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1.4-Arylation of β-(4-acetylaminobenzoyl)acrylic Acid with Activated Aromatic Hydrocarbons under Friedel-Crafts Conditions and Some Studies with the Products

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THE BEHAVIUOR of 3-(4-acetylaminobenzoyl) prop-2-enoic acid 1 with *m*-xylene and\or *p*-xylene under Friedel-Craft's reaction conditions yielded 2- (2,4-Dimethyl and/or 2,5-dimethyl) phenyl-3-(4-acetylaminobenzoyl)propanoic acids (2a,b) and thia-Micheal of acid 1 afforded 2- phenyl sulfanyl-3-(4-acetylamino benzoyl propanoic acid (3). Interaction of acids 2,3 with N_2H_4 , AC2O, NH2OH.HCl and PhNHNH2, yielded pyridazinone 4 , Furanone 5 1, 2oxazine 6 and 2-phenyl pyridazinone derivatives, respectively. Treatment of pyridazinone 4 with different interesting alkyl halides afforded the pyridazine derivatives 8 .

Keywords: 3-Aroyl prop-2-enoic acid. Pyridazinone. Furanone, oxazinone and Alkyl pyridazine .

Pyridazinone derivatives were reported to exhibit diverse pharmacological activities anti-depressant[1], antihypertensive[2,3], anti-thrombotic[4], anti-convulsant [5], cardiotonic [6] , antibacterial [7] , diuretics [8] , anti HIV [9] , as anticancer [10a] and as analgesic agent [10b] . Some pyridazinone derivatives like indolidan [11] bemoradan [12], pyimobendan [13], levosimedan [14], menaprine [15], emorfazone[16] and azanrinone [17] , already appeared in the clinical market. It is observed that the 6-phenyl-2(3H)pyridazinone residue considered as pharmacophoric group in the position six in pyridazinone becomes more active than the pyridazenone moiety. Also, from the medicinal chemistry research point of view the presesce of aryl and alkyl groups as the position of 2- and 6- in pyridazinone made ten times more active than itself. In recently published papers [18-19] the pyridazinone carrying the aryl and alkyl group in position 2- and 6- are more potent . So we have synthesized some new pyridazinone derivatives carring the lipophilic aryl and alkyl groups in the positions 2-, 4- and 6- . The Friedel–Crafts acylation of aromatic hydrocarbon with maleic anhydride afforded β -aroyl propenoic acid. Interaction of β-aroyl prop-2-enoic acid with aromatic hydrocarbon in the presesce of a Lewis acid anhydrous $AlCl_3$ under Friedel-Crafts Condition afforded α-aryl-β-aroyl propanoic acid. Treatment of the product with N_2H_4 and for $PhNHNH_2$ afforded the desired target .

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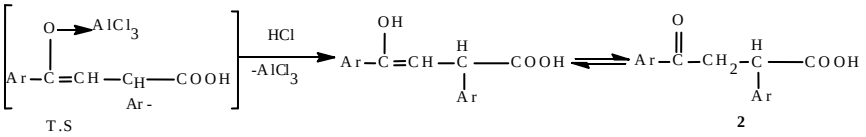
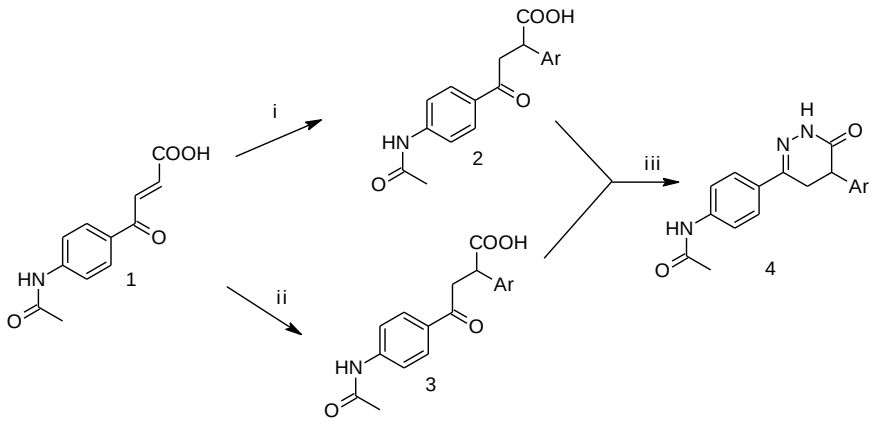
Results and Discussion

The β- aroylacrylic acid derivative , 4 (4-acetylamino phenyl)-4-oxo-but-2-enoic acid (1) [20-29] has interacted with hydrocarbons *m*-xylene and *p*-xylene in the presence of the anhydrous aluminium chloride under Friedel – Crafts reaction to afford 2-(2,4 dimethyl and \or 2,5dimethyl) phenyl-3-(4-acetylamino benzoyl) propionic acid (2). The acids 2 used as key starting materials for synthesizing the interesting heterocyclic systems, the structure of compounds 2 was established by their correct analytical data and their IR spectra which exhibited strong absorption at the regions 1688-1670 and 3330-3160 cm^{-1} attributable to υCO and υNH, respectively. EIMS for compounds 2 exhibited m/z 339(M^+).The reaction takes place *via* nucluphilic addition of hydrocarbon to the α, β unsaturated carbonyl moiety of the acid 1 that gave the less electrostatic repulsion transition state as below



On the other hand, interaction of acid 1 [30,31] with thiophenol in benzene in the presence of piperidine as acatalyst , it afforded thia-Michael adduct of 3-(4-acetylaminobenzoyl) -2-phenyl mercapto propionic acid 3 , its IR spectrum exhibits strong absorption hands at 1689-1670 , 3300-3170 cm^{-1} attributable to υCO and υNH, respectively . The ^{1}H-NMR spectrum of compound 3 revealed singlet at δ 2.15 ppm assigned to CH_3 group, two douplet at δ 2.3 ppm assigned to diasteriotopic protons (CH_2-CH), 3.7 ppm assigned to methine proton , multiplet at 6.8-7.8 assigned for aromatic protons and finally two exchangeable singlet at δ 8.1 and 13.1 ppm consistent with protons of (NH and OH), respectively . EIMS for compound 3 exhibited m/z 343 corresponding to (M^+) . Pyridazinone is an important clam of heterocycles , which have been the subject of extreme research particularly are the pharmaceutical and agrochemical which have their broad activities such as antihypertensive activity and anti inflammatory [32-34] , their synthesis application have been compressively reviewed [35,36], anticipated NSAID [37,38] . Thus, when acids 2,3 were reacted with N_2H_4 in boiling ethanol. They afforded 6 (4- acetylamino phenyl)-4-(2,4 and /or 2,5 dimethyl phenyl and phenyl mercapto)-2,3,4,5 tetrahydro 3(2H) pyridazinone 4 (Scheme 1). IR spectra for compounds 4 exhibit strong absorption bands at 1690-1670cm^{-1} and 3288-3285cm^{-1}corrsponding to υCO and υNH, respectively. The ^{1}H-NMR spectrum of compound 4_b revealed singlet at δ 2.2 ppm assigned to 3 methyl groups,2.8 ppm assigned 2.8 (2dd, 2H,diasterotopic protons), 3.4 (dd,1H,CH-CO, pyridazine moiety), multiplet at 6.8-7.4 ppm assigned to aromatic protons and exchangeable protons , singlet at 8.5 and 13 ppm corresponding to NH and OH groups, respectively. EIMS for compound 4c exhibited m\z 339 corresponding to (M^+).



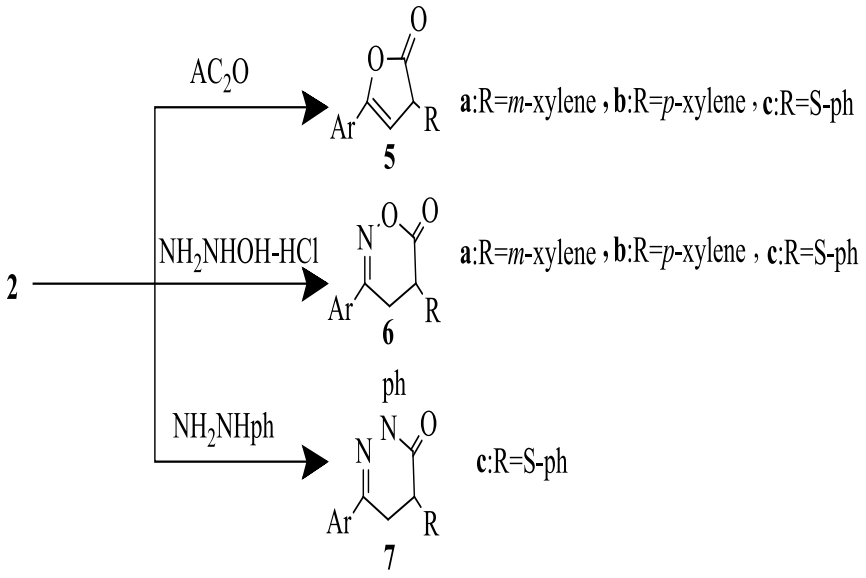
i = a) *m* -xylene/$AlCl_3$; b) *p* - xylene ii = PhSH/Piperidine iii = NH_2NH_2/Ethanol

a) Ar =C_6H_3(2,4 -CH_3) b) Ar =C_6H_3(2,5 -CH_3) c) Ar = SPh

Scheme 1.

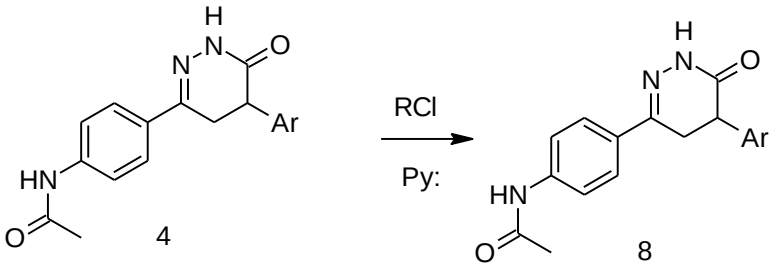
Furthermore due to their common occurrence in nature, oxygen containing in 2 (5H)- Furanone has UV-induced unimolecular photochemistry [39]. Its important target for synthesis either as final product or as useful synthetic intermediates, the synthesis of lactones can be achieved by the lactonization of hydroxyl acids Baeyer- villiger oxidation,the insertion of a carbonyl group by transition metals, intramolecular cyclization of diones [40] .Thus, when acids 2,3 were allowed to react with acetic anhydride under reflux and for heating or in water bath for 1hr , afforded 5-(4-acetamido phenyl)-3-(2,4-dimethyl/2,5 dimethyl and /or phenyl mercapto)- 2 (3H) furanone 5. IR spectra revealed strong absorption bands at 1762-1750 cm^{-1} attributable to υCO . The ^{1}H-NMR spectrum of compound 5_b in DMSO exhibited signals at δ 2.5 ppm assigned to 3- methyl groups , 4 ppm assigned to chiral center, doublet at 6.7 ppm assigned to olefinic protons in furanone ring , 7.5-7.9 ppm multiplet aromatic protons and exchangeable proton of (NH) groups at 13.5ppm. EIMS for compounds 5_a,5_c exhibited m\z 322 and 325 corresponding to (M^+), respectively. On the other hand , when compounds 2,3 were allowed to react with hydroxyl amine hydrochloride in boiling pyridine afforded 3-(4-acetomido phenyl)-5- (2,4 or 2,5 dimethyl phenyl and /or phenyl mercapto)-1,2 oxazin-6-one(6).IR spectra revealed strong absorption bands at 1735 and 3140-3147cm^{-1} attributable to υCO,υNH, respectively. Several studies have indicated that NH group to CO group and azine system may be an essential structural requirement in the binding of 3(2H)-pyridazinone to variety of biological receptors [41] . However ,the numerous syntheses of 3(2H) pyridazinones that have been published in recent years have made only limited progress in terms of the efficient protection of the 2-position in the heterocyclic ring. Although all structural studies on this nucleus have shown that 3 (2H) pyridazinones exist in the keto from[42]. Reaction involving ambident ring that possess a tautomeric structure are often inefficient and lack regio

control. Thus treatment of compound (3) with phenyl hydrazine in boiling ethanol afforded 2-phenyl-4-(phenyl mercapto)-6-(4-acetyl aminophenyl)3(H) pyridazinone (7) which was established by its correct analytical data . IR spectrum exhibits strong absorption bands at 1687-1650 cm^{-1} corresponding to two carbonyl groups υCO and 3279 cm^{-1} for υNH (Scheme 2).



Scheme 2.

Moreover, the authors used the pyridazinone as starting material to afford 2-alkyl pyridazinone derivatives in which the position-2 is blocked in lactam structure . So, interaction of 3(2H) pyridazinone derivatives 4_a and 4_b with different alkyl halides in pyridine , afforded the corresponding 2-alkyl pyridazinone derivatives 8 . The structure of compounds 8 was estabalished by their correct analytical data and IR spectra which exhibited strong absorption bands at the regions 1730-1670 cm^{-1} attributable to υCO for all derivatives 8, the compounds 8_k and 8_l have υCO at 1670 broad bands due to vibrational coupling of 2 carbonyl groups attached which by good inductor atom, *e.g* nitrogen atom (-CO-N-CO-) and the derivatives 8_i and 8_j have 2 carbonyl regions at 1730 and 1745 cm^{-1} due to ester group. The ^{1}H-NMR of 8_l in DMSO 1.1 (t,3H,CH_2CH_3) 2.3 (s,9H,CH_3) [3.1(2dd,2H, disterotopicprotons), 3.7(dd,1H,CH of methine in pyridazine moiety],4.1(q,2H,CH_2CH_3) ,4.8(s,2H,N-CH_2) 7.17.9(m,7H,ArH) . EIMS for compound 8_b and 8_g exhibited m/z 348 and 426, respectively corresponding to M^+.The compound 8_k exhibited m\z 336 corresponding to (M^+ - $COCH_3$) .



Ar =C_6H_3(2,4 -CH_3)
a) CH_3 c) C_2H_5
e) CH_2=CH CH_2
g) Ph CH_2 i) CH_3CO
k) CH_2COOEt

Ar =C_6H_3(2,5 -CH_3)
b) CH_3 d) C_2H_5
f) CH_2=CH CH_2
h) Ph CH_2 j) CH_3CO
l) CH_2COOEt

Scheme 3.

Experimental

All melting points are uncorrected. Elemental analyses were carried out in the Microanalytical Center, Cairo University, Egypt. IR spectra were recorded in (KBr) disks on Shimadzu FTIR 8101Pe and ^{1}H-NMR spectra recorded on a Varian 300 MHz in($CDCl_3$)or (DMSO-d_6) as solvents, (chemical recorded on Shimadzu GCMS-QP-1000EX mass spectrometer at 70 eV. Homogeneity of all compounds synthesized was checked by TLC. Characterization data of the various prepared compounds are given in Table 1.

2-(3,4-Dimethyl and / or2,4dimethyl) phenyl-3-(4-acetylamino) benzoylpropionic acids (2a,b)

A solution of the 3(4-acetylamino) benzoyl acrylic acid 1 (2.4g,0.01 mol) in *m*-xylene and/or *p*-xylene (50 ml) was treated with anhydrous aluminum chloride (0.04 mol) and the mixture was heated on the water bath for 10 hr. The mixture was treated with ice\HCl. The organic layer was washed with water, and the excess solvent was removed by steam distillation. The organic material was extracted by ether. The ethereal layer was washed by10% aq Na_2CO_3 solution, and was acidified by dil HCl. The solid was separated out , filtered off , dried and recrystallized from the proper solvent to afford 2a and b .

IR Spectra for compounds 2a and 2b exhibit υOH (b) 3330 , υCHAr 3050, υ CHAli 2950,υCO1688-1670cm^{-1} ^{1}H-NMRspectrum for 2a in DMSO 2.45 (s,9H,CH3), 3.1 (2dd,2H,diasterotopic protons), 3.9(dd,1H, CH-COO),6.8-7.8(m,7H,ArH), 11.2 (s,1H,COO) , 13.2(s,1H,NH).EIMS appear m/z at 339 corresponding to molecular ion peak.

2-Phenyl sulfanyl-4-oxo-(4-acetylamino) phenyl-propanoic acid (3)

A mixture of 3-(4-acetylaminobenzoyl)-prop-2-enoic acid (2.4 g,0.01 mol) and Thiophenol 0.01 mole (1ml) in 20 ml dry benzene and drops of piperidine for 4 hr. The product that separated was recrystallized from ethanol to give compound 3. IR Spectrum for compound 3 exhibited υNH 3300,υCHAr 3050, υCO 1689-1670 cm$^{-1.}$ ^{1}H-NMR spectrum for 3 in DMSO 2.15 (s,3H), 2.3 (2dd,2H,diasterotopic protons), 3.7(dd,1H,CH-COOH),6.8-7.8 (m,9H,ArH)), 8.1(s,1H,COOH), 13.1(s,1H,NH).

4-(2,4-or2,5 Dimethyl)phenyl and/or 4- phenyl sulfanyl 6-(4-acety aminophenyl)-1, 4, 5,6-tetrahydro-3(2H)-pyridazinone (4)

A mixture of propionic acid derivatives 2,3 (0.01 mol) and hydrazine hydrate (0.5 mL,0.01 mol) was heated under reflux in butanol (30 ml) for 3 hr . The reaction mixture was concentrated.The solid was separated out, filtered off, dried and recrystallized from the proper solvent to afford the pyridazinone 4. IR spectrum for compound 4 exhibits υNH 3285,υCHAr 3050,υCO 1670 cm^{-1}, the ^{1}H-NMR spectrum for 4b in DMSO 2.2 (s,9H), 2.8 (2dd,2H,diasterotopic protons), 3.4 (dd,1H,CH-CO , pyridazine moiety),6.8-7.4(m,7H,ArH),8.5 and 13.2(bs,2H,NH).

2-Phenyl-4-(2,4-dimethyl or 2,5-dimethyl)phenyl and/or phenyl-phenylsulfanyl-5(4H)-furanone (5)

A mixture of propionic acids 2 (0.01 mol) and acetic anhydride (0.01 mol) was heated under reflux for 3 hr. The reaction mixture was concentrated. The solid was separated out, filtered off, dried and recrystallized from the proper solvent to afford the furanone 5. IR Spectra for compounds 5 exhibit υCHAr 3050, υCO 1762-1750 cm^{-1} . ^{1}H-NMR spectrum for 5b in (DMSO) 2.5 (s,9H,CH_3) ,4(dd,1H, CH-CO),6.7(s,1H, CH-R, furanone moiety), 7.5-7.9(m,7H,ArH),13.5 (s,1H,NH, exchangeable proton). EIMS of 5a and 5c m/z at 322 and 325 corresponding to molecular ion peak, respectively .

3- Acetylamino phenyl-5-[(2,4- and 2,5-dimethyl) phenyl and/or phenyl sulfanyl]-4,5,6-trihydro1,2-oxazin-6-one (6)

A mixture of 2 (0.01 mol) and hydroxyl amine hydrochloride(0.01 mol) was heated under reflux in pyridine (30 ml) for 3 hr. The reaction mixture was

filtered off on hot, then left to cool and pour into ice/HCl. The solid was separated out, filtered off, dried and recrystallized from the proper solvent to give 1,2 oxazin-6-one **6**.IR υNH 3220, υCHAr 3050, υSH 2300, υCO 1735cm^{-1} . ^{1}H-NMR of 6a in DMSO 2.45 (s,9H,CH_3), 2.9 (2dd,2H, diasterotopic protons,CH_2-CH) , 3.6 (dd,1H,CH-CO, oxazine moiety) ,7.3-7.9(m,7H), 11.3 (s,1H,exchangeable NH) .

2-Phenyl-3-acetylamino phenyl-5-phenyl sulfanyl-1, 4, 5,6-tetrahydro-pyridazin-6-one(7)

A mixture of acid 2c (0.01 mol) and phenyl hydrazine (0.01 mol) in ethanol (30 ml) was heated under reflux for 3 hr. The reaction mixture was poured on ice after cooling. The separated solid was filtered off , dried and recrystallized from ethanol . IR υCHAr 3050 , υCHAli 2886cm^{-1} , υCO 1687-1670. ^{1}H-NMR in (DMSO) 2.5 (s,6H) , 3.1 (2dd,2H,disterotopicprotons) 3.7 (dd,1H,CH-) [pyridazine moiety],7.17.9(m,14H) ,11.4 (s,1H, NH).

2- Alkyl-4- (2,4-/ 2,5-dimethyl) phenyl-6-Acetylamino phenyl-1, 4, 5,6-tetrahydro pyridazinone (8)

A mixture of pyridazinone 4a,b (0.01 mol) and alkyl halide (0.01 mol) namely methyl iodide , ethyl iodide, allyl bromide , benzyl chloride ,acetyl chloride and ethyl chloro acetate in dry pyridine was refluxed for 3 hr. The reaction mixture was poured on ice/HCl . The separated solid was filtered off , dried and recrystallized from the proper solvent to afford alkyl pyridazine 8. IR υCHAr 3070-3050, υCHAil 1945-2886 , υCO 1730-1670 cm^{-1} . ^{1}H-NMR of 8a in (DMSO) 2.3 (s,9H,CH_3),3.1 (2dd,2H,disterotopicprotons) , 3.7 (dd,1H,CH-) [pyridazine moiety] , 7.17.9 (m,7H,ArH) ^{1}H-NMR of 8*l* in (DMSO) 1.1 (t,3H,CH_2CH_3) 2.3 (s,9H,CH_3) , 3.1 (2dd,2H,disterotopic protons) , 3.7 (dd,1H,CH-)[pyridazine moiety], 4.1 (q,2H.CH_2CH_3) ,4.8 (s,2H,N-CH_2)7.1-7.9(m,7H,ArH). EIMS for compounds 8_b and 8_g exhibited m/z 348 and 426 respectively corresponding to M .The compound 8_k exhibited m\z 336 corresponding to (M -$COCH_3$) .

TABLE 1. Characterization and physical data for synthesized compounds .

Cpd. No	M.P.°C	Yield %	Solvent Of Cryst.	Formula M.Wt	Analysis % calcd/found			
					C	H	N	S
2_a	205 -207	70	Ethanol	$C_{20}H_{21}NO_4$(339)	70.7 70.4	6.5 6.25	4.1 3.9	-
2_b	218-220	60	Ethanol	$C_{20}H_{21}NO_4$ (339)	70.7 70.4	6.5 6.25	4.1 3.9	-
3	210-212	55	Ethanol	$C_{18}H_{17}NO_4S$(343)	62.9 62.6	4.9 4.3	4.1 4.3	9.3 9.4
4a	150-153	80	Ethanol	$C_{20}H_{21}N_3O_2$(335)	71.6 71.4	6.3 6.5	12.8 12.7	-
4b	140-142	75	Ethanol	$C_{20}H_{21}N_3O_2$(335)	71.6 71.4	6.3 6.5	12.8 12.7	-
4c	105-107	50	Ethanol	$C_{18}H_{17}N_3O_2S$(339)	63.7 63.4	5.0 5.2	12.4 12.7	9.4 9.6
5_a	123-125	85	Ethanol	$C_{20}H_{19}NO_3$(321)	74.7 74.4	5.9 5.5	4.4 4.6	-
5_b	130-133	70	Ethanol	$C_{20}H_{19}NO_3$(321)	74.7 74.6	5.9 5.6	4.4 4.4	-
5_c	125-128	60	Ethanol	$C_{18}H_{14}$NO3S(324)	66.6 66.3	4.3 4.3	4.3 4.1	9.8 9.8
6a	220-223	65	Butanol	$C_{20}H_{20}N_2O_3$(336)	71.4 71.7	5.9 5.7	8.3 8.6	-
6b	225-228	60	Butanol	$C_{20}H_{20}N_2O_3$(336)	71.4 71.2	5.9 5.6	8.3 8.3	-
6c	200-204	50	Dioxan	$C_{18}H_{16}N_2O_3S$(340)	63.5 63.4	4.7 4.3	8.3 8.6	9.4 9.8
7c	110-113	50	Ethanol	$C_{24}H_{21}N_3O_2S$(415)	69.4 69.1	5.1 5.4	10.1 10.4	7.7 7.1
8a	128-132	70	Ethanol	$C_{21}H_{23}N_3O_2$(349)	72.2 72.4	6.6 6.7	12.0 11.9	-
8b	133-335	80	Ethanol	$C_{21}H_{23}N_3O_2$(349)	72.2 72.0	6.6 6.4	12.0 11.9	-
8c	155-158	50	Ethanol	$C_{22}H_{25}N_3O_2$(363)	72.7 72.1	6.9 6.4	11.6 11.3	-
8d	162-165	50	Ethanol	$C_{22}H_{25}N_3O_2$(363)	72.7 72.1	6.9 6.4	11.6 11.3	-
8e	175-178	70	Ethanol	$C_{23}H_{25}N_3O_2$(375)	73.6 73.7	6.6 6.6	11.2 11.5	-
8f	180-183	60	Ethanol	$C_{23}H_{25}N_3O_2$(375)	73.6 73.3	6.6 6.4	11.2 11.0	-
8g	205-208	55	Dioxan	$C_{27}H_{27}N_3O_2$(425)	76.2 76.4	6.4 6.5	9.9 9.4	-
8h	200-203	60	Dioxan	$C_{27}H_{27}N_3O_2$(425)	76.2 76.0	6.4 6.5	9.9 9.6	-
8i	180-183	75	Dioxan	$C_{22}H_{25}N_3$O3(377)	70.0 70.5	6.1 6.3	11.1 11.4	-
8j	185-188	80	Dioxan	$C_{22}H_{25}N_3$O3(377)	70.0 70.0	6.1 6.2	11.1 11.0	-
8_k	105-108	85	Ethanol	$C_{24}H_{27}N_3O_4$(421)	68.4 68.5	6.4 6.3	10.0 10.0	-
8_l	115-118	80	Ethanol	$C_{24}H_{27}N_3O_4$(421)	68.4 68.4	6.4 6.2	10.0 10.3	-

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تفاعل١- ٤- اسيتا ل امينو البنزويل حمض اللا كريليكك مع الهيدروكربونات الاروماتية الناشطة في ظروف فريدل كرافت ودراسة سلوك النواتج كميائيا

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١- تحضير بعض الاحماض البروبيونيك الحاملة مجموعات الاريل و الكبريتو الاريل و الارويل(ناتج الاضافة(٢و٣) . وذلك من خلال معالجة حمض ٣(٤-استيل الامينو بنزويل) -٢- البروبينك مع الميثا والبارا زيلين عن طريق فريدل كرافت و ايضا مع الثيوفينول عن طريق اضافة مايكل للحصول على ناتج الاضافة .الذى يستخدم لتحضير العديد من المركبات الغير متجانسة الحلقة مثل البيريدازينون و الاكزازينون والفيورانون.

٢-اجراء بعض التجارب على مشتقات البيريدازينون للحصول على مركبات اكثر فاعلية من -NSAID2

٣-اثبات المركبات المحضرة بأجهزة التحاليل الدقيقة مثل الاشعة تحت الحمراء و الرنين المغناطيسى والكتلة الاكترونى.