# Study of the Reactivity of α-Acylenaminoketones. Synthesis of Pyrazoles



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The reactions of 4-(methylamino)-3-penten-2-one with diazoketones yielded the α-acylenaminoketones **1-3** in good yields. Preparation of the α-acylenaminoketone **4** was carried out by treatment of 4-(*t*-butylamino)-3-penten-2-one with benzoyl chloride being followed by reaction of transamination with methylamine. The reactions were carried out in five different solvents and were submitted to gas chromatography/mass spectrometry analysis, with the goal of obtaining substituted pyrazoles and determining which of the carbonyls would preferentially be attacked by the nucleophile. The reactions of compounds **1-4** with hydrazine reagents led to the formation of the pyrazoles **5-7a-q**. Small amounts of 4-methylamino-2-pentenones **10a-q**, amides **11a-q** and pyrazoles **12a-q** were also obtained in these reactions. The unexpected formation of pyrazoles **15d,h,q** was detected when methanol and *N*,*N*-dimethylformamide were used as solvents in the reactions of α-acylenaminoketone **4** with hydrazine reagents.

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## Introduction.

The ease of preparation of enaminones, whose regio- and stereoselective syntheses and functionalization have been subject of research for some time, makes them attractive intermediates for organic synthesis [1,2]. Diazodiphenylethanone reacts with enaminones *via* its copper(II)-stabilized carbene to form pyrroles [3] or *via* diphenylketene under noncatalytic thermal conditions to form nucleophilic addition products [4]. 3-Diazo-1,3-dihydro-2*H*-indol-2-one derivatives react with enaminones to form triazoles [5]. The quinone diazides were reacted with enaminones to produce the novel azoenaminones. The potential usefulness [6] of the push-pull azoenaminones in nonlinear optics, as second harmonic generators, was proposed based on theoretical finite-field static calculations. Enaminoketones and enaminoesters [7-10] can be reduced to γ-aminoalcohols or β-aminoacids, which are important classes of organic compounds of proved biological and pharmacological activity. β-Enaminoketones and esters have found application as 1,3-bielectrophilic synthons in the syntheses of heterocycles [11-20].

The most important derivatives of pyrazole are pyrazolones, which have important pharmacological properties and of which a few naturally-occurring examples exist. For this reason, there is increasing interest in the development of a new procedure for the synthesis of pyrazoles and their derivatives. The standard syntheses for pyrazoles involve the reaction of β-dicarbonyl compounds with hydrazine. *N*-Substituted pyrazoles are of interest as chiral auxiliary for stereoselective synthesis and for the resolution of certain racemic compounds. A great many papers have been reported so far concerning the synthesis or biological activity of pyrazole derivatives [21-24]. By treatment with various nucleophiles, *N*-acylpyrazoles were converted into the corresponding amides, esters, ketones and β-keto esters [25]. Amongst pyrazole derivatives, *C*-aminopyrazoles are the most used in heterocyclic chemistry as starting materials because of their versatility in reactions with conjugated ketones, esters and nitriles [26]. Reaction of hydrazines with acetoacetamides affords pyrazoles retaining the amine moiety [27].

Solvent effects on organic reactivity [28-29] and on absorption spectra have been studied for more than a century. Organic chemists have usually attempted to understand these solvent effects in terms of the polarity of the solvent. Solvents whose molecules possess a permanent dipole moment are designated dipolar as opposed to apolar or nonpolar for those lacking a dipole moment [30]. The dielectric constants play a particular role in the characterization of solvents. Their importance over other criteria is due to the simplicity of electrostatic models of solvation and they have become a useful measure of solvent polarity. The dielectric constant represents the ability of a solvent to separate charge and to orient its dipole [30].

Our continuing interest in the structure-reactivity relationships of enaminones has led us to examine the chemistry of 4-methylamino-3-penten-2-ones with acetyl derivatives in the 3-position [4]. The study of the reactivity of α-acylenaminoketones **1-4** and **18** aroused our interest because of the different ways that the two ketonic carbonyls could react; different kinds of heterocycles may be formed depending on the reaction conditions employed.

## Results and Discussions.

As part of this study, it has become necessary to determine the structures of compounds **1-4** (Figure 1) in greater detail than was obtained by spectroscopic data. The presence of an intramolecular NH chelated proton in compounds **1-4** and **18** is clearly observed in the $^1$H NMR

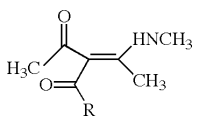


Figure 1. **1**, R = $CH(Ph)_2$ **2**, R = $CH(CH_3)Ph$ **3**, R = $CH(CH_3)_2$ **4**, R = Ph

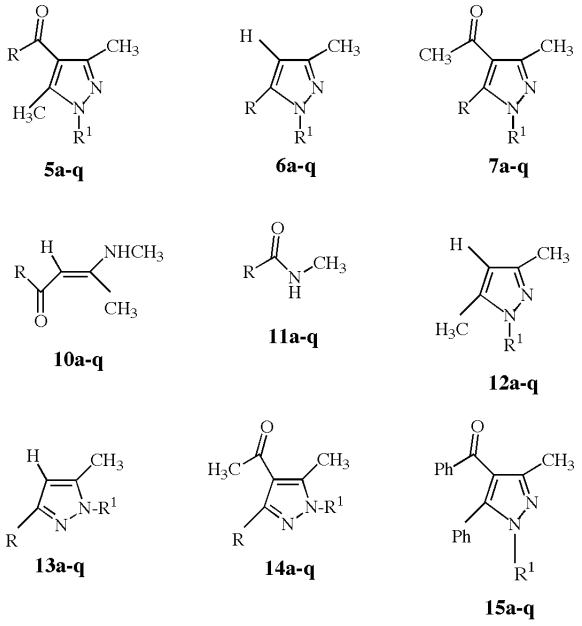


Figure 2. **a**)R = $CH(Ph)_2$, $R^1$ = $CH_3$; **b**) R = $CH(CH_3)Ph$, $R^1$ = $CH_3$; **c**) R = $CH(CH_3)_2$, $R^1$ = $CH_3$; **d**) R = Ph, $R^1$ = $CH_3$; **e**) R = $CH(Ph)_2$, $R^1$ = Ph; **f**) R = $CH(CH_3)Ph$, $R^1$ = Ph; **g**) R = $CH(CH_3)_2$, $R^1$ = Ph; **h**) R = Ph, $R^1$ = Ph; **i**) R = $CH(Ph)_2$,$R^1$ = p-Ph-$NO_2$; **j**) R = $CH(CH_3)Ph$, $R^1$ = p-Ph-$NO_2$; **l**) R = $CH(CH_3)_2$, $R^1$ = p-Ph-$NO_2$; **m**) R = Ph, $R^1$ = p-Ph-$NO_2$; **n**) R = $CH(Ph)_2$, $R^1$ = $H(H_2O)$; **o**) R = $CH(CH_3)Ph$, $R^1$ = $H(H_2O)$; **p**) R = $CH(CH_3)_2$, $R^1$ = $H(H_2O)$; **q**) R = Ph, $R^1$ = $H(H_2O)$.

spectra at 12.40 ppm. Although the N-H chemical shift of **1-4** shows that it is intramolecularly hydrogen bonded, it is not possible to determine which carbonyl is involved and thus *cis* with respect to the nitrogen. Another aspect of the structure that we consider important to its reactivity involves the conformation of the second carbonyl with respect to the conjugated enaminone system.

The AM1 package seems to be one of the most reliable semiempirical methods known today [31] for calculation of geometric structures, heats of formation, dipole moments, and some other properties of molecules. Our interest in understanding the reactivity of compounds **1-4** has led us to attempt to correlate experimental results with theoretical studies in the case of the reactions of these compounds with hydrazine reagents. Quantum chemical calculations using the AM1 (Austin Model 1) [32] semiempirical method were carried out for compounds **1-4** using the AMPAC package which was locally modified to handle a larger number of atoms. Geometries were fully optimized without imposing any symmetry constraints. Standard bond angles and bond lengths were used as input and intramolecular hydrogen bonding was assumed in both geometric forms. Frontier orbital energies (eV) calculated by AM1 in the *E* configuration are given in Table 1.

The AM1 molecular orbital calculations show that compounds **1-4** have HOMOs with large coefficients on both the α-carbon and nitrogen atoms. The absolute magnitude of the two coefficients is somewhat greater at the α-carbon atom. Compounds **1-3** have LUMOs with large coefficients on both the β-carbon atom and carbonyl carbon of the acetyl group. The absolute magnitude of the two coefficients is somewhat greater at the β-carbon atom, as shown in Table 2. The α-acylenaminoketone **4** has LUMO with large coefficient on the benzoyl group. These calculations do not take solvent effects into account. The AM1 geometry optimization indicated a tendency for one intramolecular hydrogen bond with the carbonyl carbon of the acetyl group, favouring *E* configuration and conjugation of the acetyl group with the double bond.

Crystallographic analysis of **1** was performed to identify the key structural features of these molecules. X-ray crystallographic data for **1** indicated good agreement between X-ray and AM1 calculated geometries [33]. The results obtained show that, whichever the configuration, the diphenylacetyl group tends to be approximately perpendicular to the plane of the enaminone, most likely because of steric factors. The heat of formation for the *Z* configuration is larger [compound **1** (-5.14 Kcal); compound **2** (-40.16 Kcal) and compound **4** (-35.94 Kcal)] than for the *E* configuration [compound **1** (-7.24 Kcal); compound **2** (-43.65 Kcal); compound **3** (-79.97 Kcal) and compound **4** (-37.42 Kcal)].

Considering that pyrazole formation involves reaction on two of the electrophilic sites of compounds **1-4** ($C_\beta$ and one of the two carbonyl groups) and that their yields in reactions with hydrazine reagents can be approximately proportional to the LUMO energy of the α-acylenaminoketone reagent used, we felt that the reaction might be frontier orbital controlled. When the HOMO/LUMO interaction is the major factor governing differential reactivity, the reaction is said to be frontier-orbital controlled. Thus, a molecular orbital method that calculates reliable energy levels of frontier orbitals as well as electron density at each atom is needed in reactivity studies.

Reactions of **1-4** with hydrazines were carried out in benzene, methylene chloride, tetrahydrofuran, methanol and *N*,*N*-dimethylformamide with the aim of determining the relative reactivity of the two carbonyls during a nucleophilic attack in order to obtain information on the solvent dependence of the regiochemistry of the pyrazole formed. The reaction mixtures were submitted to gas chromatography/mass spectrometry analyses, in an attempt to identify all products (Figure 2) and any possible intermediates formed during the reactions.

The principal products obtained, the pyrazoles **5-7a-q**, can be explained by a Michael-type reaction, in which the amino group of the hydrazine reagents attacks the β-carbon atom of compounds **1-4** to form adduct **8a-q**, which reacts with elimination of methylamine to form the β-hydrazino-unsaturated ketones **9a-q**. The

Table 1

Frontier Orbital Energies (eV) of **1-4** in *E* Configuration Calculated by AM1.

| | HOMO | LUMO |
|---|---|---|
| **1** | -8.80 | 0.118 |
| **2** | -8.79 | 0.115 |
| **3** | -8.83 | 0.131 |
| **4** | -8.82 | -0.276 |

β-hydrazino-unsaturated ketones can exist in various tautomeric and geometric forms. The carbonyl group of the acetyl fragment in compounds **1-4** seems to be sterically less hindered and therefore more active; so the subsequent heterocyclization of (*E*)-isomers of intermediates **9a-q** yielded the pyrazoles **5a-q** while the pyrazoles **7a-q** were obtained through the (*Z*)-isomers of intermediates **9a-q** (Figure 3). These intermediates were not detected by GC/MS. This observed variation can be attributed to a different isomeric form or the possibility of an intermolecular hydrogen bond.

The formation of the deacetylated pyrazoles **6a-q** can be explained by the nucleophilic attack of the methylamine eliminated in these reactions on the carbonyl carbon of the acetyl group on compounds **1-3** leading to the formation of two products: deacetylated enaminoketones- 4-methylamino-2-pentenones (**10a-q**) and *N*-methylacetamide. The subsequent nucleophilic attack of hydrazine reagents on the β-carbon atom of deacetylated enaminoketones **10a-q** with intramolecular heterocyclisation followed by elimination of water, yield the deacetylated pyrazoles **6a-q**, as it is shown in Figure 4. To test for the formation of **10f**, compound **3** was reacted with methylamine and produced deacetylated enaminone **10f** in 66% yield.

Table 2

Site Selectivity - Largest Coefficients of Compounds **1-4**.

| | Carbon* | HOMO/LUMO |
|---|---|---|
| **1** | C*=O($CH_3$) | 0.06/0.29 |
| **1** | C*α | 0.65/0.24 |
| **1** | C*β | 0.22/0.49 |
| **1** | C*=O(R) | -0.05/0.10 |
| **2** | C*=O($CH_3$) | 0.07/0.36 |
| **2** | C*α | 0.68/0.29 |
| **2** | C*β | 0.23/0.60 |
| **2** | C*=O(R) | -0.04/0.07 |
| **3** | C*=O($CH_3$) | -0.06/0.39 |
| **3** | C*α | -0.66/0.32 |
| **3** | C*β | -0.23/0.62 |
| **3** | C*=O(R) | -0.04/0.05 |
| **4** | C*=O($CH_3$) | 0.06/0.04 |
| **4** | C*α | 0.69/0.02 |
| **4** | C*β | 0.23/0.04 |
| **4** | C*=O(R) | -0.02/0.37 |

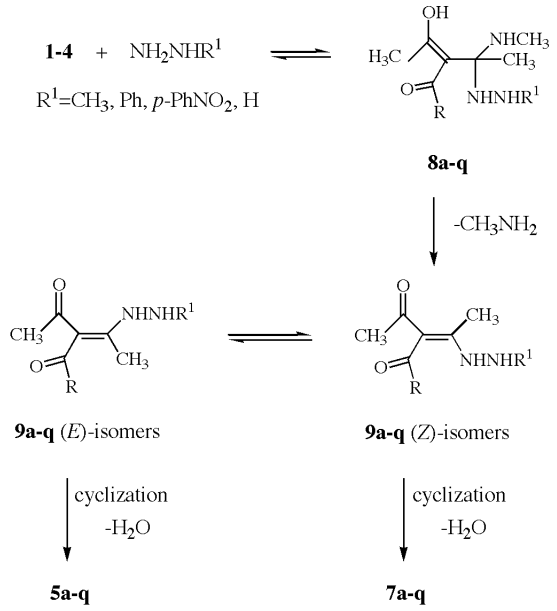


Figure 3

Small amounts of amides **11a-q** and pyrazole **12a-q** were also obtained in these reactions. The formation of small amounts of pyrazoles **13-14a-q** can be explained by a Michael-type reaction in which the substituted nitrogen of the hydrazine reagent attacks the β-carbon atom of compounds **1-3**.

Reactions of α-Acylenaminoketones **1-4** with Methylhydrazine.

Reaction of compounds **1-4** with methylhydrazine afforded mixtures of positional isomers **5a-d** and **7a-d**. The pyrazoles **5b,c** synthesized in high yield according to Table 3 were favoured in benzene, methylene chloride and methanol probably because in these solvents the (*E*)-isomers of β-hydrazino-unsaturated ketones **9b,c** were favoured. This could be the result of more favorable intramolecular interactions that occur during lattice packing. The stability of the *E* configuration in intermediates **9b,c** may be attributed to one intramolecular hydrogen bond between the carbonyl carbon of the acetyl group and the hydrogen of the amino group of the methylhydrazine at the β-position and this configuration should also be preferred for its steric effects. When tetrahydrofuran and *N,N*-dimethylformamide were used as solvents, in these reactions, the (*Z*)-isomers of **9b,c** were favoured leading to the formation of pyrazoles **7b,c**. Only a very small amount of pyrazoles **6a,c** and the deacetylated enaminone **10c**, formed by a deacetylation process, was obtained.

Very interestingly, the pyrazole **5a** was obtained as the principal product in all solvents used. In compound **1**, there is one more acidic hydrogen, hence this compound has most likely a keto-enolic equilibrium, rendering the nonconjugated carbonyl less reactive during a nucleophilic attack.

Table 3

Yields (in percentage) of Compounds **5-15** using Methylhydrazine

| Entry | Substrate | Solvent | Main Products [a] | Side Products [a] |
|---|---|---|---|---|
| 1 | **1** | Benzene | **5a** (78) [a] | **7a** (14) [a], **11a** (5) |
| 2 | **2** | Benzene | **5b** (60) | **7b** (7), **11b** (25) |
| 3 | **3** | Benzene | **5c** (37), **7c** (37) | **10c** (3) |
| 4 | **4** | Benzene | **7d** (54) | **5d** (30), **15d** (5) |
| 5 | **1** | $CH_2Cl_2$ | **5a** (70) | **7a** (8), **11a** (11) |
| 6 | **2** | $CH_2Cl_2$ | **5b** (58) | **6b** (16), **7b** (17), **11b** (4) |
| 7 | **3** | $CH_2Cl_2$ | **5c** (58) | **7c** (25), **13c** (2) |
| 8 | **4** | $CH_2Cl_2$ | **7d** (53) | **5d** (28), **15d** (3) |
| 9 | **1** | THF | **5a** (73) | **7a** (14), **11a** (4) |
| 10 | **2** | THF | **5b** (43), **9b** (43) | **11b** (7) |
| 11 | **3** | THF | **7c** (49), **5c** (39) | **6c** (1) |
| 12 | **4** | THF | **7d** (68) | **5d** (23), **11d** (8) |
| 13 | **1** | MeOH | **5a** (42) | **6a** (9), **11a** (9), **13a** (4) |
| 14 | **2** | MeOH | **5b** (52) | **6b** (23), **13b** (7), **7b** (5), **11b** (7) |
| 15 | **3** | MeOH | **5c** (35) | **10c** (20), **6c** (7), **7c** (9), **14c** (2) |
| 16 | **4** | MeOH | **15d** (34), **7d** (30) | **5d** (24), **11d** (12) |
| 17 | **1** | DMF | **5a** (62) | **7a** (19), **11a** (8) |
| 18 | **2** | DMF | **7b** (55) | **5b** (32), **11b** (6) |
| 19 | **3** | DMF | **7c** (73) | **5c** (24) |
| 20 | **4** | DMF | **7d** (51) | **15d** (36), **5d** (13) |

[a] The amounts of each pyrazole were determined by integration of the areas of the corresponding peaks, which was performed using HP-Chemstation Software and comparison with the areas of isolated pyrazoles with known concentrations.

Only when methanol was used as solvent, was compound **5a** obtained in low yield. This may be attributed to a combination of the effects of solvent polarity and the formation of the intermolecular hydrogen bonds between the carbonyls of compound **1** and methanol. The keto/enol ratio often depends on solvent polarity [30]. The enol is stabilized in solvents that can act as hydrogen bond acceptors, while the keto form is favored in protic solvents acting as hydrogen bond donors, such as methanol [30].

Isomers **5a-c** and **7a-c** were distinguished based on the α-cleavage fragments of these compounds observed in their mass spectra. The presence of fragments ions corresponding to ($M^+$-R) and ($M^+$-$CH_3$) unambiguosly assigns isomers

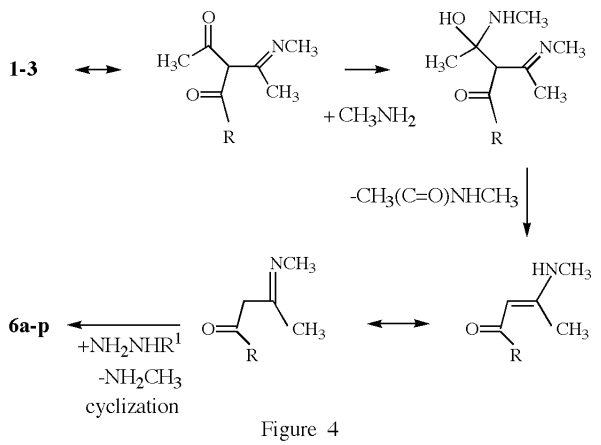


Figure 4

**5a-c** and **7a-c**, respectively, showing that they are isomers resulting from the reaction of hydrazine reagents at different electrophilic positions of the enaminone system. The structures of regioisomeric pyrazoles **6a-c** and **13a-c**, **7a-c** and **14b,c** were differentiated by their mass spectral fragmentation patterns obtained in GC/MS analyses.

The formation of small amounts of pyrazoles **13-14b,c** was observed, but in many cases only pyrazoles **6-7a-d** were obtained, corresponding to that formation derived from the attack of the primary amino group on the β-carbon atom of compounds **1-4**. Therefore, the products formed are consistent with a LUMO-controlled process in which initial attack occurred at the β-carbon atom. The mass spectra of compounds **14b,c** show a fragment at m/z 137 (~90%) that corresponds to the loss of the R group. Probably this loss is favoured when the R group is at the 3-position of the pyrazole moiety, or better, at β-position in relation to substituted nitrogen of the pyrazole moiety. The mass spectrum of compound **6a** shows a fragment in m/z 144 (~10%), which corresponds to the loss of methylcyanide. The fragmentation of the pyrazolic rings involving the loss of methylcyanide, are known [34].

The assignment of the structure of the positional isomers was also carried out on the basis of detailed nmr investigations. The Nuclear Overhauser Enhancement (NOE) difference spectroscopy utilizing a through-space connection between the 5-position of the pyrazole moiety and protons of the *N*-1 substituent is proposed as a simple method for the assignment of pyrazole-*H* resonances and for the differentiation between "asymmetric" isomers in

Table 4

Yields (in percentage) of Compounds **5-15** using Phenylhydrazine

| Entry | Substrate | Solvent | Main Products [a] | Side Products [a] |
|---|---|---|---|---|
| 21 | **1** | Benzene | **6e** (39), **5e** (21) | **12e** (10), **11e** (11) |
| 22 | **2** | Benzene | **6f** (51) | **12f** (8), **13f** (2), **5f** (1) |
| 23 | **3** | Benzene | **5g** (30), **6g** (24) | **10g** (2), **7g** (4), **12g** (4), **13g** (4) |
| 24 | **4** | Benzene | **5h** (43) | **7h** (24), **6h** (6) |
| 25 | **1** | $CH_2Cl_2$ | **6e** (39), **5e** (20) | **12e** (18), **11e** (14) |
| 26 | **2** | $CH_2Cl_2$ | **6f** (61) | **12f** (19), **11f** (6), **10f** (4), **5f** (8) |
| 27 | **3** | $CH_2Cl_2$ | **6g** (38), **5g** (33) | **12g** (5) |
| 28 | **4** | $CH_2Cl_2$ | **6h** (70) | **5h** (7) |
| 29 | **1** | THF | **5e** (56) | **6e** (9), **12e** (14), **11e** (7) |
| 30 | **2** | THF | **5f** (57) | **6f** (25), **12f** (14), **10f** (4) |
| 31 | **3** | THF | **5g** (54) | **6g** (15), **7g** (8) |
| 32 | **4** | THF | **5h** (48), **7h** (32) | **11h** (17) |
| 33 | **1** | MeOH | **5e** (27), **6e** (26) | **12e** (9), **11e** (8) |
| 34 | **2** | MeOH | **6f** (39), **5f** (21) | **12f** (13), **11f** (10) |
| 35 | **3** | MeOH | **6g** (44), **5g** (30) | **12g** (14) |
| 36 | **4** | MeOH | **15h** (28), **5h** (26) | **7h** (19), **11h** (13) |
| 37 | **1** | DMF | **5e** (61) | **12e** (13), **11e** (8), **6e** (6) |
| 38 | **2** | DMF | **5f** (28), **11f** (21) | **12f** (14), **10f** (6), **6f** (4) |
| 39 | **3** | DMF | **5g** (38) | **12g** (10), **13g** (5), **10g** (6), **6g** (6) |
| 40 | **4** | DMF | **15h** (44), **5h** (42) | **11h** (2), **12h** (8) |

[a] The amounts of each pyrazole were determined by integration of the areas of the corresponding peaks, which was performed using HP-Chemstation Software and comparison with the areas of isolated pyrazoles with known concentrations.

various pyrazole derivatives [35]. Irradiation of the *N*-methyl resonance, in compound 7b in deuteriochloroform, led to a significant enhancement of the signal attributable to the benzylic proton resonance at δ 5.6 ppm, the methyl group resonance at δ 1.6 ppm and of the phenyl group resonance at δ 7.2 ppm. All these protons are in the 1-phenyl-ethyl group, whereas the high-field of two methyl signals at δ 2.4 ppm remained unaffected. Thus, the resonance at δ 5.6, 1.6 and 7.2 ppm have to be attributed to the protons of a 1-phenyl-ethyl group attached to the 5-position of the pyrazole ring, due to the spatial closeness of these protons and the methyl protons.

In the reactions of α-acylenaminoketone 4 with methylhydrazine, when benzene, methylene chloride and tetrahydrofuran were used as solvents, the pyrazole **5d** was obtained in high yield (Table 3). Interestingly, the use of *N*,*N*-dimethylformamide as solvent led to the formation of pyrazole **5d**, but a significant amount of an unexpected pyrazole, the benzoyl pyrazole **15d** was also formed. The same reaction utilizing methanol as solvent gave a mixture of four products, with predominance of pyrazole **15d**. The mass spectrum of pyrazole **15d** showed a molecular ion at m/z 276 (60%) which corresponds to the molecular ion of pyrazole **5d** plus 62 a.m.u, and fragments at m/z 275 (100%) and at m/z 199 (60%), which correspond to the loss of 1 a.m.u and the loss of phenyl group, respectively.

*N*-Methylbenzamide **11d** was also isolated as a product in reactions of compound **4** with hydrazine reagents, showing that the elimination of methylamine with subsequent attack on the benzoyl carbonyl carbon of the α-acylenaminoketone 4 occurred. Two reactions were tried in order to find out how pyrazoles **15d,h,q** were formed. Initially we supposed that the 3-benzoyl-4-(methylamino)-3-penten-2-one **4** would react with *N*-methylbenzamide **11d** leading to the formation of 1-phenyl-2-benzoyl-3-methylamino-2-butenone **16**; the pyrazole **15d** could then be formed by simply treating **16** with methylhydrazine. However, the reaction did not take place, only starting material was isolated from the reaction, independent of the conditions employed. Compound **16** could be also formed through the reaction of 1-phenyl-3-methylamino-2-butenone with *N*-methylbenzamide. The other attempt was to react the pyrazole **5d** with *N*-methylbenzamide **11d**, but the formation of pyrazole **15d** was not observed and therefore there was a significant recovery of starting material. All attempts to isolate the products, which might help explain the formation of benzoyl pyrazoles **15**, were unsuccessful.

Reactions of α-Acylenaminoketones **1-4** with Phenylhydrazine.

The use of phenylhydrazine as a nucleophile in the reactions of α-acylenaminoketones **1-3**, and the use of benzene, methylene chloride and methanol as solvents led to the formation of deacetylated pyrazoles **6e-g**, whereas with tetrahydrofuran and *N*,*N*-dimethylformamide as solvents. The attack of the secondary amino group of the hydrazine reagent on the carbonyl carbon of acetyl group takes place, favouring the formation of pyrazoles **5e-g**. Only a very small amount

of pyrazole **7g** was obtained, while no pyrazoles **7e,f** were detected (Table 4). A more subtle effect of size involves steric interaction between the nitrogen substituent of hydrazine reagents and the carbonyl bonded to R group, which can cause the substituted nitrogen of hydrazine to bend toward the acetyl group.

Irradiation of the methyl-*H* resonance at δ 2.4 ppm in compound **6e** in deuteriochloroform solution led to a significant enhancement of the signal attributable to pyrazole-*H* resonance at δ 5.8 ppm, whereas the signal of the protons of the *N*-phenyl group remained unaffected, thus confirming that the methyl group is situated at the 3-position of the pyrazole moiety. The same perturbation of pyrazole-*H* frequency in compound **6e** led to smaller negative NOE's on the multiplet signals of the protons of two phenyl groups at δ 7.1-7.4 ppm bonded to 1,1-diphenylmethyl group at the 5-position of the pyrazole moiety. The smaller magnitude of the NOE is due to a larger distance of the spins involved, but the observed effect is strong enough to allow an unambiguous assignment. The occurrence of negative NOEs is due to the spatial closeness between this group and the proton that is at 4-position of the pyrazole moiety, which is suffering the effect of irradiation of the methyl group, whereas the signal at δ 5.4 ppm (benzylic proton) remained unaffected. Instead, a NOE is observed on the pyrazole H-4 signal, which is consistent with one adjacent methyl group at the 3-position of the pyrazole moiety.

Irradiation of the methyl-H resonance in compound **6f** in deuteriochloroform solution led to a significant enhancement of the signal attributable to pyrazole-H resonance at δ 6.2 ppm, whereas the low-field phenyl protons signal at δ 7.3 ppm remained unaffected. The resonance at δ 6.2 ppm has to be attributed to pyrazole H-4 due to the spatial closeness between H-4 and the methyl protons. In all cases discussed above the perturbed resonances are singlets being well separated from the pyrazole-H signals. In these cases it turned out to be more advantageous to perturb the pyrazole-H resonances and to observe NOE's on the protons of the benzene moiety. The assignment of the structure of the other isomers can be made by analogy with **6e**, **6f** and **7b** and were supported by NOE-experiments. The principal isomers formed correspond to the initial attack of primary amino group of hydrazine on the β-carbon atom, and these data are in agreement with the results of the theoretical data obtained by (AM1) semi-empirical quantum chemical calculations.

The pyrazole **5h** was obtained as principal product in the reaction of compound **4** with phenylhydrazine, utilizing benzene and tetrahydrofuran as solvents. The same reaction using methylene chloride as solvent led to formation of 3-methyl-1,5-diphenyl pyrazole (**6h**). The 3-methyl-1,5-diphenyl pyrazole and 5-methyl-1,3-diphenyl pyrazole are already known. The isomer obtained in this reaction was identified by comparison with reported spectroscopic data [36a-d]. When α-acylenaminoketone **4** was reacted with phenylhydrazine under the same conditions, using methanol and *N,N*-dimethylformamide as solvents the principal product was the pyrazole **15h**. This unexpected product was isolated and spectral data and combustion analysis are in the experimental section. These *n*-donor solvents are particularly important for the solvation of cations and they are also known as coordinating solvents [30]. Probably, the formation of pyrazoles **15d,h,q** involved a cation as a probable intermediate, which was stabilized by solvation in these solvents.

Reactions of α-Acylenaminoketones **1-4** with *p*-Nitrophenylhydrazine.

The reactions using *p*-nitrophenylhydrazine as nucleophile were more sluggish and led to the formation of deacetylated pyrazoles **6i-l**, as can be seen in Table 5. Small amounts of pyrazoles **5l** and **7l** were obtained when we did the reaction of α-acylenaminoketone **3** with this nucleophile using *N,N*-dimethylformamide as solvent.

The deacetylated pyrazole **6i** was obtained as principal product in the reactions of α-acylenaminoketone **1** with *p*-nitrophenylhydrazine using methylene chloride and methanol as solvents. Very interestingly, when these reactions were carried out in benzene and tetrahydrofuran, the formation of pyrazole **6i** did not occur, only pyrazole **12i** and *N*-methyl-1,1-diphenyl acetamide **11i** were formed as products. Under the same conditions, using *N,N*-dimethylformamide as solvent, there was also evidence for spurious side reactions of the solvent with the methylamine eliminated in this reaction, as is shown in Figure 5, and the yield of *N,N*-dimethyl-1,1-diphenyl-ethanone **17** was 32%.

The reactions of α-acylenaminoketone **4** were not successful with the less nucleophilic *p*-nitrophenyl-hydrazine and the pyrazoles were isolated in low yield. Using methylene chloride as solvent, the deacetylated pyrazole **6m** was obtained as major product and in *N,N*-dimethylformamide the principal products formed were the pyrazoles **5m** and **7m**. The use of *N,N*-dimethyl-formamide as solvent favoured the reaction on the nonconjugated carbonyl bonded to the phenyl group. In the other solvents the reaction did not take place and therefore there was a significant recovery of unreacted starting material.

Reactions of α-Acylenaminoketones **1-4** with Hydrazine Hydrate.

The reactions of α-acylenaminoketones **1-4** with hydrazine hydrate, utilizing benzene, methylene chloride, tetrahydrofuran and *N,N*-dimethylformamide as solvents, gave a mixture of positional isomers, with predominance of the pyrazoles **7n-q**. The nucleophilic attack on carbonyl bonded to the R group occurred preferentially due to the high nucleophilic power of the two nitrogens of the hydrazine hydrate. When methanol was

Table 5

Yields (in percentage) of Compounds **5-15** using *p*-Nitrophenylhydrazine.

| Entry | Substrate | Solvent | Main Products | Side Products |
|---|---|---|---|---|
| 41 | **1** | Benzene | **11i** (46) | **12i** (31) |
| 42 | **2** | Benzene | **6j** (42) | **12j** (11), **11j** (12) |
| 43 | **3** | Benzene | **6l** (67) | **13l** (11), **12l** (6) |
| 44 | **1** | $CH_2Cl_2$ | **7i** (49) | **12i** (18), **11i** (23) |
| 45 | **2** | $CH_2Cl_2$ | **6j** (71) | **12j** (13), **11j** (7) |
| 46 | **3** | $CH_2Cl_2$ | **6l** (64) | **13l** (4), **12l** (3) |
| 47 | **4** | $CH_2Cl_2$ | **6m** (43) | - |
| 48 | **1** | THF | **11i** (34) | **12i** (16) |
| 49 | **2** | THF | **6j** (47) | **12j** (4), **11j** (7) |
| 50 | **3** | THF | **6l** (41) | **13l** (2) |
| 51 | **1** | MeOH | **7i** (43) | **12i** (26), **11i** (11) |
| 52 | **2** | MeOH | **6j** (79) | **12j** (8) |
| 53 | **3** | MeOH | **6l** (65) | **12l** (4) |
| 54 | **1** | DMF | **11i** (22), **12i** (22) | - |
| 55 | **2** | DMF | **6j** (53) | **12j** (14), **11j** (18) |
| 56 | **3** | DMF | **5l** (21), **6l** (20), **7l** (20) | **12l** (3) |
| 57 | **4** | DMF | **7m** (44) | **5m** (11), **6m** (3) |

used as solvent, the (*E*) isomers of intermediates **9n-q** were favoured leading to the formation of pyrazoles **5n-q**. Protic solvents shift the alkene (*E*)/(*Z*) ratio in the direction of the (*E*)-form [30]. Only when tetrahydrofuran and *N*,*N*-dimethylformamide were used as solvents, the formation of deacetylated products occurred in small quantities, as can be seen in Table 6.

When methanol was used as solvent under the same conditions, the reaction of α-acylenaminoketone **4** with hydrazine hydrate led to the formation of pyrazole **15q**. This nucleophile favoured the reaction on the nonconjugated carbonyl group, bonded to the R group. The tautomerism of 5(3)-methyl-3-(5)-phenylpyrazole was studied by Parrilla [37] in the liquid state using multinuclear nmr spectroscopy at low temperatures and in the solid state by X-ray crystallography to determine the tautomeric equilibrium constants.

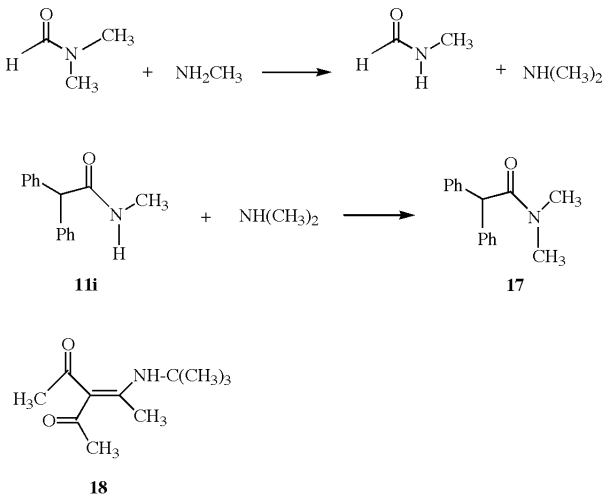


Figure 5

Reactions of α-Acylenaminoketone **18** with Methylhydrazine and Phenylhydrazine

The reactions of α-acylenaminoketone **18** with methylhydrazine and phenylhydrazine were carried out utilizing the same five solvents for a better understanding of the deacetylation process and led to the formation of pyrazoles **19a,b**, deacetylated pyrazoles **20a,b**, *N*-*t*-butylacetamide **21** and 4-(*t*-butylamino)-3-penten-2-one **22** (Figure 6).

When methylhydrazine was used as nucleophile, the principal product was the pyrazole **19a** using benzene, methylene chloride, tetrahydrofuran and *N*,*N*- dimethylformamide as solvents. While, using methanol as solvent, the deacetylated pyrazole **20a** was preferentially formed. It is interesting to observe that the utilization of methanol as solvent favoured the nucleophilic attack of *t*-butylamine formed in these reactions on the carbonyl carbon of the

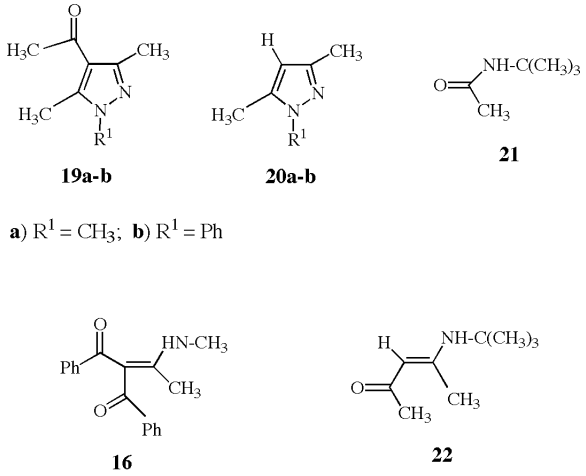


Figure 6

Table 6

Yields (in percentage) of Compounds **5-15** using Hydrazine Hydrate.

| Entry | Substrate | Solvent | Main Products | Side Products |
|---|---|---|---|---|
| 58 | **1** | Benzene | **7n** (35), **5n** (25) | **10n** (11), **6n** (8), **11n** (13) |
| 59 | **2** | Benzene | **7o** (46), **10o** (27) | **6o** (10), **5o** (8), **11o** (4) |
| 60 | **3** | Benzene | **7p** (38), **10p** (30) | **6p** (24), **5p** (7) |
| 61 | **4** | Benzene | **7q** (48) | **5q** (18), **6q** (7) |
| 62 | **1** | $CH_2Cl_2$ | **7n** (45), **5n** (21) | **10n** (9), **6n** (13), **11n** (8) |
| 63 | **2** | $CH_2Cl_2$ | **7o** (33), **10o** (27) | **6o** (3), **5o** (3), **11o** (13) |
| 64 | **3** | $CH_2Cl_2$ | **7p** (64) | **5p** (13), **6p** (13), **10p** (5) |
| 65 | **4** | $CH_2Cl_2$ | **7q** (53) | **5q** (22) |
| 66 | **1** | THF | **7n** (73) | **5n** (14), **11n** (7) |
| 67 | **2** | THF | **7o** (59) | **10o** (13), **5o** (8), **11o** (14) |
| 68 | **3** | THF | **7p** (67) | **5p** (16), **6p** (17) |
| 69 | **4** | THF | **7q** (60) | **5q** (18), **11q** (22) |
| 70 | **1** | MeOH | **5n** (68) | **10n** (6), **6n** (10), **11n** (8) |
| 71 | **2** | MeOH | **5o** (49) | **6o** (37), **7o** (8) |
| 72 | **3** | MeOH | **7p** (36), **6p** (34), **5p** (30) | - |
| 73 | **4** | MeOH | **15q** (45) | **11q** (39), **5q** (13), **7q** (3) |
| 74 | **1** | DMF | **7n** (50) | **5n** (33), **11n** (17) |
| 75 | **2** | DMF | **7o** (75) | **5o** (16), **11o** (9) |
| 76 | **3** | DMF | **7p** (81) | **5q** (19) |
| 77 | **4** | DMF | **7q** (43), **15q** (31) | **11q** (15), **5q** (10) |

acetyl group, leading to the formation of 4-(*t*-butylamino)-3-penten-2-one **22** by loss of the acetyl group and consequent formation of *N*-*t*-butylacetamide **21**, as can be seen in Table 7.

The reactions of compound **18** with phenylhydrazine in all solvents used led to the formation of deacetylated pyrazole **20b**. In these reactions, the formation of **21** was more favoured, principally when tetrahydrofuran was used as solvent, showing that the reduction of nucleophilicity of the substituted nitrogen of hydrazine increased the nucleophilic attack of *t*-butylamine eliminated during the reactions on the carbonyl carbon of the acetyl group. When methylene chloride was used as solvent, the formation of acetylphenylhydrazine was observed with 20% yield in the chromatogram. Thus, the deacetylation of the α-acylenaminoketones can also occur through the nucleophilic attack of the primary amino group of phenylhydrazine on the carbonyl carbon of the acetyl group. The products **19-20a,b** were obtained in low yield, thus, the increase in size of the nitrogen substituent of α-acylenaminoketone may slow down reaction because of steric hindrance.

In summary, the deacetylation of the α-acylenaminoketones **1-3** and **18** was favoured by the decrease in the nucleophilicity of secondary amino group of hydrazine, favouring the formation of products obtained *via* a deacetylation process. The *N*-methylamine eliminated in these reactions was a nucleophile that competed with the hydrazine reagents for the two carbonyls of α-acylenaminoketones susceptible to nucleophilic attack. The carbonyl group of the acetyl fragment seems to be sterically less hindered and therefore more active.

Tetrahydrofuran and *N*,*N*-dimethylformamide favoured the (*E*)-isomers of possible intermediates **9a-q** when phenylhydrazine was used as nucleophile, showing that in

Table 7

Yields (in percentage) of Compounds **19-22** using Methylhydrazine and Phenylhydrazine as Nucleophiles.

| Entry | Substrates | Solvent | Main Products | Side Products |
|---|---|---|---|---|
| 78 | **18** + $CH_3$-NH-$NH_2$ | Benzene | **19a** (42) | - |
| 79 | **18** + $CH_3$-NH-$NH_2$ | $CH_2Cl_2$ | **19a** (33) | - |
| 80 | **18** + $CH_3$-NH-$NH_2$ | THF | **19a** (94) | - |
| 81 | **18** + $CH_3$-NH-$NH_2$ | MeOH | **20a** (25), **19a** (23) | **22** (10), **21** (3) |
| 82 | **18** + $CH_3$-NH-$NH_2$ | DMF | **19a** (39) | - |
| 83 | **18** + Ph-NH-$NH_2$ | Benzene | **20b** (63) | **19b** (12) |
| 84 | **18** + Ph-NH-$NH_2$ | $CH_2Cl_2$ | **20b** (53) | **21** (9) |
| 85 | **18** + Ph-NH-$NH_2$ | THF | **21** (47), **20b** (42) | **19b** (6) |
| 86 | **18** + Ph-NH-$NH_2$ | MeOH | **20b** (39) | **21** (11), **19b** (4), **22** (6) |
| 87 | **18** + Ph-NH-$NH_2$ | DMF | **20b** (25) | **19b** (12) |

phenylhydrazine the (*E*)-isomers were preferentially adopted due to steric hindrance. The same solvents favoured the (*Z*)-isomers of possible intermediates **9a-q** when methylhydrazine was used as nucleophile. In spite of their simplicity, only some of the pyrazoles formed in this study have been previously reported. Homonuclear NOE-difference experiments have proven to be a versatile tool for the unambiguous identification and thus for the differentiation between regioisomers for a variety of 1-substituted pyrazoles.

## EXPERIMENTAL

Melting points, which are uncorrected, were obtained on a Reichert apparatus. Infrared spectra, were recorded on Perkin-Elmer model FTIR spectrometer and values are given in $cm^{-1}$. The $^1H$ nmr and $^{13}C$ nmr spectra were recorded with Bruker model AW-80, Bruker AC-300/P or Varian Gemini-300 spectrometer, chemical shifts are given in ppm (d) with respect to tetramethylsilane and coupling constants (J) are in Hertz. Ultraviolet spectra were obtained for 1% solutions in ethanol using a Varian uv/vis spectrometer.

The analyses done using gas chromatography/mass spectrometry were recorded with Hewlett Packard model 5988A coupled with a HP-5890 gas chromatography equipped with a HP Ultra 1 fused silica column 25m x 0.3mm, temperature program 35-250 °C at 8 °C/min with a 10 minute hold at 250 °C, injector temperature 250 °C, detector temperature 250 °C and the mass spectrometer was set to scan 40-650 atomic mass units per nominal second with an ionizing voltage of 70 eV. Combustion analyses were obtained on Perkin-Elmer model 2400 equipment. Mass spectra were recorded on a Varian MAT-311A with an ionizing voltage of 70 eV. Chromatography was performed using silica gel, Si 60 (70 - 230 mesh, E. Merck, Darmstadt, Germany). The amount of each pyrazole was determined by integration of the areas of the corresponding peaks, which was performed using HP-Chemstation software and comparison with the areas corresponding to known amounts of isolated pyrazoles **5-7a-q**.

General Procedure for Preparations of Enaminoketones **1-3**.

Diazoketones reacted with acyclic enaminoketones to form products of electrophilic attack of the ketocarbene on the α-carbon of enaminoketone, confirming that the Wolff rearrangement occurred. The 4-(methylamino)-3-penten-2-one was prepared by reaction of acetylacetone with methylamine [4]. The 4-(methylamino)-3-penten-2-one was reacted with 1,2-diphenyl-2-diazoethanone to yield **1**, with 2-diazo-1-phenylpropanone to yield **2** and with 3-diazo-2-butanone to yield **3**. A solution of 5.0 mmol of the corresponding diazoketone and 5.0 mmol of 4-(methylamino)-3-penten-2-one in ethanol-free methylene chloride (25 mL) was left at a temperature of 30 °C to yield 1 and at temperature 50 °C to yield **2** and **3**, in the absence of light for 7 days and stopped 2 days after the disappearance of the characteristic absorption of the diazo bond at 2080 $cm^{-1}$ in the ir spectrum.

The absence of the Cα H vinylic proton signal in the $^1H$ nmr spectrum showed that the reaction occurred at the nucleophilic Cα carbon position. After, evaporation of the solvent, the crude material was submitted to column chromatography with neutral aluminum oxide using mixtures of hexane, methylene chloride and methanol as eluents. The α-acylenaminoketones were recrystallized with methylene chloride/hexane.

3-Acetyl-1,1-diphenyl-4-(methylamino)-3-penten-2-one (**1**).

The product was eluted with hexane/$CH_2Cl_2$ (40:60) and recrystallized from methylene chloride/hexane to yield 0.9 g, 68% of **1**; mp 122-124 °C; ir(potassium bromide): ν C=O 1653, 1595 and (C=C) 1580 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.85 [s, 3H, (C=C)$CH_3$], 2.03 [s, 3H ,(C=O)$CH_3$], 2.92 (d, 3H, J=4.0 Hz, N-$CH_3$), 5.40 (s, 1H, CH), 7.23 (m, 10H, 2xPh), 12.40 (1H, l, NH); ms m/z (relative intensity): 307(1) ($M^+$), 167 (7) [$CH(Ph)_2^+$], 165 (7) ($C_{13}H_9^+$), 140 (100) [$M^+$ - $CH(Ph)_2$], 98 (55) [$M^+$ - $CH(Ph)_2$ – $CH_2CO$].

3-Acetyl-1-phenyl-1-methyl-4-(methylamino)-3-penten-2-one (**2**).

The product was eluted with hexane/methylene chloride (50:50) and recrystallized from methylene chloride/hexane to yield 0.81 g, 66% of **2**; mp 70-4 °C; ir (potassium bromide): ν C=O 1649, 1581 and (C=C) 1568 $cm^{-1}$; $^1H$ nmr (carbon tetrachloride): δ 1.55 (d, 3H, J = 8.0 Hz, $CH_3$), 1.70 [s, 3H, (C=C)$CH_3$], 2.02 [s, 3H, (C=O)$CH_3$], 2.91 (d, 3H, J = 4.0 Hz, N-$CH_3$), 4.12 (q, 1H, J = 8.0 Hz, CH), 7.32 (m, 5H, Ph), 12.20 (1H, l, NH); ms m/z (relative intensity): 245 (5) ($M^+$), 230 (2) ($M^+$ - $CH_3$), 140 (100) [$M^+$ - $CH(Ph)(CH_3)$], 98 (50) [$M^+$ - $CH(Ph)(CH_3)$ – $CH_2CO$].

3-Acetyl-1,1-dimethyl-4-(methylamino)-3-penten-2-one (**3**).

The product was eluted with hexane/methylene chloride (70:30) and recrystallized from methylene chloride/hexane to yield 1.0 g, 61% of **3**; mp 67-9 °C; ir (potassium bromide): ν C=O 1652, 1575 and (C=C) 1560 $cm^{-1}$; $^1H$ rmn (carbon tetrachloride): δ 1.03 (d, 6H, J = 7.7 Hz, 2x$CH_3$), 1.90 [s, 3H, (C=C)$CH_3$], 2.13 [s, 3H, (C=O)$CH_3$], 2.71 (m, 1H, J = 7.7 Hz, CH), 3.00 (d, 3H, J = 4.0 Hz, N-$CH_3$), 12-20 (1H, l, NH); ms m/z (relative intensity): 183 (13) ($M^+$), 140 (96) [$M^+$ - $CH(CH_3)_2$], 98 (100) [$M^+$ - $CH(CH_3)_2$ – $CH_2CO$].

Preparation of the α-Acylenaminoketones **4** and **18**.

The α–acylenaminoketone **4** was prepared by reaction of 4-(*t*-butylamino)-3-penten-2-one (1.55g, 0.01 mol) with benzoyl chloride (1.15 mL) using tetrahydrofuran (20 mL) as solvent. In this reaction was added triethylamine (1.4 mL) and pyridine (0.79 mL). The mixture was refluxed during two days and 20 mL of distilled water were added. The organic layer was washed with saturated solution of sodium bicarbonate, dried over magnesium sulfate, filtered and the solvent was evaporated in a rotary evaporator under vacuum. The product was separated by column chromatography on neutral aluminum oxide using mixtures of hexane, methylene chloride and methanol as eluents. Solid product was recrystallized from methylene chloride/hexane. Transamination reaction occurred through the reaction of 3-benzoyl-4-(*t*-butylamino)-3-penten-2-one (0.3 g, 1.15 mmol) initially obtained with an excess of methylamine (3 mL) in methylene chloride (3 mL). The mixture was agitated during two days and 10 mL of distilled water were added. The organic layer was washed with water, dried over magnesium sulfate, filtered and the solvent was evaporated in a rotary evaporator under vacuum. The residual semisolid was purified on neutral aluminum oxide column (2.5 x 45 cm) using mixtures of hexane, methylene chloride and methanol as eluents. Solid product was recrystallized from methylene chloride/hexane.

3-Benzoyl-4-(*t*-butylamino)-3-penten-2-one.

The product was eluted with hexane/methylene chloride (40:60) and recrystallized from methylene chloride/hexane to yield 1.64 g, 63% of 3-benzoyl-4-(*t*-butylamino)-3-penten-2-one; ir (potassium bromide): ν C=O 1641, 1597 and (C=C) 1589 $cm^{-1}$; $^1H$ nmr (carbon tetrachloride): 1.42 (s, 9H, 3x$CH_3$), 1.73 [s, 3H, (C=C)$CH_3$], 2.03 [s, 3H, (C=O)$CH_3$], 7.32 - 7.95 (m, 5H, Ph), 12.50 (1H, l, NH); ms m/z (relative intensity): 259 (35) ($M^+$), 202 (100)[$M^+$ - $C(CH_3)_3$], 105 (65) ($COPh^+$).

*Anal*. Calcd. for $C_{16}H_{21}O_2N$: C, 74.23; N, 5.40; H, 8.10. Found: C, 74.22; N, 5.42; H, 8.06.

3-Benzoyl-4-(methylamino)-3-penten-2-one (**4**).

The product was eluted with hexane/methylene chloride (20:80) and recrystallized from methylene chloride/hexane to yield 0.19 g, 79% of **4**; mp 86-89 °C; ir (potassium bromide): ν C=O 1638, 1590 and (C=C) 1570 $cm^{-1}$; $^1H$ nmr (carbon tetrachloride): δ 1.83 [s, 3H, (C=C)$CH_3$], 1.95 [s, 3H, (C=O)$CH_3$], 3.01 (d, 3H, J = 4.8 Hz, $NCH_3$), 7.20 - 7.80 (m, 5H, Ph), 12.40 (1H, l, NH); ms m/z (relative intensity): 217 (55) ($M^+$), 216 (50) ($M^+$ - 1), 188 (50)($M^+$ - H - CO), 105 (100) ($PhCO^+$).

*Anal*. Calcd. for $C_{13}H_{15}O_2N$: C, 71.88; N, 6.45; H, 6.91. Found: C, 71.90; N, 6.41; H, 6.96.

3-Acetyl-4-(*t*-butylamino)-3-penten-2-one (**18**).

The α–acylenaminoketone **18** was prepared by reaction of 4-(*t*-butylamino)-3-penten-2-one (0.5 g, 3.22-mmol) with acetic anhydride (3.59 g, 3.5-mmol) in methylene chloride (20 mL). The mixture was refluxed during two days and saturated solution of sodium bicarbonate was slowly added. The organic layer was washed with water, dried over magnesium sulfate, filtered and the solvent was evaporated in a rotary evaporator under vacuum. The residual semisolid was purified on neutral aluminum oxide column (2.5 x 45 cm) using mixtures of hexane, methylene chloride and methanol as eluents. Solid product was recrystallized from methylene chloride/hexane. The product was eluted with hexane/methylene chloride (20:80) and recrystallized from methylene chloride/hexane to yield 0.48 g, 63% of **18**; m.p. 96-99 °C; ir (potassium bromide): ν C=O 1663, 1599 and (C=C) 1581 $cm^{-1}$; $^1H$ nmr (carbon tetrachloride): δ 1.41 [s, 9H, $C(CH_3)_3$], 2.23 (s, 9H, 3x$CH_3$), 12.60 (1H, l, NH); ms m/z (relative intensity): 197 (15) ($M^+$), 140 (25) [$M^+$ - $C(CH_3)_3$], 126 (100) ($C_7O_2H_{10}^+$).

*Anal*. Calcd. For $C_{11}H_{19}O_2N$: C, 67.0; H, 9.64; N, 7.10. Found: C, 66.98; H, 9.62; N, 7.10.

General Procedure for Reactions of Compounds **1-4** with Hydrazine Reagents using Five Different Solvents.

The reactions of α-acylenaminoketones **1-4** with methylhydrazine, phenylhydrazine, *p*-nitrophenylhydrazine and hydrazine hydrate needed a stoichiometric ratio of 1:4 between α-acylenaminoketones and the hydrazine reagents.

The α-acylenaminoketones (100 mg) of **1** (0.32-mmol), **2** (0.4-mmol), **3** (0.54-mmol) and **4** (0.46-mmol) were dissolved in 2 mL of the chosen solvent (benzene, methylene chloride, tetrahydrofuran, metanol and *N*,*N*-dimethylformamide) and to this solution was added 2.00 mmol of the hydrazine reagent. The mixture was allowed to react at room temperature, for two days using methylhydrazine and phenylhydrazine as nucleophiles, ten days using *p*-nitrophenylhydrazine and one day using hydrazine hydrate, after which 10 mL of distilled water were added. The products were extracted with three portions of 10 mL of methylene chloride and the organic layer was washed with water, dried over magnesium sulfate, filtered and the solvent was evaporated in a rotary evaporator under vacuum. The crude material was submitted to column chromatography on neutral aluminum oxide using mixtures of hexane, methylene chloride and methanol as eluents. All the isolated products were further purified by preparative thin-layer chromatography (TLC). It was carried out on silica using methanol/chloroform solution (1:100) as eluent.

4-(1,1-Diphenylacetyl)-1,3,5-trimethylpyrazole (**5a**).

Utilizing tetrahydrofuran as solvent in the reaction of 1 with methylhydrazine, the pyrazole **5a** was preferentially obtained. The product eluted with hexane/methylene chloride (40:60) and was recrystallized from methylene chloride/hexane to give 68.32 mg (69%) of **5a**; mp 139-41 °C; ir (potassium bromide): ν C=O 1640 $cm^{-1}$; $^1H$ nmr (carbon tetrachloride): δ 2.30 (s, 3H, $CH_3$), 2.45 (s, 3H, $CH_3$), 3.61 (s, 3H, $NCH_3$), 5.62 (s, 1H, CH), 7.25 (s, 10H, 2xPh); ms m/z (relative intensity): 304 (1) ($M^+$), 137 (100) [$M^+$ - $CH(Ph)_2$], 167(12) [$^+CH(Ph)_2$].

*Anal*. Calcd. for $C_{20}H_{20}N_2O$: C, 78.94; N, 9.21; H, 6.57. Found: C, 78.90; N, 9.19; H, 6.56.

4-(1-Phenyl-1-methyl-acetyl)-1,3,5-trimethylpyrazole (**5b**).

Utilizing methylene chloride as solvent in the reaction of **2** with methylhydrazine, the pyrazole **5b** was preferentially obtained. The product eluted with hexane/methylene chloride (30:70) and formed a colorless oil to give 54.32 mg (55%) of **5b**; ir (neat): ν C=O 1654 $cm^{-1}$; $^1H$ nmr (carbon tetrachloride): δ 1.45 (d, 3H, J = 8.0 Hz, $CH_3$), 2.30 (s, 3H, $CH_3$), 2.45 (s, 3H, $CH_3$), 3.64 (s, 3H, $NCH_3$), 4.21 (q, 1H, J = 8.0 Hz, CH), 7.20 (s, 5H, Ph); ms m/z (relative intensity) 242 (1) ($M^+$), 137 (100) [$M^+$ - $CH(Ph)(CH_3)$], 105 (2) [$CH(Ph)(CH_3)^+$].

*Anal*. Calcd. for $C_{15}H_{18}N_2O$: C, 74.38; H, 7.44; N, 11.57. Found: C, 74.40; H, 7.48; N, 11.55.

4-Acetyl-5-(1-phenylethyl)-1,3-dimethylpyrazole (**7b**).

Utilizing *N*,*N*-dimethylformamide as solvent in the reaction of **2** with methylhydrazine, the pyrazole **7b** was preferentially obtained. The product eluted with hexane/methylene chloride (50:50) and formed a colorless oil to give 49.38 mg (50%) of **7b**; ir (neat): ν C=O 1655 $cm^{-1}$; $^1H$ nmr (carbon tetrachloride): δ 1.63 (d, 3H, J = 8.0 Hz, $CH_3$), 2.52 (s, 6H, 2x$CH_3$), 3.30 (s, 3H, $NCH_3$), 5.55 (q, 1H, J = 8.0 Hz, CH), 7.21-7.45 (m, 5H, Ph): ms m/z (relative intensity): 242 (31) ($M^+$), 227 (16) ($M^+$ - $CH_3$), 212 (45)($M^+$ - 2x$CH_3$), 151 (100)($M^+$ - $CH_2Ph$); $^{13}C$ nmr (carbon tetrachloride): δ 15.8 ($CH_3$), 16.0 ($CH_3$), 31.0 (C-H), 33.0 [(C=O)$CH_3$], 37.89 (N-$CH_3$), 119.0 (pyrazole C4), [126.0, 127.0, 128.0, 141.8] (benzenic ring), [147.0, 150.0] (pyrazolic ring), 192.8 (C=O).

*Anal*. Calcd. for $C_{15}H_{18}N_2O$: C, 74.38; N, 11.57; H, 7.44. Found: C, 74.35; N, 11.58; H, 7.46.

4-(1,1-Dimethylacetyl)-1,3,5-trimethylpyrazole (**5c**).

Utilizing methylene chloride as solvent in the reaction of **3** with methylhydrazine, the pyrazole **5c** was preferentially obtained. The product eluted with hexane/methylene chloride (40:60) and formed a colorless oil to give 52.13 mg (53%) of

**5c**; ir ν (neat): C=O 1655 $cm^{-1}$; $^1H$ nmr (carbon tetrachloride): δ 1.12 (d, 6H, J = 8.0 Hz, 2x$CH_3$), 2.33 (s, 3H, $CH_3$), 2.48 (s, 3H, $CH_3$), 3.01 (m, 1H, J = 8.0 Hz, CH), 3.63 (s, 3H,$NCH_3$); ms m/z (relative intensity): 180 (5) ($M^+$), 137 (100) [$M^+$ - $CH(CH_3)_2$].

*Anal*. Calcd. for $C_{10}H_{16}N_2O$: C, 66.66; H, 8.88; N, 15.55. Found: C, 66.64; H, 8.86; N, 15.52.

4-Acetyl-5-(1-methylethyl)-1,3-dimethylpyrazole (**7c**).

Utilizing *N*,*N*-dimethylformamide as solvent in the reaction of **3** with methylhydrazine, the pyrazole **7c** was preferentially obtained. The product eluted with hexane/methylene chloride (60:40) and formed a colorless oil to give 68.85 mg (70%) of **7c**; ir n(neat): C=O 1654 $cm^{-1}$; $^1H$ nmr (carbon tetrachloride) δ 1.35 (d, 6H, J = 8.0 Hz, 2x$CH_3$), 2.30 (s, 6H, $CH_3$), 3.61 (m, 1H, J = 8.0 Hz, CH), 3.75 (s, 3H, $NCH_3$); ms m/z (relative intensity): 180 (27) ($M^+$), 165 (100) ($M^+$ - $CH_3$); $^{13}C$ nmr (deuteriochloroform): δ 16.0 ($CH_3$), 20.0 (2x$CH_3$), 26.0 [(CO)$CH_3$], 31.8 (CH), 38.0 ($NCH_3$), 119.0 (pyrazole C4), 148.0 (pyrazole C5), 152.0 (pyrazole C3), 195.5 (C=O).

*Anal*. Calcd. for $C_{10}H_{16}N_2O$: C, 66.66; H, 8.88; N, 15.55. Found: C, 66.64; H, 8.84; N, 15.52.

4-Acetyl-5-phenyl-1,3-dimethylpyrazole (**7d**).

Utilizing tetrahydrofuran as solvent in the reaction of **4** with methylhydrazine, the pyrazole **7d** was preferentially obtained. The product eluted with hexane/methylene chloride (20:80) and formed a yellow oil to give 61.14 mg (62%) to **7d**. ir (neat): ν C=O 1638 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.93 (s, 3H, $CH_3$), 2.55 [s, 3H, (C=O)$CH_3$], 3.60 (s, 3H, $NCH_3$), 7.31 - 7.62 (m, 5H, Ph); ms m/z (relative intensity): 214 (20) ($M^+$), 199 (100) ($M^+$ - $CH_3$).

*Anal*. Calcd. for $C_{13}H_{14}N_2O$: C, 72.89; N, 13.08; H, 6.54. Found: C, 72.91; N, 13.08; H, 6.53.

4-Benzoyl-1,3,5-trimethylpyrazole (**5d**).

Utilizing tetrahydrofuran as solvent in the reaction of **4** with methylhydrazine, the pyrazole **5d** was isolated in 20% yield. The product was eluted with methylene chloride and formed a yellow oil to give 19.72 mg (20%) of **5d**; ir (neat): ν C=O 1658 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 2.03 (s, 3H, $CH_3$), 2.31 (s, 3H, $CH_3$), 3.82 (s, 3H, $NCH_3$), 7.24 - 7.80 (m, 5H, Ph); ms m/z (relative intensity): 214 (60) ($M^+$), 213 (100) ($M^+$ - H), 137 (85) ($M^+$ - Ph).

*Anal*. Calcd. for $C_{13}H_{14}N_2O$: C, 72.89; N, 13.08; H, 6.54. Found: C, 72.90; N, 13.1; H, 6.53.

4-(1,1-Diphenyl-acetyl)-3,5-dimethyl-1-phenylpyrazole (**5e**).

Utilizing *N*,*N*-dimethylformamide as solvent in the reaction of **1** with phenylhydrazine, the pyrazole **5e** was preferentially obtained. The product eluted with hexane/methylene chloride (50:50) and was recrystallized from methylene chloride/hexane to give 69.93 mg (57%) of **5e**; mp 107-10 °C; ir (potassium bromide): ν C=O 1655 $cm^{-1}$; $^1H$ nmr (carbon tetrachloride) δ 2.40 (s, 3H, $CH_3$), 2.55 (s, 3H, $CH_3$), 5.63 (s, 1H, CH), 7.25 (s, 10H, 2xPh), 7.40 (s, 5H, Ph); ms m/z (relative intensity): 366 (1) ($M^+$), 199 (100) [$M^+$ - $CH(Ph)_2$], 167 (19) [$CH(Ph)_2$]; uv - λmáx.(ethanol) nm, 260, 254, 248 and 222.

*Anal*. Calcd. for $C_{25}H_{22}N_2O$: C, 81.96; N, 7.65; H, 6.01. Found: C, 82.01; N, 7.68; H, 6.03.

5-(1,1-Diphenylmethyl)-3-methyl-1-phenylpyrazole (**6e**).

Utilizing methylene chloride as solvent in the reaction of **1** with phenylhydrazine, the pyrazole **6e** was preferentially obtained. The product eluted with hexane/methylene chloride (60:40) and was recrystallized from methylene chloride/hexane to give 38.08 mg (36%) of **6e**; mp 130-32 °C; $^1H$ nmr (carbon tetrachloride): δ 2.35 (s, 3H, $CH_3$), 5.45 (s, 1H, CH), 5.80 (s, 1H, CH), 7.15 - 7.47 (m, 15H, 3xPh); ms m/z (relative intensity): 324 (100) ($M^+$), 323 (18) ($M^+$ - H), 309 (9) (M+ - $CH_3$), 165 (18) ($C_{13}H_9^+$).

*Anal*. Calcd. for $C_{23}H_{20}N_2$: C, 85.18; N, 8.64; H, 6.17. Found: C, 85.20; N, 8.65; H, 6.15.

4-(1-Phenyl-1-methylacetyl)-3,5-dimethyl-1-phenylpyrazole (**5f**).

Utilizing tetrahydrofuran as solvent in the reaction of **2** with phenylhydrazine, the pyrazole **5f** was preferentially obtained. The product eluted with hexane/methylene chloride (40:60) and formed a colorless oil to give 65.76 mg (53%) of **5f**; ir (neat): ν C=O 1656 $cm^{-1}$; $^1H$ nmr (carbon tetrachloride): δ 1.45 (d, 3H, $CH_3$), 2.40 (s, 3H, $CH_3$), 2.45 (s, 3H, $CH_3$), 4.34 (q, 1H, CH), 7.20 (s, 5H, Ph), 7.42 (s, 5H,Ph); ms m/z (relative intensity): 304 (1) ($M^+$), 199 (100) [$M^+$ - CH(Ph)($CH_3$)]. uv - λmáx (ethanol) nm 260, 254, 248 and 226.

*Anal*. Calcd. for $C_{20}H_{20}N_2O$: C, 78.94; N, 9.21; H, 6.58. Found: C, 78.90; N, 9.20; H, 6.55.

5-(1-Phenylethyl)-3-methyl-1-phenylpyrazole (**6f**).

Utilizing methylene chloride as solvent in the reaction of **2** with phenylhydrazine, the pyrazole **6f** was preferentially obtained. The product eluted with hexane/methylene chloride (60:40) and formed a colorless oil to give 64.14 mg (52%) of **6f**; $^1H$ nmr (carbon tetrachloride): δ 1.57 (d, 3H, J = 8.0 Hz, $CH_3$), 2.33 (s, 3H, $CH_3$), 4.12 (q, 1H, J = 8.0 Hz, CH), 6.28 (s, 1H, CH), 7.05 - 7.55 (m, 10H, Ph); ms m/z (relative intensity): 262 (100) ($M^+$), 261 (34) ($M^+$ - H), 247 (63) ($M^+$ - $CH_3$), 169 (42) ($C_{11}N_2H_9^+$). uv λmáx. (ethanol) nm 244 and 209.

*Anal*. Calcd. for $C_{18}H_{18}N_2$: C, 82.44; N, 10.68; H, 6.87. Found: C, 82.42; N, 10.66; H, 6.82.

4-(1,1-Dimethylacetyl)-3,5-dimethyl-1-phenylpyrazole (**5g**).

Utilizing tetrahydrofuran as solvent in the reaction of **3** with phenylhydrazine, the pyrazole **5g** was preferentially obtained. The product eluted with hexane/methylene chloride (40:60) and formed a colorless oil to give 66.12 mg (50%) of **5g**; iv (neat): ν C=O 1657 $cm^{-1}$; $^1H$ mnr (carbon tetrachloride): δ 1.18 (d, 6H, J = 8.0 Hz, 2x$CH_3$), 2.51 (s, 6H, 2x$CH_3$), 3.20 (m, 1H, J = 8.0 Hz, CH), 7.45 (s, 5H, Ph); ms m/z (relative intensity): 242 (5) ($M^+$), 199 (100) [$M^+$ - $CH(CH_3)_2$].

*Anal*. Calcd. for $C_{15}H_{18}N_2O$: C, 74.38; N, 11.57; H, 7.44. Found: C, 74.35; N, 11.55; H, 7.48.

5-(1-Methylethyl)-3-methyl-1-phenylpyrazole (**6g**).

Utilizing methanol as solvent in the reaction of **3** with phenylhydrazine, the pyrazole **6g** was preferentially obtained. The product eluted with hexane/methylene chloride (50:50) and formed a colorless oil to give 43.79 mg (40%) of **6g**; $^1H$ nmr (carbon tetrachloride): δ 1.13 (d, 6H, J = 8.0 Hz, 2x$CH_3$), 2.20 (s, 3H, $CH_3$), 3.03 (m, 1H, J = 8.0 Hz, CH), 5.95 (s, 1H, CH), 7.43 (s, 5H, Ph); ms m/z (relative intensity): 200 (63) ($M^+$), 199 (18) ($M^+$ - H), 185 (100) ($M^+$ - $CH_3$).

*Anal*. Calcd. for $C_{13}H_{16}N_2$: C, 78.00; H, 8.00; N, 14.00. Found: C, 78.03; H, 7.98; N, 13.98.

4-Benzoyl-3,5-dimethyl-1-phenylpyrazole (**5h**).

Utilizing tetrahydrofuran as solvent in the reaction of **4** with phenylhydrazine, the pyrazole **5h** was preferentially obtained. The product eluted with hexane/methylene chloride (50:50) and formed a yellow oil to give 66.12 mg (50%) of **5h**; ir (neat): ν C=O 1661 $cm^{-1}$; $^1$H nmr (carbon tetrachloride): δ 1.82 (s, 3H, $CH_3$), 2.53 (s, 3H, $CH_3$), 7.01 - 7.94 (m, 10H, 2xPh); ms m/z (relative intensity): 276 (70) ($M^+$), 275 (100) ($M^+$ - H), 199 (48) ($M^+$ - Ph).

*Anal*. Calcd. for $C_{18}H_{16}N_2O$: C, 78.26; N, 10.14; H, 5.79. Found: C, 78.24; N, 10.12; H, 5.76.

4-Acetyl-3-methyl-1,5-diphenylpyrazole (**7h**).

Utilizing tetrahydrofuran as solvent in the reaction of **4** with phenylhydrazine, the pyrazole **7h** was isolated with 30% yield. The product eluted with hexane/methylene chloride (60:40) and formed a yellow oil to give 38.20 mg (30%) of **7h**; ir (neat): ν C=O 1640 $cm^{-1}$; $^1$H nmr (carbon tetrachloride): δ 2.23 (s, 3H, $CH_3$), 2.40 (s, 3H, $CH_3$), 7.04 - 7.95 (m, 10H, 2xPh); ms m/z (relative intensity): 276 (44) ($M^+$), 261 (100) ($M^+$ - $CH_3$).

*Anal*. Calcd. for $C_{18}H_{16}N_2O$: C, 78.26; N, 10.14; H, 5.79. Found: C, 78.22; N, 10.12; H, 5.80.

3-Methyl-1,5-diphenylpyrazole (**6h**).

Utilizing methylene chloride as solvent in the reaction of **4** with phenylhydrazine, the pyrazole **6h** was preferentially obtained. The product eluted with hexane/methylene chloride (50:50) and formed a yellow oil to give 73.35 mg (68%) of **6h**; $^1$H nmr (carbon tetrachloride): δ 2.45 (s, 3H, $CH_3$), 6.20 (s, 1H, CH), 7.23 (s, 10H, 2xPh); ms m/z (relative intensity): 234 (100) ($M^+$), 233 (90) ($M^+$ - H).

*Anal*. Calcd. for $C_{16}H_{14}N_2$: C, 82.05; H, 5.98; N, 11.96. Found: C, 82.03; H, 5.97; N, 12.01.

4-Benzoyl-3-methyl-1,5-diphenylpyrazole (**15h**).

Utilizing *N,N*-dimethylformamide as solvent in the reaction of **4** with phenylhydrazine, the pyrazole **15h** was isolated with 39% yield. The product eluted with hexane/methylene chloride (40:60) and formed a yellow oil to give 60.79 mg (39%) of **15h**; ir (neat): ν C=O 1661 $cm^{-1}$; $^1$H nmr (carbon tetrachloride): δ 2.22 (s, 3H, $CH_3$), 7.03 - 7.89 (m, 15H, 3xPh); ms m/z (relative intensity): 338 (80) ($M^+$), 337 (100) ($M^+$ - H), 261 (40) ($M^+$ - Ph).

*Anal*. Calcd. for $C_{23}H_{18}N_2O$: C, 81.65; H, 5.32; N, 4.14. Found: C, 81.62; H, 5.32; N, 4.12.

5-Diphenylmethyl-3-methyl-1-*p*-nitrophenylpyrazole (**6i**).

Utilizing methylene chloride as solvent in the reaction of **1** with *p*-nitrophenylhydrazine, the pyrazole **6i** was preferentially obtained. The product eluted with hexane/methylene chloride (10:90) and formed a orange oil to give 56.48 mg (47%) of **6i**; ir (neat): ν $NO_2$ 1338 $cm^{-1}$; $^1$H nmr (deuteriochloroform): δ 2.31 (s, 3H, $CH_3$), 5.43 (s, 1H, CH), 5.84 (s, 1H, CH), 7.03 - 8.41 (m, 14H, 3xPh); ms m/z (relative intensity): 369 (100) ($M^+$), 292 (18) ($M^+$ - Ph), 165 (25) ($C_{13}H_9^+$).

*Anal*. Calcd. for $C_{23}H_{19}N_3O_2$: C, 74.79; H, 5.14; N, 11.38. Found: C, 74.73; H, 5.12; N, 11.35.

5-(1-Phenylethyl)-3-methyl-1-*p*-nitrophenylpyrazole (**6j**).

Utilizing methanol as solvent in the reaction of **2** with *p*-nitrophenylhydrazine, the pyrazole **6j** was preferentially obtained. The product eluted with hexane/methylene chloride (30:70) and formed a yellow oil to give 92.88 mg (74%) of **6j**; ir (neat): ν $NO_2$ 1339 $cm^{-1}$; $^1$H nmr (deuteriochloroform): δ 1.63 (d, 3H, J = 8.0 Hz, $CH_3$), 2.33 (s, 3H, $CH_3$), 4.21 (q, 1H, J = 8.0 Hz, CH), 6.24 (s, 1H, CH), 7.03 - 8.40 (m, 9H, 2xPh); ms m/z (relative intensity): 307 (100) ($M^+$), 292 (68) ($M^+$ - $CH_3$), 246 (68) ($M^+$ - $CH_3$–$NO_2$).

*Anal*. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.35; N, 13.68; H, 5.53. Found: C, 70.32; N, 13.65; H, 5.51.

3-Methyl-5-(1-methylethyl)-1-*p*-nitrophenylpyrazole (**6l**).

Utilizing methylene chloride as solvent in the reaction of **3** with *p*-nitrophenylhydrazine, the pyrazole **6l** was preferentially obtained. The product eluted with hexane/methylene chloride (30:70) and formed yellow crystals to give 80.90 mg (60%) of **6l**; mp 86-88 °C; ir (potassium bromide): ν $NO_2$ 1343 $cm^{-1}$; $^1$H nmr (carbon tetrachloride): δ 1.23 (d, 6H, J = 8.0 Hz, 2x$CH_3$), 2.24 (s, 3H, $CH_3$), 3.21 (m, 1H, J = 8.0 Hz, CH), 6.03 (s, 1H, CH), 7.40-8.45 (AA'BB',4H, J = 7.8 Hz, Ph); ms m/z (relative intensity): 245 (100) ($M^+$), 230 (36) ($M^+$ - $CH_3$), 184 (58) ($M^+$ - $CH_3$–$NO_2$), 143 (32) (m/z 184 -$CH_3CN$); uv λmáx. (ethanol) nm 310 and 237.

*Anal*. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.67; N, 17.14; H, 6.12. Found: C, 63.64; N, 17.08; H, 6.11.

4-(2,2-Dimethylacetyl)-3,5-dimethyl-1-*p*-nitrophenylpyrazole (**5l**).

Utilizing *N,N*-dimethylformamide as solvent in the reaction of **3** with *p*-nitrophenylhydrazine, the pyrazole **5l** was isolated with 19% yield. The product eluted with hexane/methylene chloride (20:80) and formed orange crystals to give 29.79 mg (19%) of **5l**; mp 160-163 °C; ir (potassium bromide): ν C=O 1648, $NO_2$ 1341 $cm^{-1}$; $^1$H nmr (deuteriochloroform): δ 1.21 (d, 6H, J = 8.0 Hz, 2x$CH_3$), 2.50 (s, 3H, $CH_3$), 2.65 (s, 3H, $CH_3$), 3.22 (m, 1H, J = 8.0 Hz, CH), 7.60 - 8.40 (AA'BB', 4H, J = 7.8 Hz, Ph); ms m/z (relative intensity): 287 (3) ($M^+$), 244 (100) [$M^+$ - $CH(CH_3)_2$], 198 (39) [$M^+$ - $CH(CH_3)_2$ – $NO_2$].

*Anal*. Calcd. for $C_{15}H_{17}N_3O_3$: C, 62.71; N, 14.63; H, 5.92. Found: C, 62.69; N, 14.60; H, 5.90.

4-Acetyl-5-(diphenylmethyl)-3-methylpyrazole (**7n**).

Utilizing tetrahydrofuran as solvent in the reaction of **1** with hydrazine hydrate, the pyrazole **7n** was preferentially obtained. The product eluted with methanol/methylene chloride (1:10) and formed colorless crystals to give 64.81 mg (69%) of **7n**; mp 240-5 °C; ir(potassium bromide): ν NH 3221, C=O 1655 $cm^{-1}$; $^1$H nmr (deuteriochloroform): δ 2.34 (s, 3H, $CH_3$), 2.50 (s, 3H, $CH_3$), 6.23 (s, 1H, CH), 7.03 - 7.45 (m, 10H, 2xPh); ms m/z (relative intensity): 290 (68) ($M^+$), 275 (45) ($M^+$ - $CH_3$), 199 (98) ($M^+$ - $CH_2Ph$), 165 (100) ($C_{13}H_9^+$).

*Anal*. Calcd. for $C_{19}H_{18}N_2O$: C, 78.62; N, 9.65; H, 6.20. Found: C, 78.69; N, 9.67; H, 6.18.

3,5-Dimethyl-4-(2,2-diphenylacetyl)-pyrazole (**5n**).

Utilizing methanol as solvent in the reaction of **1** with hydrazine hydrate, the pyrazole **5n** was preferentially obtained. The product eluted with methanol/methylene chloride (3:10) and formed colorless crystals to give 58.56 mg (62%) of **5n**; mp 164-166 °C: iv (potassium bromide): ν NH 3193, C=O 1654

cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 2.41 (s, 6H, 2x$CH_3$), 5.64 (s, 1H, CH), 7.25 (s, 10H, 2xPh); ms m/z (relative intensity): 290 (1) ($M^+$), 123 (100) [$M^+$ - $CH(Ph)_2$].

*Anal*. Calcd. for $C_{19}H_{18}N_2O$: C, 78.62; N, 9.65; H, 6.20. Found: C, 78.60; N, 9.67; H, 6.22.

4-Acetyl-5-(1-phenylethyl)-3-methylpyrazole (**7o**).

Utilizing *N*,*N*-dimethylformamide as solvent in the reaction of **2** with hydrazine hydrate, the pyrazole **7o** was preferentially obtained. The product eluted with methanol/methylene chloride (1:10) and formed colorless crystals to give 60.9 mg (64%) of **7o**; mp 171-175 °C; ir (potassium bromide): ν NH 3170, C=O 1628 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 1.64 (d, 3H, J = 8.0 Hz, $CH_3$), 2.35 (s, 3H, $CH_3$), 2.55 (s, 3H, $CH_3$), 4.81 (q, 1H, J = 8.0 Hz, CH), 7.23 (s, 5H, Ph). ms m/z (relative intensity): 228 (64) ($M^+$), 213 (82) ($M^+$ - $CH_3$), 169 (50) ($C_{11}N_2H_9^+$), 137 (100) ($M^+$ - $CH_2Ph$); uv λmáx. (ethanol) nm 248 and 243.

*Anal*. Calcd. for $C_{14}H_{16}N_2O$: C, 73.68; N, 12.28; H, 7.01. Found: C, 73.65; N, 12.31; H, 6.69.

3,5-Dimethyl-4-(2-phenyl-2-methylacetyl)-pyrazole (**5o**).

Utilizing methanol as solvent in the reaction of **2** with hydrazine hydrate, the pyrazole **5o** was preferentially obtained. The product eluted with methanol/methylene chloride (3:10) and formed colorless oil to give 42.80 mg (46%) of **5o**; ir (neat): ν NH 3190, C=O 1654 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 1.53 (d, 3H, J = 8.0 Hz, $CH_3$), 2.54 (s, 6H, 2x$CH_3$), 4.31 (q, 1H, J = 8.0 Hz, CH), 7.20 - 7.45 (m, 5H, Ph); ms m/z (relative intensity): 228 (3) ($M^+$), 123 (100) [$M^+$ - $CH(CH_3)Ph$].

*Anal*. Calcd. for $C_{14}H_{16}N_2O$: C, 73.68; N, 12.28; H, 7.01. Found: C, 73.64; N, 12.26; H, 7.00.

4-Acetyl-5-(1-methylethyl)-3-methylpyrazole (**7p**).

Utilizing *N*,*N*-dimethylformamide as solvent in the reaction of **3** with hydrazine hydrate, the pyrazole **7p** was preferentially obtained. The product eluted with methanol/methylene chloride (1:10) and formed a colorless crystals to give 70.72 mg (78%) of **7p**; mp 63-65 °C; ir (potassium bromide): ν NH 3187, C=O 1660 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 1.36 (d, 6H, J = 8.0 Hz, 2x$CH_3$), 2.40 (s, 3H, $CH_3$), 2.55 (s, 3H, $CH_3$), 3.62 (m, 1H, J = 8.0 Hz, CH); ms m/z (relative intensity): 166 (32) ($M^+$), 151 (100) ($M^+$ - $CH_3$), 123 (36) [$M^+$ - $CH(CH_3)_2$]; uv λmáx. (ethanol) nm 248.

*Anal*. Calcd. for $C_9H_{14}N_2O$: C, 65.06; N, 16.87; H, 8.43. Found: C, 65.02; N, 16.84; H, 8.46.

3,5-Dimethyl-4-(2,2-dimethylacetyl)-pyrazole (**5p**).

Utilizing methanol as solvent in the reaction of **3** with hydrazine hydrate, the pyrazole **5p** was isolated with 27% yield. The product eluted with methanol/methylene chloride (2:10) and formed a colorless oil to give 24.47 mg (27%) of **5p**; ir (neat): ν NH 3200, C=O 1654 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 1.23 (d, 6H, J = 8.0 Hz, 2x$CH_3$), 2.55 (s, 6H, 2x$CH_3$), 3.21 (m, 1H, J = 8.0 Hz, CH); ms m/z (relative intensity): 166 (1) ($M^+$), 123 (100) [$M^+$ - $CH(CH_3)_2$]; uv λmáx (ethanol) nm 246.

*Anal*. Calcd. for $C_9H_{14}N_2O$: C, 65.06; N, 16.87; H, 8.43. Found: C, 65.03; N, 16.86; H, 8.40.

4-Acetyl-3-methyl-5-phenylpyrazole (**7q**).

Utilizing tetrahydrofuran as solvent in the reaction of **4** with hydrazine hydrate, the pyrazole **7q** was preferentially obtained. The product eluted with methanol/methylene chloride (1:100) and formed a colorless oil to give 53.45 mg (58%) of **7q**; ir (neat): ν NH 3167, C=O 1668 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 2.03 (s, 3H, $CH_3$), 2.25 (s, 3H, $CH_3$), 7.44 (s, 5H, Ph); ms m/z (relative intensity) 200 (35) ($M^+$), 185 (100) ($M^+$ - $CH_3$).

*Anal*. Calcd. for $C_{12}H_{12}N_2O$: C, 72.0; H, 6.0; N, 14.0. Found: C, 72.08; H, 5.95; N, 13.92.

4-Benzoyl-3,5-dimethylpyrazole (**5q**).

Utilizing tetrahydrofuran as solvent in the reaction of **4** with hydrazine hydrate, the pyrazole **5q** was isolated with 17% yield. The product eluted with methanol/methylene chloride (2:100) and formed a colorless oil to give 15.66 mg (17%) of **5q**; ir (neat): ν NH 3359, C=O 1637 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 2.25 (s, 6H, 2x$CH_3$), 7.40 - 7.80 (m, 5H, Ph); ms m/z (relative intensity): 200 (60) ($M^+$), 199 (100) ($M^+$ - H), 123 (90) ($M^+$ - Ph).

*Anal*. Calcd. for $C_{12}H_{12}N_2O$: C, 72.0; H, 6.0; N, 14.0. Found: C, 71.98; H, 6.09; N, 13.99.

*N*-Methyl-1,1-diphenylacetamide (**11i**).

The compound was obtained in the reaction of **1** with *p*-nitrophenylhydrazine. The product eluted with hexane/methylene chloride (20:80) and formed colorless crystals, mp 167-168 °C; ir (potassium bromide): ν NH 3280, C=O 1640 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 2.75 (d, 3H, J = 4.0 Hz, $NCH_3$), 4.90 (s, 1H, CH), 6.10 (1H, l, NH), 7.30 (s, 10H, Ph); ms m/z (relative intensity): 225 (5) ($M^+$), 168 (100) ($M^+$ - $CONCH_3$).

*N*-Methyl-1-phenyl-1-methylacetamide (**11b**).

The compound was obtained in the reaction of **2** with methylhydrazine. The product eluted with hexane/methylene chloride (60:40) and formed a yellow oil; ir (neat): ν NH 3369, C=O 1656 cm$^{-1}$; $^1$H nmr (carbon tetrachloride): δ 1.56 (d, 3H, J = 8.0 Hz, $CH_3$); 2.81 (d, 3H, J = 4.8 Hz, $NCH_3$); 3.62 (q, 1H, J = 8.0 Hz, CH); 7.23-7.60 (m, 5H, Ph); ms m/z (relative intensity): 163 (14) ($M^+$), 106 (100) ($M^+$ - $CONCH_3$), 105 (77) [$CH(CH_3)Ph^+$], 91 (90) ($CH_2Ph^+$).

1,1-Dimethyl-4-(methylamino)-3-penten-2-one (**10p**).

The compound was obtained in the reaction of **3** with hydrazine hydrate. The product eluted with hexane/methylene chloride (20:80) and formed a yellow oil; $^1$H nmr (carbon tetrachloride): δ 1.15 (d, 6H, J = 7.8 Hz, 2x$CH_3$), 1.90 (s, 3H, $CH_3$), 2.95 (d, 3H, J = 4.0 Hz, $NCH_3$); 3.60 (m, 1H, J = 7.8 Hz, CH); 6.05 (s,1H, CH); ms m/z (relative intensity): 141 (14) ($M^+$), 98 (100) [$M^+$ - $CH(CH_3)_2$].

Mass Spectral Data of Compound Obtained in Low Yield.

1-Methyl-1-phenyl-4-(methylamino)-3-penten-2-one(**10o**).

Ms m/z (relative intensity): 203 (7) ($M^+$), 98 (100) ($M^+$ - COPh).

*N*,*N*-Dimethyl-1,1-diphenylethanone (**16**).

Ms m/z (relative intensity): 239 (32) ($M^+$), 167 (72) [$^+CH(Ph)_2$], 165 (32), 72 (100) [$(CH_3)_2N$-C=O$^+$].

5-(1,1-Diphenyl-methyl)-1,3-dimethylpyrazole (**6a**).

Ms m/z (relative intensity): 262 (100) ($M^+$), 247 (45) ($M^+$ - $CH_3$), 185 (87)($M^+$ - Ph), 165 (32) ($C_{13}H_9^+$).

3-(1,1-Diphenyl-methyl)-1,5-dimethylpyrazole (**13a**).

Ms m/z (relative intensity): 262 (73) ($M^+$), 261 (100) ($M^+$ - H), 247 (36) ($M^+$ - $CH_3$), 165 (73) ($C_{13}H_9^+$).

4-Acetyl-5-(1,1-diphenyl-methyl)-1,3-dimethylpyrazole (**7a**).

Ms m/z (relative intensity): 304 (50) ($M^+$), 289 (18) ($M^+$ - $CH_3$), 213 (100) ($M^+$ - $CH_2Ph$), 165 (27) ($C_{13}H_9^+$).

5-(1-Phenyl-ethyl)-1,3-dimethylpyrazole (**6b**).

Ms m/z (relative intensity): 200 (36) ($M^+$), 185 (100) ($M^+$ - $CH_3$).

3-(1-Phenyl-ethyl)-1,5-dimethylpyrazole (**13b**).

Ms m/z (relative intensity): 200 (64) ($M^+$), 185 (100) ($M^+$ - $CH_3$), 144 (27) (m/z= 185 - $CH_3CN$), 77 (32) ($Ph^+$).

4-Acetyl-3-(1-phenylethyl)-1,5-dimethylpyrazole (**14b**).

Ms m/z (relative intensity): 242 (100) ($M^+$), 227 (55) ($M^+$ - $CH_3$), 212 (45) ($M^+$ - 2x$CH_3$), 151 (64) ($M^+$ - $CH_2Ph$), 137 (82) ($M^+$ - COPh).

5-(1-Methyl-ethyl)-1,3-dimethylpyrazole (**6c**).

Ms m/z (relative intensity): 138 (32) ($M^+$), 123 (100) ($M^+$ - $CH_3$).

4-Acetyl-3-(1-methylethyl)-1,5-dimethylpyrazole (**14c**).

Ms m/z (relative intensity): 180 (49) ($M^+$), 165 (100) ($M^+$ - $CH_3$), 137 (93) [$M^+$ - $CH(CH_3)_2$].

3-(1-Phenyl-ethyl)-5-methyl-1-phenylpyrazole (**13f**).

Ms m/z (relative intensity): 262 (100) ($M^+$), 247 (98) ($M^+$ - $CH_3$), 232 (45) ($M^+$ - 2x$CH_3$), 118 (45) ($CH_3CNPh^+$), 77 (72) ($Ph^+$).

3-(1-Methyl-ethyl)-5-methyl-1-phenylpyrazole (**13g**).

Ms m/z (relative intensity): 200 (41) ($M^+$), 185 (100) ($M^+$ - $CH_3$), 77 (32) ($Ph^+$).

4-Acetyl-5-(1-methyl-ethyl)-3-methyl-1-phenylpyrazole (**7g**).

Ms m/z (relative intensity): 242 (36) ($M^+$), 227 (100) ($M^+$ - $CH_3$), 77 (27) ($Ph^+$).

3-(1-Methylethyl)-5-methyl-1-*p*-nitrophenylpyrazole (**13l**).

Utilizing benzene as solvent in the reaction of **3** with *p*-nitrophenylhydrazine, the pyrazole **13l** was formed with 11% of yield. Ms m/z (relative intensity): 245 (41) ($M^+$), 230 (100) ($M^+$ - $CH_3$), 184 (55) ($M^+$ - $CH_3$ - $NO_2$).

4-Acetyl-5-(1-methylethyl)-3-methyl-1-p-nitrophenylpyrazole (**7l**).

Utilizing *N*,*N*-dimethylformamide as solvent in the reaction of **3** with *p*-nitrophenylhydrazine, the pyrazole **7l** was formed with 20% of yield. Ms m/z (relative intensity): 287 (24) ($M^+$), 286 (18) ($M^+$ - H), 272 (100) ($M^+$ - $CH_3$), 226 (36) ($M^+$ - $CH_3$ - $NO_2$).

5-(1,1-Diphenylmethyl)-3-methylpyrazole (**6n**).

Ms m/z (relative intensity): 248 (82) ($M^+$), 247 (28) ($M^+$ - H), 165 (100) ($C_{13}H_9^+$).

5-(1-Phenyl-ethyl)-3-methylpyrazole (**6o**).

Ms m/z (relative intensity): 186 (68) ($M^+$), 171 (100) ($M^+$ - $CH_3$), 77 (45) ($Ph^+$).

5-(1-Methylethyl)-3-methylpyrazole (**6p**).

Ms m/z (relative intensity): 124 (30) ($M^+$), 109 (100) ($M^+$ - $CH_3$).

4-Benzoyl-3,5-dimethyl-1-*p*-nitrophenylpyrazole (**5m**).

Ms m/z (relative intensity): 321 (60) ($M^+$), 320 (100) ($M^+$ - H).

3-Methyl-5-phenyl-1-*p*-nitrophenylpyrazole (**6m**).

Ms m/z (relative intensity): 279 (100) ($M^+$), 278 (50) ($M^+$ - H), 232 (30) ($M^+$ - H – $NO_2$).

4-Acetyl-3-methyl-5-phenyl-1-*p*-nitro-phenylpyrazole (**7m**).

Ms m/z (relative intensity): 321 (40) ($M^+$), 320 (20) ($M^+$ - H), 306 (100) ($M^+$ - $CH_3$), 260 (50) ($M^+$ - $CH_3$ – $NO_2$).

4-Benzoyl-1,3-dimethyl-5-phenylpyrazole (**15d**).

Ms m/z (relative intensity): 276 (60) ($M^+$), 275 (100) ($M^+$ - H), 199 (60) ($M^+$ - Ph), 77 (20) ($Ph^+$).

4-Benzoyl-3-methyl-5-phenylpyrazole (**15q**).

Ms m/z (relative intensity): 262 (64) ($M^+$), 261 (100) ($M^+$ - H), 185 (50) ($M^+$ - Ph), 77 (30) ($Ph^+$).

*N*-Methylbenzamide (**11q**).

The compound **11q** was obtained in the reaction of **4** with hydrazine and formed colorless crystals, mp 65-70 °C; ir (potassium bromide): ν NH 3324, C=O 1633 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 3.0 (d, 3H, J = 4.8 Hz, $CH_3$), 6.5 (1H, l, NH), 7.2 -7.8 (m, 5H, Ph); MS m/z (relative intensity): 135 (27) ($M^+$), 134 (41) ($M^+$ - H), 105 (86) ($COPh^+$), 77 (100) ($Ph^+$).

Reaction of α–Acylenaminoketone **18** with Methylhydrazine and Phenylhydrazine.

The reactions of α–acylenaminoketone **18** (25 mg, 0.12-mmol) with methylhydrazine and phenylhydrazine (0.5 mmol) were carried out in the same five solvents and the reaction mixtures were submitted to gas chromatography/mass spectrometry analyses.

4-Acetyl-1,3,5-trimethylpyrazole (**19a**).

This product was principally obtained using methylhydrazine as nucleophile. Ms m/z (relative intensity): 152 (27) ($M^+$), 137 (100) ($M^+$ - $CH_3$).

1,3,5-Trimethylpyrazole (**20a**).

This product was principally obtained using methylhydrazine and methanol as solvent. Ms m/z (relative intensity): 110 (100) ($M^+$), 109 (98) ($M^+$ - H), 95 (32) ($M^+$ - $CH_3$).

*N*-*t*-Butylacetamide (**21**).

MS m/z (relative intensity): 115 (15) ($M^+$), 100 (15) ($M^+$ - $CH_3$), 58 (100) ($NH_2COCH_2^+$).

4-(*t*-Butylamino)-3-penten-2-one (**22**).

Ms m/z (relative intensity): 155 (23) ($M^+$), 140 (14) ($M^+$ - $CH_3$), 84 (100) ($C_5OH_8^+$).

4-Acetyl-3,5-dimethyl-1-phenylpyrazole (**19b**).

Ms m/z (relative intensity): 214 (37) ($M^+$), 199 (100) ($M^+$ - $CH_3$).

3,5-Dimethyl-1-phenylpyrazole (**20b**).

The compound **20b** was principally obtained using phenylhydrazine as nucleophile. Ms m/z (relative intensity): 172 (100) ($M^+$), 171 (73) ($M^+$ - H).

Acetylphenylhydrazine.

The mass spectrum of acetylphenylhydrazine displayed molecular ion at m/z=150 (32%) ($C_8ON_2H_{10}^+$) and fragments at m/z=108 (100%) [$M^+$ - ($CH_2$=C=O)] and at m/z=77 (32%) ($Ph^+$).

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