Regioselective Base-induced Condensations of Acrylic Acid Derivatives

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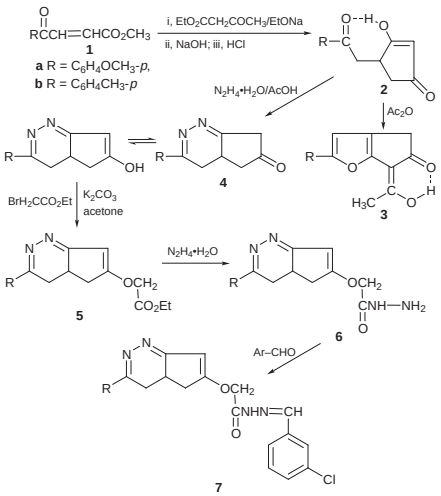
The orientation of cyclization of the reaction of methyl aroylacrylate (**1**) and aroylacrylic acid (**8**) with ethyl acetoacetate and/or thiourea leading to the formation of 4-aroylmethylcyclopentane-1,3-dione (**2**) 5-aryl-3-oxocyclohexene-1,2-dicarboxylic acid (**9**), 2-imino-5-aroylmethylthiazolidin-4-one (**11**) and 6-aryl-2-sulfonylpyrimidine-4-carboxylic acid (**14**) depends on the medium employed; some compounds show moderate antiviral activities against tobacco necrosis virus.

Aroylacrylic acid derivatives can be used in a wide range of the addition reaction.[1] The strong electron-attracting power of their arylcarbonyl group enhances the reactivity of the adjacent double bond-function and promotes the nucleophilic addition at this centre. Simultaneous or subsequent cyclization of the adducts gives access to various 5- or 6-membered cyclic structures.[2] Because pyridazine,[1,3] pyrimidine[4] and thiazolidine[5] derivatives are associated with diverse pharmacological activities, I was prompted to study the antiviral activity (*in vivo*) of some newly synthesized compounds. The synthesis of compounds **2–17** was accomplished as shown in Schemes 1 and 2.



Scheme 1

Results and discussion

Ethyl acetoacetate reacted with methyl aroylacrylates **1a,b** in a sodium ethoxide solution followed by hydrolysis to site 4-aroylmethylcyclopentane-1,3-diones **2a,b** in excellent yield. The presence of ν(OH) as a broad band indicates that **2** exist in their enolic form in the solid state, and the usual 3400–3200 cm^{-1} associated hydroxy band is shifted to $\sim$ 2500 cm^{-1} owing to the formation of very strong hydrogen bonds.[6]

Cyclization of **2a** with acetic anhydride at 150 °C afforded the acetyl derivative **3a**, which showed a ν(C=O) band at 1726 cm^{-1}, while the condensation of **2a,b** upon treatment with hydrazine hydrate in acetic acid gave 3-arylcyclopenteno[1,2-*c*]pyridazine derivatives **4a,b**. These products are believed to exist in equilibrium with their enols which are stabilized through hydrogen bonding. The ^{1}H NMR spectra of **2** and **4** were complex, containing signals for each tautomeric form.

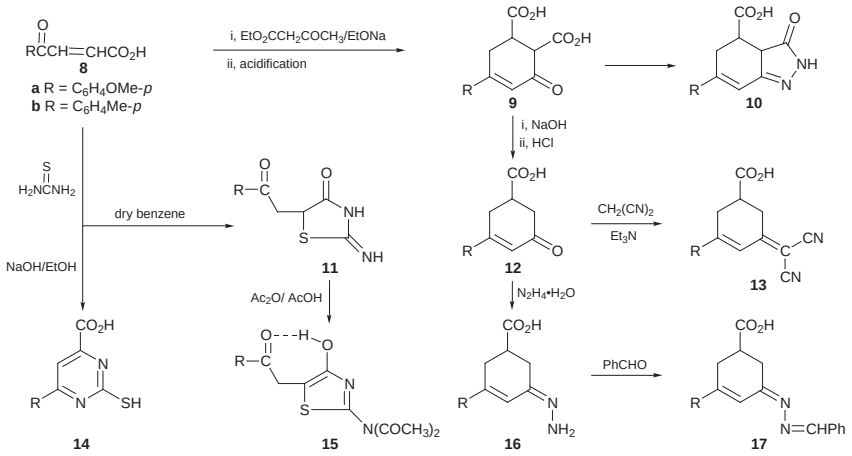
Treatment of cyclopentenopyridazine **4b** with ethyl bromoacetate afforded **5b**.[7] The structure of ester **5b** was derived from its infrared spectrum, which showed ν(C=O) (ester) at 1744 cm^{-1}, and by ^{1}H NMR spectroscopy. The reaction of **5b** with hydrazine hydrate in boiling ethanol[1] yielded the hydrazide derivative **6b**. The analytical and mass spectral data of **6b** were consistent with the molecular formula $C_{16}H_{18}N_4O_2$. The IR spectrum of **6b** was devoid of a ν(C=O) (ester) band; whereas its mass spectrum showed the molecular ion at *m/z* 298, and a fragment at *m/z* 239 owing to (M – $CONHNH_2$). Condensation of **6b** with *m*-chlorobenzaldehyde gave the hydrazone derivative **7b**. The product **7b** identified by elemental analysis and ^{1}H NMR, which indicated the CH=N function at δ 8.43. The structures of 3, 5 and 7, assigned on the basis of their analytical and spectral data, are thermodynamically the most stable because they are more conjugated than the other possible isomers.

By replacing methylaroylacrylate **1** with aroylacrylic acid **8a,b** in the same reaction and under the same conditions, the 2-cyclohexenone derivatives **12a,b** were obtained. Structures **12a,b** were established as products by the ^{13}C NMR spectrum of **12a** which showed δ (ppm) 197.6 and 172.5 (attributed to the ring (C=O) and (CO_2H) which should appear at a similar position).[8] The attempted preparation of **2a,b** *via* condensation of **8a,b** with ethyl acetoacetate failed. The difference in behaviour between **1** and **8** towards ethyl acetoacetate is attributed to the different electrophilicity of the carboxylate carbon in **8**.

The reaction may be carried out in one pot (Schemes 1 and 2). The initial addition of an active methylene moiety in ethyl acetoacetate to an activated double bond of **1** and/or **8** yielded an acyclic Michael adduct. The intermediate can, however, lose methanol by an internal Claisen ester condensation or undergo the nucleophilic addition at the aromatic ketone groups (followed by elimination of water) to give the cyclized derivatives, which, being the ester of a β-ketoacid, may in turn readily undergo hydrolysis and decarboxylation to give **2** and **12**, respectively.

Cyclohexenone derivatives **9a,b** were obtained on dilution and acidification of the reaction mixture of **8a,b**, before the decarboxylation process. Reaction of **9a** with hydrazine hydrate[9] afforded 6-aryl-3-oxo-2,4,5,3a-tetrahydro-1*H*-indazole-4-carboxylic acid (**10a**), which showed a ν(NH) band at 3287 cm^{-1} and molecular ion at *m/z* 286. Treatment of **12b** with malononitrile in the presence of triethylamine yielded the adduct **13b**, which showed ν(C$\equiv$N) bands at 2233 and 2217 cm^{-1}. The mass spectrum of **13b** showed the base peak at *m/z* 233 owing to (M – COOH).

Furthermore, the reaction of **8a** with thiourea[10] in dry benzene yielded thiazolidinone derivative **11a**, whereas thiourea in an ethanolic sodium hydroxide solution[11] afforded the pyrimidine derivative **14a**. Structures **11a** and **14a** (or possible tautomers) could be established for the reaction product



Scheme 2

based on their ^{1}H NMR and the mass spectra which revealed the base peak of **11a** at *m/z* 135 owing to ($CH_3OC_6H_4CO$) and of **14a** at *m/z* 217 owing to ($M - CO_2H$).

Acylation[12] of **11a** with an acetic anhydride/acetic acid mixture yielded **15a** whose mass spectrum showed the molecular ion at *m/z* 349 which, in turn, eliminated an acetyl radical to afford a cation at *m/z* 306, and the base peak at *m/z* 135 owing to ($CH_3OC_6H_4CO$).

Finally, the reaction of cyclohexenone **12a** with hydrazine hydrate afforded the hydrazone derivative **16a**, which was then condensed with benzaldehyde to give **17a**. The structure of these products was confirmed by ^{1}H NMR spectroscopy. Thus, the spectrum of **16a** indicated the amino function at δ 6.60 which, in turn, disappeared from the spectrum of **17a** (which showed the CH=N function at δ 8.24).

Screening of Antiviral Activity.—Tobacco necrosis virus, (strain of group 'D') was used for *in vivo* studies of antiviral activity on kidney bean plants (*Phaseolus vulgaris* var. Suisse Blank) using the method described by Pric.[13] Foliage leaves with a sufficient number of local lesions were collected.

A given constant mass (0.1 g) of **2a**, **4a**, **4b**, **7b**, **11a**, **12a**, **14a**, **15a**, **16a**, and/or **17a** dissolved in 5 ml DMSO was used for testing the antiviral activity. Equal volumes of viral sap and a tested compound were mixed together and allowed to stand in a refrigerator for 10 min. Then 100 μl of the above mixture was rinsed upon the upper surface of the foliage leaves of bean plants, after dusting with carborudum (400 meshes), and the inoculated leaves washed with distilled water.

Healthy bean plants and virus-infected plants were kept for comparison. The number of local lesions developed on each leaf was counted, the mean for 10 leaves was calculated, and a statistical analysis (*t*-test) performed. The percentage of inhibition of the virus was calculated as

$$\% \text{ inhibition} = \frac{\text{control} - \text{treatment}}{\text{control}} \times 100$$

The screening results given in Table 1 indicate that all compounds exhibited antiviral activity against the test organism, with compounds exhibited **11a**, **14a**, and **17a** showing the highest inhibitory effect.

For the cyclization of the aroylmethylcyclopentane-1,3-dione derivatives into cyclopentenopyridazine, the varied substituents increased the inhibition in the order of $CH_3 > OCH_3$. Among the *N*-benzylidene derivatives, the maximum inhibition of 37.1% was observed for **7b**, whereas all the other compounds tested (excluding **2a**) showed a moderate inhibitory activity.

Table 1 Antiviral activities of some of the compounds prepared[a]

Compound	Inhibition (%)	Compound	Inhibition (%)
2a	1.5	**12a**	54.5
4a	33.3	**14a**	73.5
4b	53.8	**15a**	34.8
7b	37.1	**16a**	52.3
11a	72.7	**17a**	62.1

[a] Mean number of control virus = 132.

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