Syntheses of Dipyrazole ketones. The Regioselectivity of The Cycloadducts Products and Simple Method for Syntheses of Pyrazolopyrazoline Derivatives

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The cycloaddition of *C*-ethoxycarbonyl-*N*–arylnitrilimine **6** with α,ß–unsaturated ketone5 gave predominantly the dipyrazolyl ketones **8** Cyclocondensation of **8** with hydrazine hydrate afforded the pyridazinone derivates **9** and **10**. Treatment of **5** with hydrazine derivatives gave the pyrazolopyrazolines **11**. Reactions **11** (R=H) with isothiocyanate derivaties leads to *N*-substituted thioureas **12** and **13**. The structures of the cycloadducts **8**, pyridazinone derivatives **9** and **10**, pyrazolopyrazoline derivatives **11** and *N*-substituted thioureas **12** and **13** were supported by MS, NMR and IR Spectroscopic Methods.

Introduction

It has been reported that the reaction of *C*-ethoxycarbonyl (*C*-phenyl)-*N*-arylnitrilimide with conjugate base of active methylene compounds (ß-ketoester) afford the corresponding 4-ethoxycarbonyl-5-aryl-pyrazoles [1-5], while their reaction with a- ß-unsaturated ketones give 5-acyl-r-aryl-2-pyrazoline derivatives [2,3,6-20]. In the present study some new dipyrazoles and dipyrazolyl-ketones have been synthesized by the 1,3-dipolar addition of nitrilimides to ethyl benzoylacetate as well as other unsaturated ketones with the two fold objective of preparing compounds with possible biological activity and studying the regiochemistry of the reaaction.

Experimental

All melting points are uncorrected. Infrared spectra (KBr) were measured on a Perkin-Elmer 298 spectrophotometer or on a Nicolet Magna 520 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained in deuterated choloform on a Bruker 250 MHz and DRX-400 FT-NMR spectrometer (operating system–X win-nmr 1.2) using tetramethylsilane as internal reference. Micro-analyses were performed by microanalysis unite, King Abdulaziz University, Jeddah, S.A. Mass spectroscopy spectra were determined on a Kratos MS30. *C*–Acetyl-*N*-phenylformohydrazidoyl chloride **1** and their C-phenyl-carbonyl- and C-ethoxy- analogous **7A** and **7B,** respectively were prepared by a known procedures [26-27]. Ethyl benzoylacetate was obtained from Merk. Reaction mixtures were analysed on Fluka gel cards with fluorescent indicator 254 on aluminum cards and the spots were detected under 254 nm uv light.

3- Acetyl-4-ethoxycarbonyul-1,5-diphenylpyrazole 2

To an ethanolic sodium ethoxide solution, prepared from sodium metal (1.1 g, 0.05 g atom) and absolute ethanol (40 ml), was added the appropriate ethyl benzoylacetate (50 mmole). After stirring the mixture for 15 minutes at 4oom temperature, the appropriate hydrazidoyl chloride 1 (50mmole) was added and stirring continued for 4h. The reaction mixture was left overnight at room temperature. The solid that precipitated was collected, washed with water and crystallized form ethanol to give the pyrazole **2** mp 88 ^{o}C; in 65% yield; IR (KBr) ν: 1736(COOEt), 1709 cm^{-1} (COMe); ^{1}H NMR ($CDC1_3$) δ 1.07 (t, 3H, J=7Hz, $OCH_2\underline{CH_3}$), 2.54 (s, 3H, CH_3 CO), 4.25 (q, 2H, J=7Hz, $OCH_2\underline{CH_3}$) and 7.,13-7.59 ppm (m, 10H, Ar-H). $C_{20}\underline{H}_{18}N_2O_3$ Calcd. : C, 71.84; H, 5.43; N, 8.37; Found : C, 72.06; H, 5.32; N, 8.43. MS : m/z (%) 334 (M^+ , 34), 319 (M-CH_3, 18), 289 (M-OEt, 71), 262 (M-COOEt, 7) 247 (25), 219 (16), 190 (8), 165 (10), 104 (8), 89 (12).

3-Methyl-5,6-diphenyl-5H-pyrazolo [3,4-d] pyridazin-7-one 4

To a solution of **3 (**5mmole**)** in ethanol (20 ml) was added hydrazine hydrate (10 mmole) and the mixture was refluxed for 5 h. The crude solid that prcipitated was collected and crystallisation from dimethylformamide gave **4** in 92% yield (Table 1).

1-Aryl-3-(4-ethoxycarbonyl-1,5-diphenylpyrazole-5-yl)-1-propen-3-one 5a-c

To a solution of **2** (5mmole) and the appropriate aldehyde (5 mmole) in ethanol (30 ml) was added sodium hydroxide solution (0.1 M, 5 ml) and the reaction mixture was stirred for 5 hours. The crude solid that prcipitated was collected, washed with water several times and crystallised from ethanol. The physical constant are listed in Table 1. **5a** : MS (EI): m/z (%) 422 (M^+ , 34), 393 ($M-C_2H_5$, 50), 349 (M-COOEt, 25), 319 (M-PhCH=CH, 15), 291 (8), 246 (7), 219 (18), 218 (6), 192 (6), 188 (21), 180 (46), 165 (5), 131 (25), 103 (58), 89 (12). **5b :** ^{13}C NMR ($CDC1_2$) δ184.8 (-COCH=CH), 164.1 (COOEt), 61.7 (OCH_2CH_3), 14.3 (OCH_2CH_3); Accurate mass Found 428.,1195 Mol. Formula $C_{25}H_{20}N_2O_3S$ Calc. 428.1194. **5c** ^{13} CNMR ($CDC1_2$) δ185.1 (C-COCH=CH), 164.2 (COOEt), 102.0 (-O-CH_2-O-), 61.7 (OCH_2CH_3), 14.3 (OCH_2CH_3).

Reaction of hydrazidoyl chloride 7 with α, ß-unsaturated ketone 5a and 5c.

General Method: Triethyl amine (0.7 ml, 5 mmole) was added to a toluene (20 ml) solution of the appropriate hydrazidoyl choloride **7** (5 mmole) and the dipolarophile **5** (5 mmole) at room temperature. The reaction mixture was heated under reflux until the complete disapperance of **5** as indicated by thin layer chromatographic analysis. The reaction mixture was cooled, washed with water three times, and the toluene layer was separated, dried over anhydrous sodium sulfate, then filtered. The solvent was evaporated under reduced pressure and the resudeue left was triturated with little ethanol. The solid which separated was collected and its ^{1}H NMR spectrum in deuterated chloroform was recorded, which showed one regiosomer.

Crystallisation of the crude solid from ethanol gave the pyrazolyl-pyrazolinyl ketone **8** in 67 – 83%. The physical constant are listed in Table 1. **8 Ac:** ^{13}C NMR ($CDC1_3$) δ190.0 ($\underline{C}$O), 163.4 (COOEt), 101.6 (-OCH_2-O-), 75.2 (=CH), 61.9 (OCH_2CH_3), 56.7 (=CH-), 14.1 (OCH_2CH_3); MS (FAB): m/z (%), 660 (M^++H^+, 25), 341(100), 319 (13), 275 (16), 180 (37), 154 (18); Accurate mass Found 660.2372, Mol. Formula $C_{41}H_{32}N_4O_5$ Calc. 660.2372. **8Ba :** ^{13}C NMR ($CDC1_3$) δ188.2 ($\underline{C}$O), 188.2 & 185.2 ($\underline{2}$COOEt), 75.3 (=CH-), 61.6 & 61.4 (2O$\underline{CH_2}$$CH_3$), 56.8 (=CH-), 14.5 & 14.1 ($2OC_2H_3$). The minor regiosomers **8'** were did not purify but only shown in the regiosomers crude in the ^{1}HNMR spectra.

Pyrazolinylpyridazin-7-one derivatives 9 and 10.

The appropriate pyrazolyketone **8 (**5 mmole) in ethanol was refluxed with hydrazine hydrate (10 mmole) for 10 hours. The reaction mixture was then concentrated and the solid which separated was recrystallised from ethanol. The physical constant are listed in Table 1.

Reaction of 5a and 5b with hydrazine derivatives.

To solution of **5a** and **5b** (5 mmole) in ethanol (20 ml) was added proper hydrazine (6 mmole) and the mixture was refluxed for 5 hours. The crude solid that precipitated was collected and crystallised from ethanol to give the corresponding pyrazolopyrazoline derivatives **11**. The physical constant are listed in Table 2. **11a** : ^{13}C NMR ($CDC1_3$) δ164.3 (COOEt), 64.4 ($CH\text{-}CH_2$-), 44.1 (CH-$\underline{CH_2}$-), 60.7 (OCH_2CH_3), 13.9 (OCH_2CH_3); MS(EI) : m/z (%), 436 (M^+, 15), 435 (M-H, 17), 389 (M-EtOH, -H, 46), 333 (8), 313 (M-EtOH, -C_6H_5, 100), 246 (10), 226 (6), 218 (5), 195 (13), 180 (17), 165 (11), 152 (6), 129 (12), 115 (10), 103 (14), 91 (8), 77 (54), 65 (6).

1-Substituted thiocarbamioyl derivatives 12 and 13.

A mixture of the appropriate pyrazolopyrazoline derivative **11** (R = H) (50 mmole), anhydrous K_2CO_3 (100 mole) in dry acetone (100 ml) was stirred and treated dropwise with a solution of the appropriate of isothiocyanate (70 mmole) in dry acetone (10 ml). After refluxing the mixture for 6 hours, the acetone was removed under reduced pressure and the solid residue was dissolved in H_2O. The crude product separated upon acidification with HC1 solution (2 mole) was purified by recrystallisation from ethanol. The physical constant are listed in Table 2. 12: ^{13}C NMR ($CDC1_3$) δ174.7 (C=S), 163.8 ($\underline{C}$OOEt), 63.5 (CH-) 61.4 (OCH_2CH_3), 44.2 (CH_2), 14.2 (OCH_2CH_3); MS(FAB) : m/z (%) 572 ($M_+ + H_+$, 42), 538 (8), 435 (14), 389 (19), 338 (62), 313 (12), 272 (10), 219 (9), 180 (23), 154 (100), 136 (82); Acc. Mass Found 572.2121 Mol. Formula [$C_{34}H_{30}N_5O_2S$] + H^+ Calc. 572.2120 and **13**: ^{13}C NMR ($CDC1_3$) δ174.3 (C=S), 163.6 ($\underline{C}$OOEt), 63.8 (CH-), 61.3 (O$\underline{CH_2}CH_{3)}$, 49.2 (-N$\underline{CH_2}$Ph), 44.0 (CH_2), 14.2 (O$\underline{CH_2}CH_3$); MS : m/z (%) 585 (M^+ , 42), 584 (M-H $_2$ 83), 490 (29), 330 (30), 253 (32), 180 (63), 91 (62) 77, (100), 64 (29), 52 (25).

Results and Discussion

The cycloaddition of hydrazidoyl chloride **1** and to a solution of the sodium salt of ethyl benzoylacetate was carried out at room temperature for 24 hours. The sole product isolated was regioisomer, cycloadduct, 3-acetyl-1,4-diphenyl-4-ethoxycarbonylpyrazole **2** (Scheme 1). The mechanism was discussed in detailed in ref.3 and 4. The other regio-isomer **3** was not identified in the reaction mixture as evidenced by 2D-TLC analysis. The structure of the cycloadduct 2 was supported by MS and other spectral data. The IR spectrum exhibited two carbonyl absorption at 1736 and 1709 cm^{-1} for the acetyl and ester groups respectively.

Its ^{1}H NMR showed triplet and quartet at 1.07 and 4.25 ppm for the ester group, a singlet of three proton intensity at 2.54 ppm for the acetyl group. Its MS spectrum showed a weak molecular ion peak at m/z 334 while the base peak is the M-OEt at m/z 289. The structure of **2** was substantiated further by the fact that on treatment with hydrazine hydrate in refluxing ethanol afforded the pyrazolo [3,4-d] pyridazine derivative **4**. Several pyrazolopyridazine derivatives were synthesised from refluxing the dicarbonylpyrazole deravatives in hydrazine hydrate [2,3,13].

Morover, aldol condensation of ketone **2** with aromatic aldehydes yielded the corresponding α,ß-unsaturated ketones **5a-c** (Scheme 1). The IR spectra of chalcones **5** displayed two absorption bands at 1719 and 1676 cm^{-1} indicative of the ester and unsaturated carbonyls respectively. The structures of **5** were further supported by their ^{1}H NMR spectra (*vide infra*) (Table 1). The mass spectrum of **5a** showed a molecular ion peak at m/z 422, while the base peak appeared at m/2 103 (PhCN). Other common prominent peaks in the spectrum were observed at m/z 393, 349, 319, 291, 246, 219, 218, 192, 188, 180, 131.

Reaction of nitrilimides **6A** and **6B,** generated in situ by treatment of corresponding hydrazonoyl chlorides **7A** and **7B,** with triethylamine, with the a,-unsaturated carbonyl compound **5a** and **5c** were carried out in refluxing toluene. The results show that the reactions studied are regioselective yielding the two possible regioisomers, namely pyrazolopyrazolinyl-ketone **8** and ketone **8'** in ratio 9.5 : 0.5 regardless of the nature of C-substituent in the nitrilimide assigned the trans configuration indicated [17-20]. The regioisomers **8** were purified by crystallization from ethanol, but the minor regiosomers **8'** were detected from the crude ^{1}H NMR spectrum of the cycloadditon reactions and did not isolate from the mother liquor during the purification of the major regioisomers **8**.

It was well know from the 1,3-dipoler cycloaddition reaction to α,ß-unsaturated ketone and ester that the 5-carbonylpyrazole derivatives are generally formed as the major cycloadducts and 4- carbonylpyrazoles as the minor cycloadducts, in ratio 7 : 3 to 6 : 4. However, we found that the sterically bulky group on the pyrazole moiety is effecting the ratio of the regioisomers produced in our case.

The differentiation of the regioisomers 5-carbonylpyrazole **8** and 4-carbonylpyrazoline **8** rests on characteristic signals in the NMR spectra. In the ^{13}C NMR spectra of the 5-carbonylpyrazoline derivatives **8** typical signals for C4 and C5 of the pyrazoline ring appear at δ75 (C5) and 56.7(C4).The chemical shift of the4-H and 5-H is in range4.7-4. (75.2) and 57-6.0 (56.7), respectively. Therefore, the $\Delta\delta_H > 1$ and $\Delta\delta_C > 15$ were indicated that the regioisomer is 5-carbonylpyrazole **8** (>95%) and the 4-carbonylpyrazole (>5%). These results are similar to the published results for the cycloaddition of hydrazonoyl chlorides with benzalacetone [1,2,4], dibenzalacetone [7], alifatic (Chiral) α,ß-unsaturated ketones [8,9] and (ester) [11], 2,6 dibenzylidene-cyclohexanone [8] (and cyclopentanone [9] and azalactone [10,12,15].

Refluxing of the cycloadduct **8** with hydrazine in ethanol yielded the 1,9-diphenyl-4-(1,4-diphenyl-3-substitutedpyrazolin-5-yl)-6H-pyrid-azin-7-ones **9** and **10.** The structures of **9** and **10** were suppored by tlc, ^{1}H NMR, elemental analyses and IR spectroscopic methods (Table 1).

On the other hand, condensation of chalcones **5a** and **5b** with hydrazine hydrate or phenylhydrazine afforded the corresponding pyrazolopyrazoline derivatives 11 (Scheme 3).

It is worthy to mention that the ester group remained intact under the reaction condition was used. The structure of the pyrazolopyrazolines **11** were assigned on the bases of their elemental analyses and spectral data (Table 2). They show in their ^{1}H NMR spectra pair of doublet and multiplet at 5.4 and 3.2-3.7 ppm for H-5 and H-4 of the pyrazoline ring respectively as well as a triplet and quartet near 1.21-1.23 and

4.19-4.23 ppm for the CH_3 and CH_2 of the ester group respectively. The structure of **11a** was further supported from its mass spectral data which showed a molecular ion peak at m/z 436, while the base peak is the M-EtOH at m/z 313.

The discovery that isoquinoline-1-carboxaldehyde thiosemi-carbazone and its several cogeners possess antineoplastic activity [21,22] and play essential role of azomential linkages play in certain biological reactons [23-25], let us to study compounds containing a thiocarbamoyl moiety in their structures. The present investigation reports the synthesis of some new 1-substituted thiocarbamoyl moiety in their structures. The present investigation reports the synthesis of some new 1-substituted thiocarbamoyl derivatives **12** and **13** by treating pyrazole derivative **11a (**R=h) with the appropriate isothiocyanate (Scheme 3). The spectral data of theses compounds were recorded in Table 2. Their biological activity will be studied in due course.

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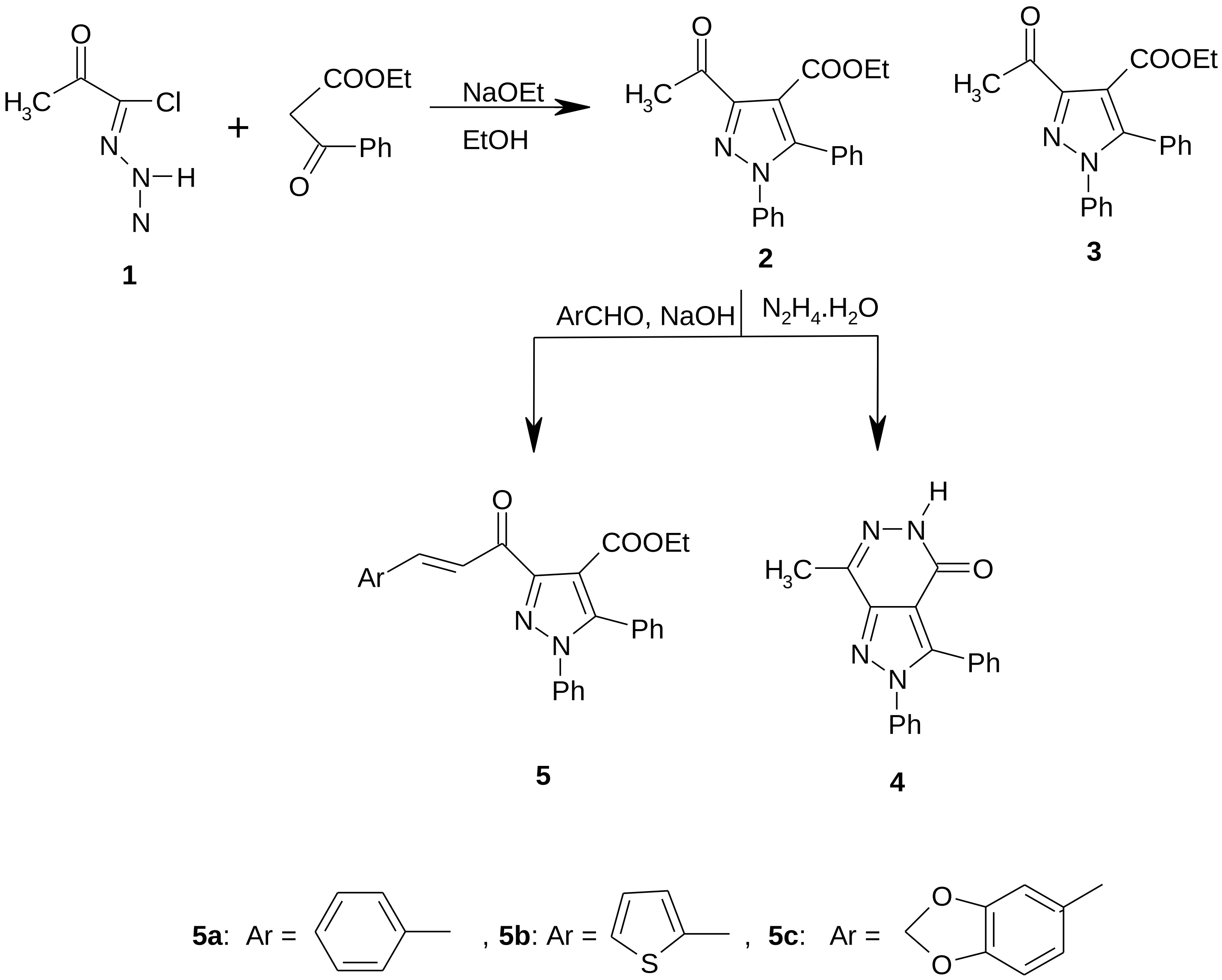
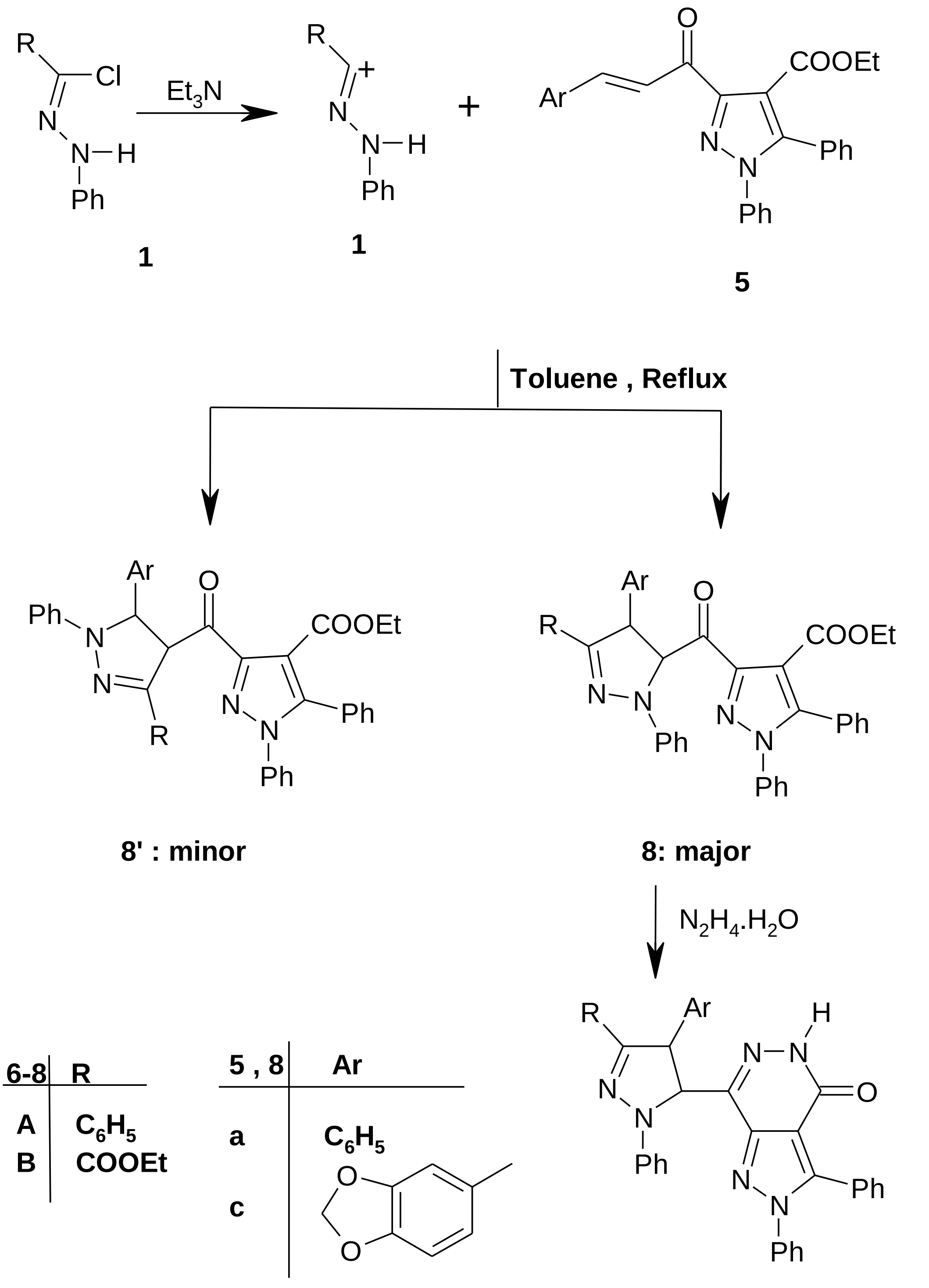


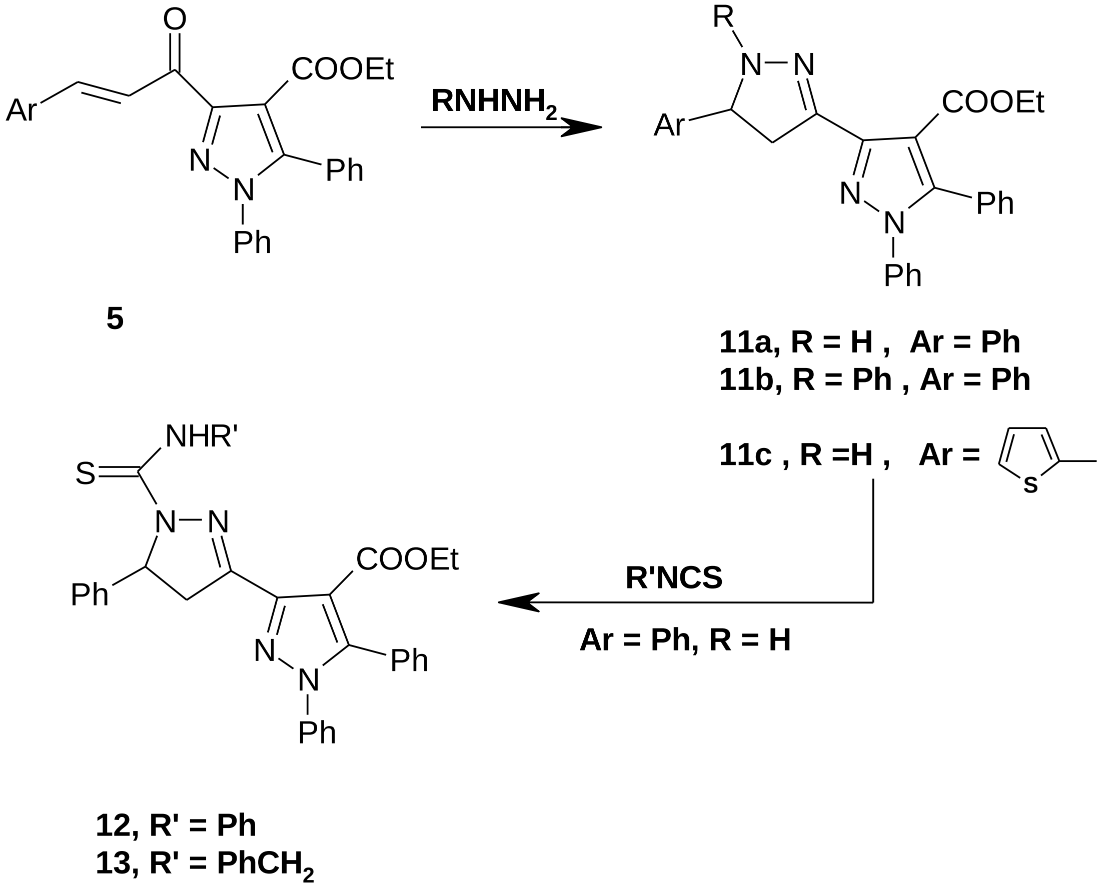
Scheme 1



9, R = Ph, Ar = Ph

10, R = COOEt , Ar = Ph

Scheme 2


Ar
O
COOEt
N
N
Ph
Ph
5
RNHNH2
R
N
N
Ar
COOEt
N
N
Ph
Ph
11a, R = H , Ar = Ph
11b, R = Ph , Ar = Ph
11c , R =H , Ar =
S
R'NCS
Ar = Ph, R = H
NHR'
S
N
N
Ph
COOEt
N
N
Ph
Ph
12, R' = Ph
13, R' = PhCH2

Scheme 3