Ain Shams University
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Aza- and thio-Michael addition reactions involving *α,β*-unsaturated keto acids

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Summary

Pyridazin-3(2*H*)-ones is an important class of heterocyclic compounds, especially in the fields of biology, pharmacology and bioorganic chemistry. Several comprehensive studies have illustrated in details their diverse pharmacological and biological actions. These observations prompted our interest to synthesize some novel 6-aryl-4,5-dihydropyridazin-3(2*H*)-ones bearing moieties with great importance like 1,3,4-thiadiazoles and thioglycolic acid at 4-carbon, accompanied by substituted 2-nitrogen.

Thus, the present work is devoted to study the interaction of *β*-aroylacrylic acid ***(1)*** with three selected 1,3,4-thiadiazoles namely, 1,3,4-thiadiazole-2,5-diamine ***(2)***, 5-amino-1,3,4-thiadiazole-2-thiol ***(3)***, 1,3,4-thiadiazole-2,5-dithiol ***(4)*** and thioglycolic acid ***(5)*** in order to synthesize aza- and thio-Michale adducts, then using the formed compounds as starting material to synthesize fused and isolated pyridazin-3(2*H*)-one systems.

Summary

In the first part of our study, the four adducts have been synthesized as follows; compound ***(1)*** has been reacted with 1,3,4-thiadiazole-2,5-diamine ***(2)*** in ethylene glycol to afford the aza-Michael adduct ***(6)***. Compound ***(1)*** were reacted with 5-amino-1,3,4-thiadiazole-2-thiol ***(3)*** in ethanol to produce thio-Michael adduct ***(7)***. Refluxing the same compound with 1,3,4-thiadiazole-2,5-dithiol ***(4)*** in toluene produced thio-Michael adduct ***(8)***. Finally, thio-Michael adduct ***(9)*** has been obtained by reacting compound ***(1)*** with thioglycolic acid ***(5)*** in methanol at room temperature.

In the second part of the study, the synthesized adducts were then reacted with some hydrazines, namely hydrazine hydrate, acetohydrazide, formohydrazide, semicarbazide and thiosemicarbazide to achieve formation of some new dihydropyridazin-3(2*H*)-one derivatives.

Thus, refluxing of aza-Michael adduct ***(6)*** with hydrazine hydrate, acetohydrazide, formohydrazide, semicarbazide or thiosemicarbazide in (DMF) at mild temperature afforded the dihydropyridazin-3(2*H*)-ones ***(10-14)***.

Similarly, both of thio-Michael adducts ***(7)*** and ***(8)*** have been refluxed in (DMF) to produce the dihydropyridazin-3(2*H*)-ones ***(15-24)***.

Following the same synthetic approach, thio-Michael adducts ***(9)*** was reacted with the selected hydrazines to afford the dihydropyridazin-3(2*H*)-ones ***(25-29)***.

In the third part of the study, aza- adduct ***(6)*** or thio-adduct ***(7)*** were reacted with diethylmalonate or ethylacetoacetate in basic solution to produce thiadiazolobutanamides ***(30-33)***.

The obtained thiadiazolobutanamides have been subjected into more investigation by interaction with different N-nucleophiles.

Thus, interaction of compounds ***(30)*** or ***(32)*** with 2 moles of hydrazines, namely hydrazine hydrate, acetohydrazide, formohydrazide, semicarbazide or thiosemicarbazide in (DMF) at moderate temperature to afforded compounds ***(34-43)***.

Under the same reaction conditions compounds ***(31)*** or ***(33)*** reacted with 2 moles of hydrazine hydrate to afford the thiadiazolopyridazin-3(*2H*)-ones ***(44)*** and ***(45)*** respectively. Then compound only ***(31)*** were reacted with the rest of hydrazine derivatives acetohydrazide, formohydrazide, semicarbazide or thiosemicarbazide to produce compounds ***(46-49)***.

In the fourth part of the study, compounds ***(16)*** and ***(18)*** were treated with some active methylene derivatives in order to synthesize fused thiadiazolopyridazin-3(*2H*)-one derivatives.

Thus, compounds ***(16)*** or ***(18)*** have been treated with malononitrile, ethyl cyanoacetate, acetylacetone or ethyl acetoacetate in acetic medium to afford the [1,3,4]thiadiazolo[2,3-b][1,3]thiazines (***50-57***).

Structures of the synthesized compounds were confirmed via elemental analysis, IR, ^{1}HNMR and Mass spectroscopy methods.

Finally, some of the obtained compounds have been investigated for their *in vitro* antimicrobial activity, and most of them exhibited promising biocidal effect.

Keywords: Aroylacrylic acid; Aza-Michael Addiction; Thio-Michael addition; 1,3,4-thidiazoles; Hydrazine derivatives; pyridazin-3(2H)-ones.

The chemistry of *β*-aroylacrylic acids

(I)- Introduction

1- General and historical:

The need for new antibiotic substances produced by microorganisms has prompted the investigations of comparatively simple synthetic compounds, particularly these bearing structural features common to several of the natural antibiotics.

Geiger and Conn[68] have called attention to the structural feature, (-CH=C-C=O) common to both penicillic acid and clavacin, and they have assumed that the antibacterial activity of both compounds is very closely associated with this grouping. The fact that clavacin, penicillic acid and many *α*,*β*-unsaturated ketones[145,146] react with sulfhydryl groups was a kind of support to this hypothesis.

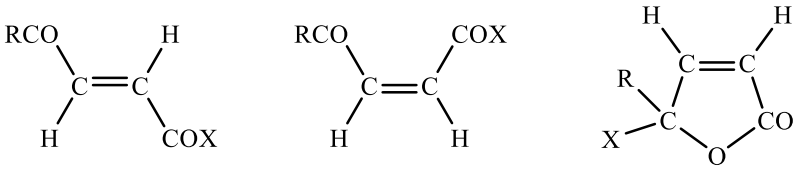
It has been reported that[68,113] *α*,*β*-unsaturated ketones in which the aromatic moiety is adjacent to the carbonyl group show bacteriostatic activity.

In general, the *β*-aroylacrylic acids[154] have shown appreciable *in vitro* activity against a wide variety of gram negative organisms, as well as against several strains of *Staphylococcus aureus*. Several of the substituted acrylic acids also have shown a pronounced *in vitro* fungistatic activity.

Thus, the present review attempts to provide a comprehensive account of the chemistry of *β*-aroylacrylic acids and their relevant derivatives. The literature has been covered from the early studies up to the end of 2015.

2- Structure:

It has been considered that *β*-benzoylacrylic acid and its methyl ester are existing in three isomeric forms[34], the *trans E-(1)*, the *cis* form *Z-(1)* and the angelica lactone form ***(2)*** (Fig. 1).



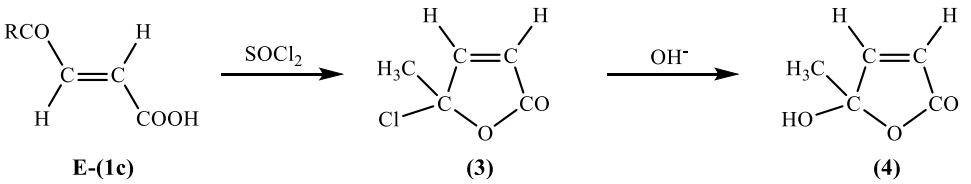
***E*-(1)** ***Z*-(1)** **(2)**

a,R = C_6H_5, X = OH
b,R = C_6H_5, X = OCH_3
c, R= CH_3, X= OH

(Fig. 1)

It has been found that the compound obtained by the Friedel-Crafts reaction of maleic anhydride with benzene is *(E)-β*-benzoylacrylic acid[13] of the form ***(1a).*** The infrared spectrum exhibited[34] absorption peaks at *v* 1700, 1670 and 1635 cm^{-1} with lack of any peaks within 1800-1750 cm^{-1} range. In the ultraviolet spectrum, two bands were observed at λ_{max} 238 and 272 mμ. While in the ^{1}HNMR spectrum[174], the olefinic protons showed doublets signal at τ = 3.12 and 1.98. The higher coupling constant value (*J* = 15.4 *Hz*) was an evidence for the existence of *β*-benzoylacrylic acid in the *trans* isomer ***E-(1a).***

Acetylacrylic acid *E-**(1c)*** was isomerized[121] by action of thionyl chloride to 2-oxofuran ***(3)***. The later in aqueous alkali converted to ***(4)*** (Scheme 1).



E-(1c) **(3)** **(4)**

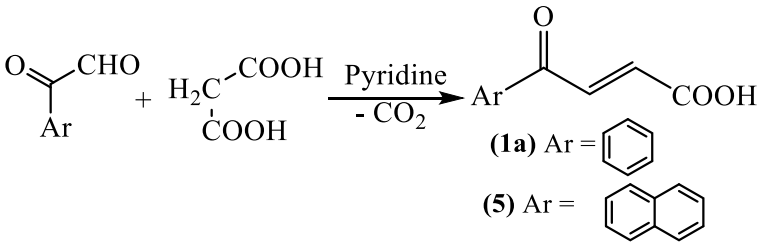
(Scheme 1)

The pKa values of *p*-substituted *trans*-*β*-aroylacrylic acids[144] were determined spectrochemically in water at 25°C and at ionic strength 0.1M (NaCl). The thermodynamic pKa values were correlated with Hammett σ,*ρ* constants.

(II)- Synthesis of *β*-aroylacrylic acids

1- Condensation of glyoxals with malonic acids:

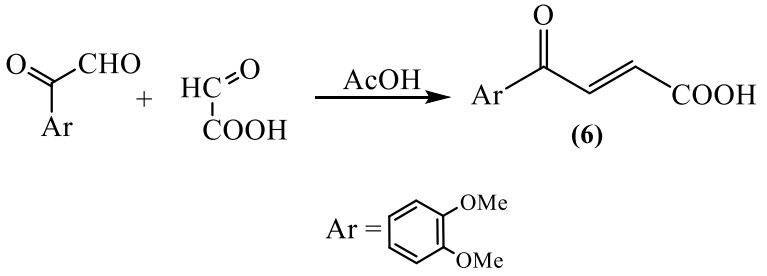
β-Benzoylacrylic acid ***(1a)*** and *β*-naphthoylacrylic acid ***(5)*** both have been prepared from condensing phenylglyoxal or 2-naphthylglyoxal with malonic acid in pyridine[172] (Scheme 2).



(Scheme 2)

2- <u>Condensation of glyoxals with glyoxylic acid</u>:

3,4-Dimethoxyacetophenone has been refluxed with glyoxylic acid[167,178] in acetic acid for (20 h) to produce *β*-aroylacrylic acid derivative ***(6)*** in good yield (Scheme 3).



(Scheme 3)

Similarly, furoylacrylic acids ***(8)*** have been prepared[85] via *in situ* reaction by treating furylketones ***(7)*** with glyoxylic acid, followed by dehydration with ($KHSO_4$) in toluene (Scheme 4).