reaction, a test for diazonium salt was negative and pyrazole was isolated in 69% yield (without inert atmosphere 42.5%). Presence of fluorobenzene as a possible reduction product of diazonium salt in the reaction mixture has been proved by means of gas chromatography-mass spectrometry. Previously, anisol has been detected in the reaction of 4-methoxybenzenediazonium tetrafluoroborate with 3-phenylaminocyclopent-2-en-1-one [25].

The reaction of β-enaminones with benzenediazonium salts in a molar ratio of 1:2 is accompanied by a color change, i.e., after approximately 20–30 min the color of the reaction mixture changes from dark red to orange. When the reaction of 4-methoxybenzenediazonium tetrafluoroborate with 5-methylaminohept-4-en-3-one (**2j**) was stopped after the color change, the yield of pyrazole **3i** was 58%. Compound **4** was isolated in 18% yield. Gas chromatography-mass spectrometry analysis of the reaction mixture detected anisole. Extension of a reaction time to 2 h and subsequent ^1H NMR analysis of the reaction mixture proved pyrazole as practically a sole product.

CONCLUSIONS

The method developed and described by us [16] has been used for synthesis of pyrazole derivatives containing fluorine atoms. At the same time its usability in the case of presence of new nitrogen substitutions of the starting enaminone (2-hydroxyethyl, antipyrine-4-yl, pyrrolidine-1-yl, and ethoxycarbonylmethyl) was tested. While using 2,6-dichloro-4-trifluoromethylbenzenediazonium tetrafluoroborate, the product of attack of *N*-phenyl group of the starting enaminone has been isolated for the first time.

Attack of diazonium ion at α-carbon of β-enaminone has been proved to be the first step of our synthesis of pyrazoles. An oxidation agent is probably the second molecule of diazonium ion, being reduced to substituted benzene (4-fluorobenzenediazonium to fluorobenzene, 4-methoxybenzenediazonium to anisole). The mechanism of the pyrazole formation is currently under examination.

EXPERIMENTAL

Tetrahydrofuran (THF) was dried by refluxing with sodium benzophenone ketyl under inert atmosphere until blue–violet coloration took place. THF was freshly distilled under inert atmosphere before use. Dichloromethane was used commercially (Fluka), dried over molecular sieves, and stored in the bottle with Sure/Seal.

Diazonium tetrafluoroborates were freshly prepared before using standard procedures (diazotization of corresponding aniline and subsequent treatment of diazonium chloride by sodium tetrafluoroborate) and dried *in vacuo*. Anhydrous sodium acetate was purchased commercially and used without change.

NMR spectra were measured in $CDCl_3$ using the Bruker AVANCE 500 spectrometer operating at 500.13 MHz (^1H), 125.77 MHz (^{13}C).

Hexamethyldisiloxane was used as internal standard for ^{1}H ($\delta = 0.05$). The ^{13}C NMR spectra were standardized by means of the middle signal of the solvent multiplet ($\delta = 76.9$). The carbon spectra were measured by standard way with the broad-band decoupling of protons or by means of the APT pulse sequence.

Diketones **1a,b,d** and enaminones **2a,h,j** were prepared according to the procedure described in the literature [10]. Diketone **1c** was purchased commercially (Aldrich).

1,1,1-Trifluoro-6-methylheptane-2,4-dione (1e). The reaction has been performed in an inert atmosphere. Sodium hydride (9.6 g, 0.4 mol) and THF (240 mL) were added to a 500-mL four-necked flask equipped with reflux condenser, thermometer, magnetic stirrer, and dropping funnel. Methyl trifluoroacetate (25.61 g, 0.2 mol) was added dropwise for 30 min. Then, 4-methylpentane-2-one (20.03 g, 0.2 mol) was added under cooling for 30 min. The mixture was stirred under inert atmosphere at laboratory temperature overnight. Reaction was quenched by ethanol (10 mL) and the mixture was poured into a flask containing 10% HCl (120 mL). Aqueous layer was extracted by ethyl acetate (2 × 50 mL). Combined organic layers were washed by saturated aqueous sodium bicarbonate (1 × 150 mL), water (1 × 150 mL), and brine (1 × 150 mL), dried with sodium sulfate, and evaporated. Diketone has been purified through copper diketonate [16]. After complex decomposition by dilute sulfuric acid, the product was distilled, bp 153–154°C ([26] 136°C). Yield: 7.66 g (19.5%). ^{1}H NMR: δ 0.94 (d, 6H, $J = 7.0$ Hz, 2 × CH_3), 2.09 (sp, 1H, $J = 6.5$ Hz, CH), 2.26 (d, 2H, $J = 7.5$ Hz, CH_2), 5.87 (s, 1H, =C—H), 14.28 (brs, 1H, NH). ^{13}C NMR: δ 22.1 (CH_3), 26.3 (CH), 47.0 (CH_2), 96.0 (q, $J = 1.8$ Hz, =CH), 116.9 (q, $J = 283.3$, CF_3), 176.3 (q, $J = 36.2$ Hz, =C—OH), 196.3 (C=O).

5-Phenylaminohept-4-en-3-one (2b). A mixture of **1c** (6.61 g, 0.05 mol), aniline (4.65 g, 0.05 mol), and catalytic amount of TsOH in toluene (30 mL) has been boiled on an oil bath for 2.5 h. Reaction water was removed azeotropically. After completion of the reaction, volatile components were distilled off *in vacuo* and the rest was subjected to a vacuum distillation. Yield: 7.54 g (74%), bp 142–144°C/0.5 kPa. ^{1}H NMR: δ 1.04 (t, 3H, $J = 7.5$ Hz, CH_3), 1.13 (t, 3H, $J = 7.5$ Hz, CH_3), 2.31 (q, 2H, $J = 7.5$ Hz, CH_2), 2.36 (q, 2H, $J = 7.5$ Hz, CH_2), 5.20 (s, 1H, =C—H), 7.09–7.10 (m, 2H, Ph), 7.16–7.19 (m, 1H, Ph), 7.30–7.33 (m, 2H, Ph), 12.48 (brs, 1H, NH). ^{13}C NMR: δ 9.7 (CH_3), 12.3 (CH_3), 25.0 (CH_2), 35.1 (CH_2), 94.2 (=CH), 125.0, 125.5, 128.9 (3 × CH_{Ar}), 138.5, 165.8, 200.0 (3 × C_q). *Anal*. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.65; H, 8.49; N, 6.96.

5-(1,5-Dimethyl-3-oxo-2-phenyl-1,2-dihydropyrazol-4-yl)-aminohept-4-en-3-one (2c). A mixture of **1c** (3.84 g, 0.03 mol) and 4-aminoantipyrine (4.06 g, 0.02 mol) has been stirred at laboratory temperature overnight. The mixture was then diluted by petroleum ether (70 mL). Separated oil solidified on standing. The solidified product was thoroughly washed with petroleum ether. Yield: 5.72 g (91.3%), mp 94–96.5°C. ^{1}H NMR: δ 1.04 (t, 3H, $J = 7.5$ Hz, CH_3), 1.10 (t, 3H, $J = 7.5$ Hz, CH_3), 2.21 (s, 3H, =C—CH_3), 2.30 (q, 2H, $J = 7.5$ Hz, CH_2), 2.34 (q, 2H, $J = 7.5$ Hz, CH_2), 3.05 (s, 3H, N—CH_3), 5.21 (s, 1H, =C—H), 7.25–7.29 (m, 1H, Ph), 7.36–7.38 (m, 2H, Ph), 7.42–7.45 (m, 2H, Ph), 11.54 (brs, 1H, NH). ^{13}C NMR: δ 9.6, 10.4, 11.5 (3 × CH_3), 25.0, 35.1 (2 × CH_2), 36.0 (CH_3), 94.0 (=C—H), 110.4 (C_q), 123.8, 126.6, 129.0 (3 × CH_{Ar}), 134.7, 150.9, 161.9, 168.0, 200.2 (5 × C_q). *Anal*. Calcd for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41. Found: C, 69.23; H, 7.32; N, 13.48.

3-(3,4-Difluorophenylamino)-1-phenylpent-2-en-1-one (2d). A mixture of diketone **1a** (1.39 g, 7.9 mmol), 3,4-difluoroaniline (1.02 g, 7.9 mmol), and catalytic amount of TsOH in toluene (15 mL) has been boiled and water formed was removed azeotropically. After 3 h, solvent was distilled off and the rest was suspended in *n*-hexane. Solid product was isolated by suction and recrystallized from *n*-hexane. Yield: 1.12 g (49.3%), mp 54–57°C. ^{1}H NMR: δ 1.14 (t, 3H, $J = 7.5$ Hz, CH_3), 2.40 (q, 2H, $J = 7.5$ Hz, CH_2), 5.94 (s, 1H, =C—H), 6.89–6.92 (m, 1H, NPh), 7.02 (ddd, 1H, $J = 10.9$, 7.0, 2.7 Hz, NPh), 7.13 (dt, 1H, $J = 8.8$, 9.5 Hz, NPh), 7.40–7.47 (m, 3H, Ph), 7.89–7.91 (m, 2H, Ph), 12.98 (brs, 1H, NH). ^{13}C NMR: δ 12.4 (CH_3), 25.4 (CH_2), 92.5 (=CH), 114.7 (d, $J = 18.5$ Hz, NPh), 117.5 (d, $J = 18.1$ Hz, NPh), 121.5 (dd, $J = 6.0$, 3.4 Hz, NPh), 127.0, 128.2, 131.0 (3 × CH, Ph), 134.9 (dd, $J = 7.7$, 3.5 Hz, NPh), 139.7 (Ph), 148.3 (dd, $J = 198.7$, 13.5 Hz, NPh), 150.3 (dd, $J = 200.7$, 13.5 Hz, NPh), 167.2 (C_q), 189.42 (C=O). *Anal*. Calcd for $C_{17}H_{15}F_2NO$: C, 71.07; H, 5.26; N, 4.88. Found: C, 71.27; H, 5.01; N, 5.10.

3-(Ethoxycarbonylmethylamino)-1-phenylpent-2-en-1-one (2e). A mixture of ethyl glycinate hydrochloride (2.38 g, 17 mmol), **1a** (3 g, 17 mmol) and $NaHCO_3$ (1.43 g, 17 mmol) in ethanol (30 mL) has been refluxed for 5.5 h. The mixture was then cooled, filtered, and the solvent was distilled off. The residue was extracted with dichloromethane (20 mL), filtered, and the filtrate was evaporated. The residue was recrystallized from hexane–cyclohexane mixture. Yield: 3.90 g (87%), mp 69–71.5°C. ^{1}H NMR: δ 1.18 (t, 3H, $J = 7.5$ Hz, CH_3), 1.26 (t, 3H, $J = 7.0$ Hz, CH_3), 2.28 (q, 2H, $J = 7.5$ Hz, CH_2), 4.06 (d, 2H, $J = 6.0$ Hz, N—CH_2), 4.21 (q, 2H, $J = 7.0$ Hz, O—CH_2), 5.75 (s, 1H, =C—H), 7.34–7.40 (m, 3H, Ph), 7.83–7.85 (m, 2H, Ph), 11.55 (brs, 1H, NH). ^{13}C NMR δ: 11.9, 14.0 (2 × CH_3), 25.2, 44.3, 61.6 (3 × CH_2), 91.0 (=CH), 126.9, 128.0, 130.5 (3 × CH_{Ar}), 140.2, 168.6, 168.9 (3 × C_q), 188.8 (C=O). *Anal*. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.12; H, 7.28; N, 5.26.

1-Phenyl-3-(pyrrolidine-1-yl)pent-2-en-1-one (2f). The procedure from Ref. [27] has been adopted. A mixture of diketone **1a** (2.05 g, 11.6 mmol), pyrrolidine (1.03 g, 14.4 mmol), and $CoCl_2 \cdot 6H_2O$ (0.14 g, 0.58 mmol) has been stirred at laboratory temperature for 72 h, then mixed with CH_2Cl_2 and filtered. Filtrate was evaporated and the residue was recrystallized from cyclohexane. Yield: 1.50 g (56.4%) mp 105–108°C. ^{1}H NMR: δ 1.24 (t, 3H, $J = 7.5$ Hz, CH_3), 1.96 (brs, 4H, 2 × CH_2), 3.12 (q, 2H, $J = 7.5$ Hz, CH_2), 3.33 (brs, 2H, CH_2), 3.56 (brs, 2H, CH_2), 5.55 (s, 1H, =C—H), 7.34–7.38 (m, 3H, Ph), 7.85–7.86 (m, 2H, Ph). ^{13}C NMR: δ 12.2 (CH_3), 24.4, 24.8, 25.4, 47.3, 48.7 (5 × CH_2), 91.5 (=CH), 127.2, 128.0, 130.1 (3 × CH_{Ar}), 143.1, 167.0 (2 × C_q), 187.0 (C=O). *Anal*. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.60; H, 8.29; N, 6.14.

1,1,1-Trifluoro-5-methyl-4-(3,4-difluorophenylamino)hept-3-en-2-one (2g). A mixture of **1e** (2.94 g, 15 mmol), 3,4-difluoroaniline (1.94 g, 15 mmol), and catalytic amount of TsOH in toluene (10 mL) has been heated to 110°C for 3 h. The mixture solidified on cooling. The solidified mixture was subjected to column chromatography (silicagel/$CHCl_3$-EtOAc 6:1). Yield: 2.66 g (57.7%). Recrystallization from aqueous

ethanol, mp 50–56°C. ^{1}H NMR: δ 0.86 (d, 6H, J = 6.6 Hz, 2 × CH_3), 1.80 (sp, 1H, J = 6.8 Hz, CH), 2.24 (d, 2H, J = 7.4 Hz, CH_2), 5.56 (s, 1H, =C—H), 6.90–6.94 (m, 1H, NPh), 7.02 (ddd, 1H, J = 2.6, 6.9, 10.0 Hz, NPh), 7.22 (dt, 1H, J = 8.7, 9.8 Hz, NPh), 12.54 (brs, 1H, NH). ^{13}C NMR: δ 22.1 (CH_3), 27.8 (CH), 40.8 (CH_2), 90.5 (=CH), 115.6 (d, J = 18.8 Hz, NPh), 117.2 (q, J = 288.3 Hz, CF_3), 117.9 (d, J = 18.4 Hz, NPh), 122.4 (dd, J = 6.3, 3.6 Hz, NPh), 133.2 (dd, J = 7.5, 3.6 Hz, NPh), 149.5 (dd, J = 250.6, 12.4 Hz, C—F), 150.1 (dd, J = 251.9, 13.6 Hz, C—F), 171.4, 177.1 (q, J = 33.3, C=O). *Anal*. Calcd for $C_{14}H_{14}F_5NO$: C, 54.73; H, 4.59; N, 4.56. Found: C, 55.11; H, 4.41; N, 4.77.

1-Cyclopropyl-3-(2-hydroxyethyl)hex-2-en-1-one (2i). A mixture of diketone **1d** (3.08 g, 0.02 mol) and ethanolamine (1.22 g, 0.02 mol) in toluene (10 mL) has been refluxed in the presence of catalytic amount of TsOH for 5.5 h. The mixture was then cooled and washed by water (10 mL). Organic phase was separated, dried by sodium sulfate, and solvent was evaporated. The residue was recrystallized from *n*-hexane. Yield: 2.5 g (63.4%), mp 68–71°C. ^{1}H NMR: δ 0.67–0.71 (m, 2H, cPr CH_2), 0.88–0.91 (m, 2H, cPr CH_2), 0.98 (t, 3H, J = 7.0 Hz, CH_3), 1.54–1.64 (m, 3H, cPr CH + CH_2), 2.17–2.20 (m, 2H, CH_2), 3.37 (q, 2H, J = 5.7 Hz, CH_2N), 3.71 (brt, 2H, J = 5.6 Hz, CH_2O), 3.85 (brs, 1H, OH), 5.13 (s, 1H, =C—H), 10.81 (brs, 1H, NH). ^{13}C NMR: δ 8.5 (CH_2), 13.8 (CH_3), 19.7 (CH), 21.1, 33.9, 44.7, 61.2 (4 × CH_2), 94.0 (=CH), 166.3 (=C—N), 196.6 (C=O). *Anal*. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.31; H, 9.39; N, 7.23.

Pyrazoles synthesis. The following pyrazoles have been prepared according to the published procedure [16].

1-(4-Fluorophenyl)-5-methyl-4-phenylamino-3-propanoyl-1H-pyrazole (3a). This is prepared from enaminone **2b** and 4-fluorobenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2, yield 42.5%, recrystallization from ethanol, mp 100–102°C. ^{1}H NMR: δ 1.16 (t, 3H, J = 7.5 Hz, CH_3), 2.10 (s, 3H, CH_3), 3.04 (q, 2H, J = 7.5 Hz, CH_2), 6.76–6.78 (m, 2H, Ph), 6.81–6.84 (m, 1H, Ph), 6.91 (brs, 1H, NH), 7.17–7.23 (m, 4H, Ph), 7.48–7.51 (m, 2H, Ph). ^{13}C NMR: δ 7.7, 12.0 (2 × CH_3), 32.0 (CH_2), 115.6 (CH_{Ar}), 116.2 (d, J_{CF} = 23.0 Hz, CH_{Ar}), 119.7 (CH_{Ar}), 126.6 (d, J_{CF} = 8.7 Hz, CH_{Ar}), 126.6 (C_q), 129.0 (CH_{Ar}), 131.6, 135.4 (d, J_{CF} = 2.9 Hz, C_q), 141.6, 144.5, 162.1 (d, J_{CF} = 249.0 Hz, C—F), 199.3 (C=O). *Anal*. Calcd for $C_{19}H_{18}FN_3O$: C, 70.57; H, 5.61; N, 12.99. Found: C, 70.77; H, 5.37; N, 12.99.

3-Benzoyl-1-(4-fluorophenyl)-4-(3,4-difluorophenylamino)-5-methyl-1H-pyrazole (3b). This compound is prepared from enaminone **2d** and 4-fluorobenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2, yield 70%, recrystallization from ethanol, mp 190–193°C. ^{1}H NMR: δ 2.14 (s, 3H, CH_3), 6.50–6.51 (m, 1H, Ph), 6.56 (ddd, 1H, J = 12.3, 6.7, 2.7 Hz, Ph), 6.99 (dt, 1H, J = 8.9, 9.9 Hz, Ph), 7.09 (brs, 1H, NH), 7.18–7.22 (m, 2H, Ph), 7.42–7.45 (m, 2H, Ph), 7.50–7.55 (m, 3H, Ph), 8.30–8.31 (m, 2H, Ph). ^{13}C NMR: δ 11.8 (CH_3), 104.2 (d, J_{CF} = 20.8 Hz), 111.1 (dd, J_{CF} = 5.4, 2.9 Hz), 116.2 (d, J_{CF} = 23.0 Hz), 117.3 (d, J_{CF} = 17.9 Hz), 126.6 (d, J_{CF} = 8.7 Hz), 128.0, 128.1, 130.5, 131.9, 132.8, 135.3 (d, J_{CF} = 3.1 Hz), 136.8, 141.6 (dd, J_{CF} = 8.2, 2.0 Hz), 142.0, 144.3 (dd, J_{CF} = 239.1, 12.8 Hz), 150.6 (dd, J_{CF} = 246.2, 13.8 Hz), 162.2 (d, J_{CF} = 249.2 Hz), 189.2 (C=O). *Anal*. Calcd for $C_{23}H_{16}F_3N_3O$: C, 67.81; H, 3.96; N, 10.31. Found: C, 67.94; H, 4.04; N, 10.32.

3-Benzoyl-1-(4-fluorophenyl)-5-phenyl-4-phenylamino-1H-pyrazole (3c). This is prepared from enaminone **2a** and 4-fluorobenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2, yield 79%, recrystallization from ethanol, mp 148–150°C. ^{1}H NMR: δ 6.56–6.61 (m, 3H, Ph), 6.86–6.89 (m, 2H, Ph), 6.97–7.00 (m, 2H, Ph), 7.10–7.13 (m, 5H), 7.26–7.28 (m, 2H, Ph), 7.42–7.46 (m, 2H), 7.50–7.53 (m, 2H), 8.31–8.33 (m, 2H). ^{13}C NMR: δ 115.8 (d, J_{CF} = 23.0 Hz, CH), 116.4, 119.7 (2 × CH), 127.3 (d, J_{CF} = 8.7 Hz, CH), 128.1, 128.2, 128.3 (3 × CH), 128.9, 128.9 (2 × C_q), 129.0, 130.4, 132.6 (3 × CH), 133.0 (C_q), 135.9 (d, J_{CF} = 3.2 Hz, C_q), 137.1, 141.9, 142.9 (3 × C_q), 161.8 (d, J_{CF} = 248.9 Hz, C—F), 189.3 (C=O). *Anal*. Calcd for $C_{28}H_{20}FN_3O$: C, 77.58; H, 4.65; N, 9.69. Found: C, 77.55; H, 4.90; N, 9.71.

1-(4-Fluorophenyl)-5-methyl-4-(1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one-4-ylamino)-3-propanoyl-1H-pyrazole (3d). This compound is prepared from enaminone **2c** and 4-fluorobenzenediazonium tetrafluoroborate. Chromatography silicagel/$CHCl_3$-EtOAc 3:2, yield 37.2%, recrystallization from ethanol, mp 184–189.5°C. ^{1}H NMR: δ 1.08 (t, 3H, J = 7.0 Hz, CH_3), 1.91 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.89–2.95 (m, 5H, CH_2 + CH_3), 6.99–7.03 (m, 2H, Ph), 7.13–7.16 (m, 1H, Ph), 7.26–7.32 (m, 6H, Ph). ^{13}C NMR: δ 7.7, 9.9, 10.0 (3 × CH_3), 31.2 (CH_2), 35.7 (NCH_3), 112.9 (C_q), 115.5 (d, J_{CF} = 23.0 Hz, CH), 123.5 (CH), 124.5 (C_q), 126.3 (CH), 126.7 (d, J_{CF} = 8.7 Hz, CH), 128.7, 131.2, 134.4 (2 × C_q), 135.0 (d, J_{CF} = 2.9 Hz, C_q), 138.0, 150.9 (2 × C_q), 161.6 (d, J_{CF} = 248.5 Hz, C—F), 163.2 (C_q), 199.2 (C=O). *Anal*. Calcd for $C_{24}H_{24}FN_5O_2$: C, 66.50; H, 5.58; N, 16.16. Found: C, 66.67; H, 5.32; N, 15.92.

3-Benzoyl-1-(2-fluorophenyl)-4-methylamino-5-phenyl-1H-pyrazole (3e). This is prepared from enaminone **2h** and 2-fluorobenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2, yield 39.5%, recrystallization from ethanol, mp 140–145°C. ^{1}H NMR: δ 2.54 (s, 3H, CH_3), 5.94 (brs, 1H. NH), 7.00–7.04 (m, 1H, Ph), 7.07–7.10 (m, 1H, Ph), 7.24–7.31 (m, 7H), 7.42–7.45 (m, 2H), 7.49–7.53 (m, 1H), 8.29–8.31 (m, 2H). ^{13}C NMR: δ 33.3 (CH_3), 116.4 (d, J_{CF} = 19.7 Hz, CH), 124.1 (d, J_{CF} = 3.9 Hz, CH), 127.7, 127.9, 128.2, 129.2 (3 × CH), 129.7 (C_q), 130.3 (CH), 130.4 (d, J_{CF} = 7.7 Hz, CH), 130.5, 132.1 (2 × CH), 137.9 (d, J_{CF} = 9.9 Hz, C_q), 138.7 (C_q), 157.0 (d, J_{CF} = 253.4 Hz, C—F), 190.0 (C=O). *Anal*. Calcd for $C_{23}H_{18}FN_3O$: C, 74.38; H, 4.88; N, 11.31. Found: C, 74.16; H, 5.17; N, 11.06.

3-Benzoyl-4-ethoxycarbonylmethylamino-1-(4-fluorophenyl)-5-methyl-1H-pyrazole (3f). The compound **3f** is prepared from enaminone **2e** and 4-fluorobenzenediazonium tetrafluoroborate. Chromatography silicagel/$CHCl_3$-EtOAc 6:1, yield 56%, oil. ^{1}H NMR: δ 1.21 (t, 3H, J = 7.0 Hz, CH_3), 2.31 (s, 3H, CH_3), 3.96 (s, 2H, CH_2), 4.17 (q, 2H, J = 7.0 Hz, CH_2), 6.02 (brs, 1H, NH), 7.15–7.18 (m, 2H), 7.41–7.44 (m, 4H), 7.50–7.53 (m, 1H), 8.28–8.29 (m, 2H). It was not possible to purify the compound sufficiently for elemental analysis.

3-Benzoyl-1-(3-trifluoromethylphenyl)-5-methyl-4-(pyrrolidine-1-yl)-1H-pyrazole (3g). This is prepared from enaminone **2f** and 3-trifluoromethylbenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2, yield 38.3%, oil. ^{1}H NMR: δ 1.94–1.97 (m, 4H, CH_2 pyrr.), 2.37 (s, 3H, CH_3), 3.18–3.20 (m, 4H, CH_2, pyrr.), 7.44–7.47 (m, 2H), 7.53–7.56 (m, 1H), 7.60–7.62 (m, 1H), 7.64–7.66 (m, 1H), 7.69–7.71 (m, 1H), 7.77 (brs, 1H), 8.11–8.13 (m, 2H). ^{13}C NMR: δ 11.0 (CH_3),

25.9, 52.4 (2 × CH_2), 121.5 (q, J_{CF} = 3.9 Hz, CH), 123.3 (q, J_{CF} = 273.0 Hz, CF_3), 124.5 (q, J_{CF} = 3.7 Hz, CH), 127.8, 128.0, 129.7, 130.5 (4 × CH), 131.6 (q, J_{CF} = 33.2 Hz, C_q), 132.6 (CH), 134.5, 134.6, 137.9, 140.1, 145.1 (5 × C_q), 189.8 (C=O). *Anal*. Calcd for $C_{22}H_{20}F_3N_3O$: C, 66.16; H, 5.05; N, 10.52. Found: C, 66.08; H, 5.34; N, 10.34.

3-Cyclopropylcarbonyl-5-ethyl-4-(2-hydroxyethylamino)-1-(4-methylphenyl)-1H-pyrazole (3h). This is prepared from enaminone **2i** and 4-methylbenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2-EtOAc 4:1, yield 65.7%, recrystallization from *n*-hexane, mp 112–114°C. ^{1}H NMR: δ 0.90–0.94 (m, 2H, cPr CH_2), 0.98 (t, 3H, J = 7.5 Hz, CH_3), 1.13–1.16 (m, 2H), 2.38 (s, 3H, C**H**$_3$Ph), 2.63 (q, 2H, J = 7.5 Hz, CH_2), 3.02 (tt, 1H, J = 4.6, 8.0 Hz, cPr CH), 3.16–3.18 (m, 2H, NCH_2), 3.60–3.62 (m, 2H, CH_2O), 4.63 (brs, 1H, OH), 7.24–7.29 (m, 4H, Ph). ^{13}C NMR: δ 11.4 (cPr CH_2), 12.9, 17.0 (2 × CH_3), 17.7 (CH_2), 21.0 (cPr CH), 50.4, 61.0 (2 × CH_2), 125.4, 129.6 (2 × CH_{Ar}), 131.8, 134.5, 137.0, 138.8, 140.9 (5 × C_q), 199.2 (C=O). *Anal*. Calcd for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41. Found: C, 69.27; H, 7.45; N, 13.58.

1-(4-Methoxyphenyl)-4-methylamino-5-methyl-3-propanoyl-1H-pyrazole (3i). This is prepared from enaminone **2j** and 4-methoxybenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2-EtOAc 4:1. Yield 62.9% mp 79–82°C ([16] 79–82°C).

1-(2-Trifluoromethoxyphenyl)-5-methyl-4-phenylamino-3-propanoyl-1H-pyrazole (3j). Prepared from enaminone **2b** and 2-trifluoromethoxybenzendiazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2, yield 23% (in an inert atmosphere 34%). ^{1}H NMR: δ 1.16 (t, 3H, J = 7.4 Hz CH_3), 1.98 (s, 3H, CH_3), 3.04 (q, 2H, J = 7.4 Hz CH_2), 6.76–6.77 (m, 2H), 6.83–6.86 (m, 1H), 6.87 (brs, 1H, NH), 7.20–7.23 (m, 2H), 7.45–7.50 (m, 2H), 7.54–7.59 (m, 2H).

1-(2,6-Dichloro-4-trifluoromethyl)-4-[4-(2,6-dichloro-4-trifluoromethylphenyldiazenyl)phenylamino]-5-methyl-3-propanoyl-1H-pyrazole (3k). Prepared from enaminone **2b** and 2,6-dichloro-4-trifluoromethylbenzenediazonium tetrafluoroborate. Chromatography silicagel/CH_2Cl_2, yield 27.3%, recrystallization from ethanol, mp 192–194°C. ^{1}H NMR: δ 1.18 (t, 3H, J = 7.3 Hz, CH_3), 2.02 (s, 3H, CH_3), 3.05 (q, 2H, J = 7.3 Hz, CH_2), 6.81–6.83 (AA′, 2H), 7.03 (s, 1H, NH), 7.64 (s, 2H, CH_{Ar}), 7.81 (s, 2H, CH_{Ar}), 7.90–7.92 (XX′, 2H). ^{13}C NMR: δ 7.6, 10.3 (2 × CH_3), 32.4 (CH_2), 114.5 (C_q), 121.9 (q, J_{CF} = 273.5 Hz, CF_3), 122.5 (q, J_{CF} = 273.1 Hz, CF_3), 123.3 (C_q), 125.7 (CH), 125.9 (q, J_{CF} = 3.7 Hz, CH), 126.0 (q, J_{CF} = 3.5 Hz, CH), 127.6 (CH), 134.0 (q, J_{CF} = 34.6 Hz, 2 × C_q), 135.2 (C_q), 136.0 (C_q), 137.5 (C_q), 144.0 (C_q), 145.8 (C_q), 149.3 (C_q), 151.4 (C_q), 198.8 (C=O). *Anal*. Calcd for $C_{27}H_{17}Cl_4F_6N_5O$: C, 47.46; H, 2.51; N, 10.25. Found: C, 47.71; H, 2.21; N, 10.29.

4-Methoxyphenyldiazenyl-5-methylaminohept-4-en-3-one (4). The compound has been prepared by the same procedure as pyrazoles **3a–j** but the molar ratio of diazo:enaminone was 1:1. The reaction was performed for 24 h under inert atmosphere. Chromatography silicagel/CH_2Cl_2-EtOAc 4:1. Yield 45.2%, oil. ^{1}H NMR (major isomer only) δ: 1.14 (t, 3H, J = 7.5 Hz, CH_3), 1.25 (t, 3H, J = 7.5 Hz, CH_3), 2.99–3.03 (m, 4H, 2 × CH_2), 3.13 (s, 3H, N—CH_3), 3.83 (s, 3H, OCH_3), 6.92–6.94 (m, 2H, AA′), 7.53–7.55 (brm, 2H, XX′), 14.53 (brs, 1H, NH). ^{13}C NMR: (major isomer only) δ 9.4, 11.5, 21.8, 28.8, 32.7, 55.3, 114.1, 121.1, 127.0, 145.8, 158.6, 165.1, 200.4. *Anal*. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.28; H, 7.40; N, 15.46.

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