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A new Synthesis of 3-arylpropenoic acids and 5-phenyl-2,4-pentadienoic acid from 4-acetyl-3-arylsydnones and arylaldehydes

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Abstract: The 3-aryl-(4-cinnamoyl)sydnones **3a-l** obtained from 4-acetyl-3-arylsydnones **2a-d** and arylaldehydes, on hydrolysis with conc.H_2SO_4 under mild conditions yielded the 3-arylpropenoic acids **4a-c**. Reusable 3-arylsydnones **1a-d** were also recovered. This simple and practical synthesis was also applied to the preparation of 5-phenyl-2,4-pentadienoic acid **6**.
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Keywords: 3-Aryl-(4-cinnamoyl)sydnones; 3-Arylpropenoic acids; 5-Phenyl-2,4-pentadienoic acid.

1. Introduction

The Perkin, Knoevenagel and Doebner reactions are the best known and simplest synthetic methods for the synthesis of 3-arylpropenoic acids by reaction of arylaldehydes with acetic anhydride / malonic acid / malonic ester in the presence of strong bases like pyridine and piperidine. These reactions have not been much improved, except for the use of cesium salt[1] catalysts in the presence of pyridine and the use of microwave heating as an alternate to thermal conditions.

Many cinnamic acids are bioactive molecules and are also precursors for many pharmacologically active molecules. Esters and amide derivatives of cinnamic acids have been shown to exihibit antibacterial and antifungal activities[2] while 4-methoxy cinnamic acid and its ethylesters have been classified as a new group of glycosidase inhibitors.[3] Some oligomers of this acid have shown to possess inhibitory action of coagulation proteinases[4]. 5-Phenyl-2,4-pentadienoic acid and its derivatives have been considered as potential antimalarials.[5] For such important biologically active acids, we have developed an alternate synthetic method, comparatively better than the earlier known methods.

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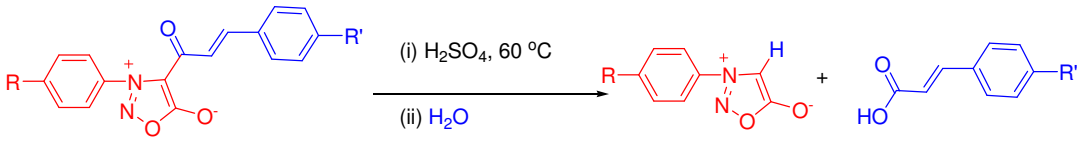
2. Results and Discussion

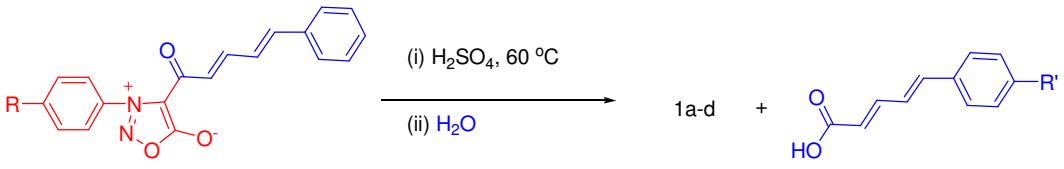
The 3-aryl-(4-cinnamoyl)sydnones[6,7] **3a-l** and the 5-phenyl-1-(3-arylsydnon-4-yl)penta-2,4-dien-1-ones **5a-d** , prepared from 4-acetyl-3-arylsydnones[6,8,,9] **(2a-d)** on heating with conc. H_2SO_4 at ~60 ^oC followed by dilution with water, yielded the corresponding cinnamic acids **4a-c** and the 5-phenyl-2,4-pentadienoic acid **6** respectively. The 3-arylsydnones **1a-d** which are the precursors for 4-acetyl-3-arylsydnones, were also recovered in ~ 70% yield **(Scheme 1).**



Compound	R	R'
3a	H	H
3b	H	OMe
3c	H	NO_2
3d	Cl	H
3e	Cl	OMe
3f	Cl	NO_2
3g	Me	H
3h	Me	OMe
3i	Me	NO_2
3j	OMe	H
3k	OMe	OMe
3l	OMe	NO_2

Compound	R
1a	H
1b	Cl
1c	Me
1d	OMe

Compound	R'
4a	H
4b	OMe
4c	NO_2

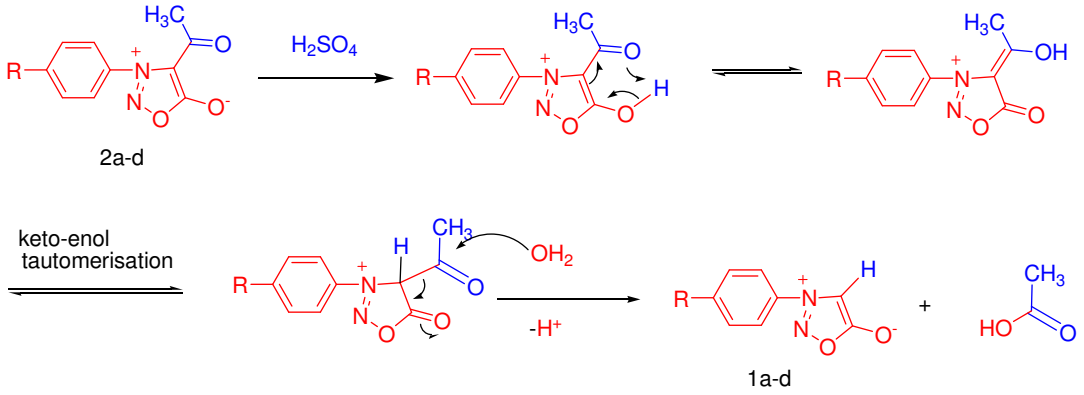


Compound	R
5a	H
5b	Cl
5c	Me
5d	OMe

Scheme 1. Hydrolysis reaction.

The impetus for this work came from the fact, that, though the sydnone ring is readily cleaved by fairly conc. HCl to form monosubstituted hydrazines[10], their 4-acetyl derivatives resist hydrolysis.

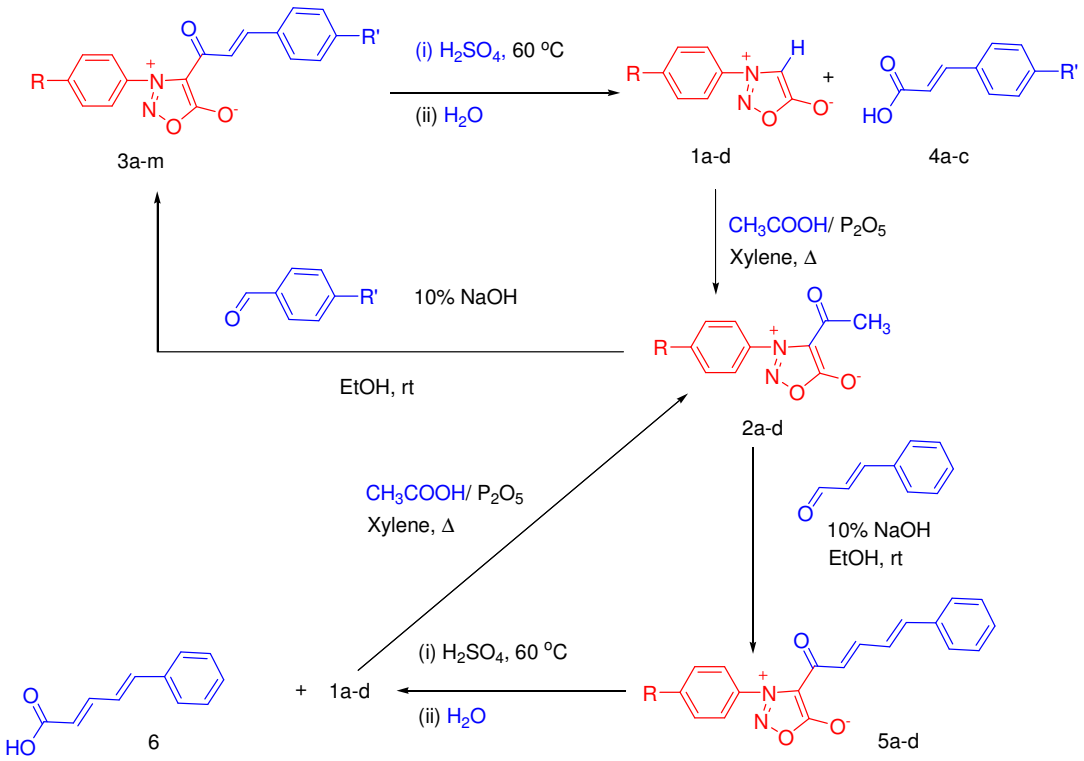
To our knowledge, there is no mechanistic study in detail on H_2SO_4-catalyzed hydrolysis of 4-acetyl-sydnones . Thus, attempted hydrolysis of 4-acetylsydnones **2a-d** by heating with conc.H_2SO_4 at ~ 60^o C for 2 h (these compounds were stable up to this temperature) and dilution with water, yielded the corresponding 3-arylsydnones **1a-d**. The 4-acetylsydnones undergo deacetylation by the cleavage of the sydnone C 4 – acyl carbon bond and it may be mentioned here that examples of such cleavage of aromatic ring carbon – acyl carbon bonds were not found in the literature (e.g. $C_6H_5COCH_3$ to C_6H_6). This facile C-C bond cleavage can be attributed only to the dipolar nature of the sydnone ring and for this reaction we propose a plausible mechanism, which is different from the HCl hydrolysis mechanism[10]**(Scheme 2).** The initial step is assumed to be the protonation at the exocyclic oxygen of the sydnone ring to give the protonated species, stabilized by conjugation with the acetyl carbonyl group. Proton shift to C4 results in a tetrahedral intermediate which rearomatises by C-C bond cleavage. Regaining aromaticity of the dipolar sydnone ring appears to be the driving force for the facile C-C bond cleavage. This is unlike the mechanism of HCl hydrolysis where protonation is proposed to occur at the N2 position followed by nucleophilic attack at C4 and subsequent ring cleavage.



Scheme 2. Proposed mechanism for hydrolysis

We thought to exploit this reaction with the 3-aryl-(4-cinnamoyl)sydnones **3a-l** in the hope of obtaining the corresponding cinnamic acids and also to verify this mechanism. As expected, a mixture of the desired cinnamic acids **4a-c** and the 3-arylsydnones **1a-d** were obtained and result is considered as sufficient evidence for the above proposed mechanism. Compounds with an electron withdrawing group on the cinnamoyl phenyl ring **3c,f,i,l** gave better yields
(arylsydnones ~75% and acids ~ 78%) than those with electron donating goups (arylsydnones ~50% and acids ~ 55%). The identiies of these acids were confirmed by their spectral data and TLC comparisons with the authentic samples.

4-Acetylsydnones **2a-d** react with cinnamaldehyde to give the so far unknown 5-phenyl-1-(3-arylsydnon-4-yl)penta-2,4-dien-1-ones **5a-d** .The structures of these compounds have been confirmed by their spectral data. We have evidenced also for the structures by an X-ray diffraction study[11] of compound **5d,** which showed the E,E-configuration for the diene moiety. Hydrolysis of these compounds as above, yielded the 5-phenyl-2,4-pentadienoic acid **6** (**Scheme 3**)**.** Compound **6** is a rare acid obtained from plants in small quantities. We could find only one report[12] of its synthesis from palladium - catalysed reaction of bromobenzene and 2,4-pentadienoic acid in the presence of triethylamine and it appears that our method is comparatively simple.



Scheme 3. Hydrolysis and acetylation of sydnones.

The 3-arylsydnones **1a-d** recovered in ~ 70% yield, have reused by converting them to the 4-acetylsydnones **2a-d** by a simple reaction with acetic acid in the presence of P_2O_5 in xylene[8].

3. Conclusions

Compared to the Perkin (requires most vigorous conditions and gives the lowest yield), Knoevenagel and Doebner methods, our method appears to be more convenient and efficient because of the following factors

1**.** All the reactions are carried out under mild conditions (3-arylsydnones are readily obtained in good yield, in three steps from primary amines, using inexpensive chemicals and simple reactions[10]). Cinnamoyl sydnones are also prepared in the solid phase by grinding the acetyl compounds and arylaldehydes.

2. The 3-arylsydnone **1** used in stoichiometric quantities in the synthesis of the cinnamoyl derivatives is obtained as one of the products, and recycled by acetylation. More important, any one arylsydnone **1** is sufficient to obtain any number of the unsaturated acids, depending upon the availability of the arylaldehydes.

3. It is noteworthy to mention that the 3-arylsydnone ring remained intact, unaffected by conc. H_2SO_4 upto ~ 60° C. This is an useful finding, since this property can be exploited for reactions of sydnones in conc. H_2SO_4 medium without the undesired cleavage of the sydnone ring.

4. Spectral characterization.

The IR spectra of the newly synthesized compounds **5a-d** showed the $\nu_{C=O}$ of sydnone ring at 1781 cm^{-1} and that of the conjugated $\nu_{C=O}$ at 1644 cm^{-1}. The ^{1}H-NMR (300 MHz) exhibited overlapping of the butadienyl protons and the aromatic protons in the region of δ 6.93-7.60 as a multiplet. The ^{13}C-NMR (300 MHz) spectra of all these compounds showed weak signals equivalent to the number of quaternary carbons while the CH carbons were less than the required number indicating magnetic equivalency of the carbons of the aromatic rings.

5. Experimental:

Melting points were determined in open capillary and are uncorrected. IR spectra were recorded on a Nicolet Impact 410 FT IR spectrophotometer as KBr pellets.^{1}H-NMR spectra were recorded on a Brucker 300 MHz FT-NMR spectrometer in DMSO-d_6 with TMS as an internal standard. Compounds **2a-d and 3a-l** were prepared by literature methods[6,10].

5.1. Synthesis of 5-Phenyl-1-(3-arylsydnon-4-yl)penta-2,4-dien-1-ones (5a-d).

A solution of 4-acetyl-3-arylsydnones **2a-d** (0.01 mol) in NaOH solution (0.5g in 5ml water and 5ml EtOH) and cinnamaldehyde (0.01 mol) was stirred at room temperature for 30 minutes. The yellow solid separated was filtered and washed with water and crystallized from methanol.

5-Phenyl-1-(3-phenylsydnon-4-yl)penta-2,4-dien-1-one (5a): Yield: 60%, M.p. 142-144 ^{o}C, ^{1}H-NMR (DMSO-d_6) (δ ppm) 6.93-7.55 (m, 14H), ^{13}C-NMR (DMSO-d_6) (δ ppm) 126.95(q), 127.58, 128.85, 129.31, 134.11, 135.86, 136.68, 144.22, 144.98(q), 165.54(q), 174.55(q), IR (ν/cm^{-1})$\nu_{C=O}$ (sydnone carbonyl) 1781,$\nu_{C=O}$ (pentadienone carbonyl) 1644. Analysis (% calculated / found) for $C_{19}H_{14}N_20_3$ (Mw 318.31) C:71.69 / 71.62, H:4.43 / 4.41, N:8.80 / 8.78.

5-Phenyl-1-[3-(4-chlorophenyl)sydnon-4-yl]penta-2,4-dien-1-one (5b): Yield: 65%, M.p. 179-181 ^{o}C, ^{1}H-NMR (DMSO-d_6) (δ ppm) 6.93-7.55 (m, 13H), ^{13}C-NMR (DMSO-d_6) (δ ppm) 115.11(q), 122.58, 123.84 (q), 129.85, 127.58, 128.85, 129.31, 134.11, 135.86, 136.68, 144.22, 144.98 (q), 165.54(q), 174.55(q), IR (ν/cm^{-1})$\nu_{C=O}$ (sydnone carbonyl) 1781, $\nu_{C=O}$ (pentadienone carbonyl)1644. Analysis (% calculated / found) for $C_{19}H_{13}N_20_3Cl$ (Mw 352.76)C:64.69 / 64.64, H:3.71 / 3.68, N:7.94 / 7.89.

5-Phenyl-1-[3-(4-methylphenyl)sydnon-4-yl]penta-2,4-dien-1-one (5c): Yield: 65%, M.p. 142-144 ^{o}C, ^{1}H-NMR (DMSO-d_6) (δ ppm) 2.45 (s,3H), 6.90-7.45 (m, 13H), ^{13}C-NMR (DMSO-d_6) (δ ppm) 25.46, 110.45 (q), 118.11, 125.56 (q), 126.95 (q), 127.58, 128.85, 129.31, 134.11, 135.86, 136.68, 144.22, 144.98 (q), 165.54 (q), 174.55 (q), IR (ν/cm^{-1})$\nu_{C=O}$ (sydnone carbonyl) 1781, $\nu_{C=O}$ (pentadienone carbonyl)1644. Analysis (% calculated / found) for $C_{20}H_{16}N_20_3$ (Mw 332.34)C:72.28 / 72.22, H:4.84 / 4.81, N:8.42/ 8.39.

5-Phenyl-1-[3-(4-methoxyphenyl)sydnon-4-yl]penta-2,4-dien-1-one (5d): Yield: 60%, M.p. 169-171 ^{o}C, ^{1}H-NMR (DMSO-d_6) (δ ppm) 3.50 (s,3H), 6.85-7.45 (m, 13H), IR (ν/cm^{-1})$\nu_{C=O}$ (sydnone carbonyl) 1781, $\nu_{C=O}$ (pentadienone carbonyl)1644. Analysis (% calculated / found) for $C_{20}H_{16}N_20_4$ (Mw 348.34) C:68.96 / 68.90, H:4.62 / 4.60, N:8.04/ 7.98.

5.2. Hydrolysis of compounds 2a-d, 3a-l and 5a-d.

The compounds **2a-d, 3a-l** and **5a-d** (0.005 mole) were added in small portions to 3 ml of H_2SO_4 and the solution was stirred at 60 ^oC on a water bath for 2 hrs. The solution after cooling was diluted with ice-cold water and then neutralized with $NaHCO_3$ solution. The solid (3-arylsydnones) was separated by filtration. The filtrate on acidification with dilute HCl gave the unsaturated acids **4a-c**, which were filtered, washed with water and crystallized from water.

Cinnamic acid 4a:Yield: 58%, M.p. 131-133 ^oC(lit[13] 133 ^oC), ^{1}H-NMR (DMSO-d_6) (δ ppm) 6.40 (d, 1H, J_{trans}=16Hz) , 7.40-7.50 (m, 5H, ArH), 7.60 (d, 1H, J_{trans}=16Hz), IR (ν/cm-^{1}) ν_{OH} 3060-2830 (br), $\nu_{C=O}$ 1686.

4-Methoxycinnamic acid 4b: Yield: 50%, M.p. 169-171^{0}C (lit[13] 173 ^oC), ^{1}H-NMR (DMSO-d_6) (δ ppm) 3.95 (s, 3H, OCH_3), 6.20 (d, 1H, J_{trans}=15Hz), 7.30 (d, 1H, J_{trans}=15Hz), 6.80 (d, 2H, J=9Hz, ArH), 7.00 (d, 2H, J=9Hz, ArH), IR (ν/cm-^{1}) ν_{OH} 3060-2830(br), $\nu_{C=O}$ 1640.

4-Nitrocinnamic acid 4c: Yield: 70%, M.p. 282-284 ^oC (lit[13] 286 ^oC), ^{1}H-NMR (DMSO-d_6) (δ ppm) 6.70 (d, 1H, J_{trans}=16Hz), 8.20 (d, 2H, J=9Hz, ArH), 7.75 (d, 1H, J_{trans}=16Hz), 8.70 (d, 2H, J=9Hz, ArH) , IR (ν/cm-^{1}) ν_{OH} 3060-2830(br), $\nu_{C=O}$ 1700, ν_{NO2} 1565 & 1420.

(2E, 4E)-5-Phenyl-2, 4-pentadienoic acid 6: Yield: 75 %, M.p. 162-164 ^oC (lit[14] 163-164 ^oC), ^{1}H-NMR ($CDCl_3$) (δ ppm) 6.35-7.80 (m, 10H), ^{13}C-NMR ($CDCl_3$) (δ ppm) 117.45, 125.80, 128.55, 129.0, 136.55 (q), 142.45, 146.77, 172.55 (q), IR (ν/cm-^{1}) ν_{OH} 3060-2830(br), $\nu_{C=O}$ 1648.

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