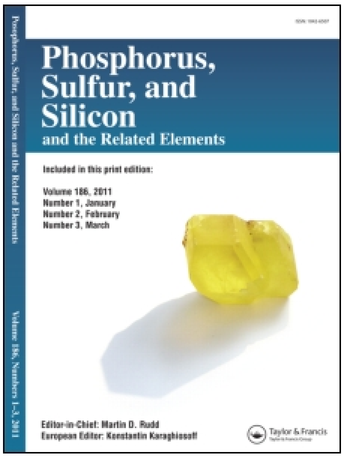

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UTILITY OF β-(3,4.DICHLOROBENZOYL)-α (PHENYLTHIO)PROPIONIC ACID IN HETEROCYCLIC SYNTHESIS

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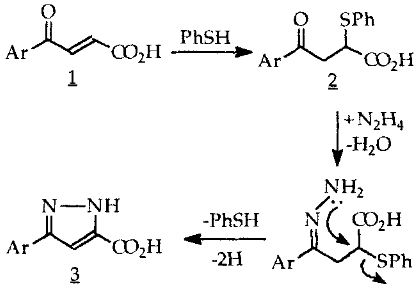
β-(3,4-Dichlorobenzoyl)-α-(phenylthio)propionic acid (2) was prepared via the treatment of β-(3,4-dichlorobenzoyl) acrylic acid (1) with thiophenol in dry benzene. The reactivity of 2 and 1 to different nucleophilic reagents was investigated, the mass spectra of some products are discussed.

β-Aroylacrylic acids are versatile reagents which have been extensively utilized in heterocyclic synthesis. The utility of these compounds has been reported [1–6]. In continuation of this work we report here the results of our investigation on the reaction of 1 and 2 with different nucleophilic reagents. The synthesized compounds are interesting for biological activity studies and for utility in further chemical transformations.

1was treated with thiophenol to give the addition product 2.



Ar=$C_6H_3Cl_2$(3,4)

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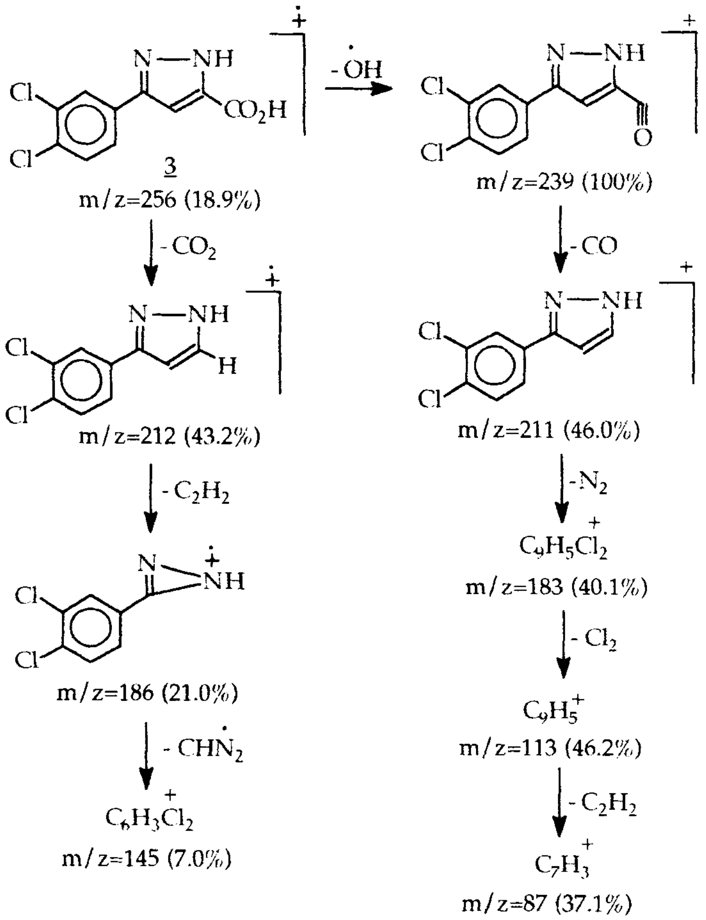
Structure 2 gets support from its reactions with hydrazine hydrate, hydroxylamine hydrochloride, acetic anhydride and/or acetylchloride and thionylchloride followed by combination with anthranilic acid.

The reaction of α-substituted β-aroyl propionic acids with hydrazine hydrate was reported to give pyridazinone derivatives[7,8] and hydrazones[9]. The reaction of 2 with hydrazine hydrate in refluxing ethanol yielded the pyrazole 3.

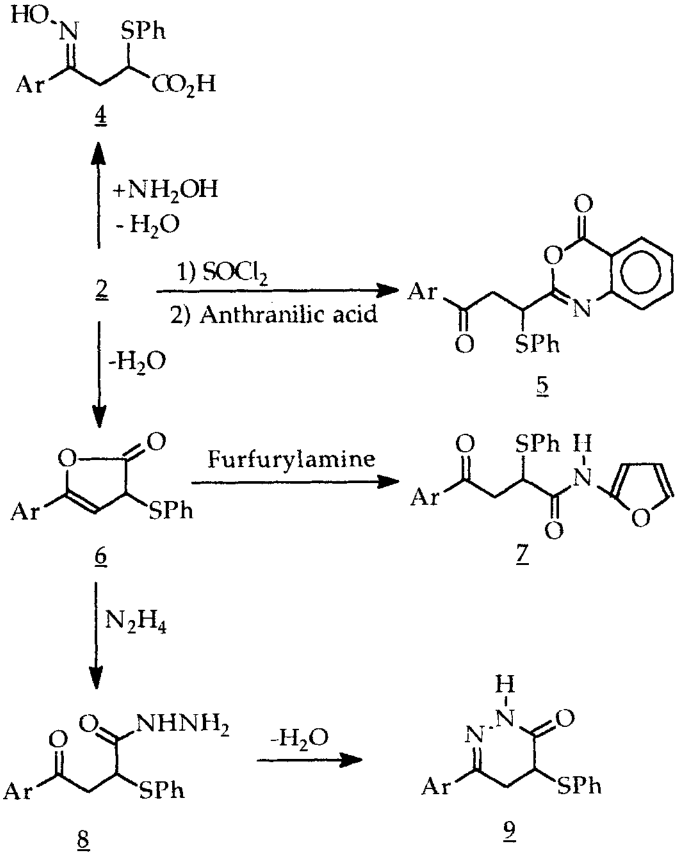
Structure 3 is based on elementary analysis, IR and ^{1}H-NMR data, the colour test for pyrazoles[10,11] and the mass spectrum (scheme 1).



SCHEME 1 Tentative MS fragmentation of 3

On the other hand, the Michael adduct 2 when treated with hydroxylamine hydrochloride in the presence of fused sodium acetate afforded the oxime 4 in quantitative yield. Attempts for cyclization of 4 using acetic anhydride to give an oxazinone derivative failed, which may suggest the Z-configuration for 4.

The butenolide 6 was obtained as light brown crystals in a fairly good yield upon treatment of 2 with acetic anhydride in the presence of fused sodium acetate[12]. The same product was obtained by refluxing 2with acetylchloride for 15 min.



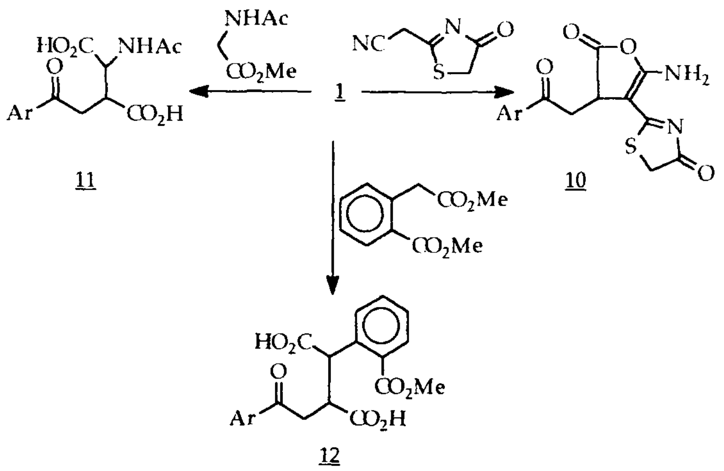
Reaction of 6 with hydrazine hydrate in boiling ethanol yielded the acid hydrazide 8 which readily cyclized in acetic anhydride to give the pyridazinone derivative 9. Furthermore, treatment of furanone 6 with furfuryl amine afforded the propionamide derivative 7.

Treatment of anthranilic acid in dry benzene with β-(3,4-dichlorobenzoyl)-α-(phenylthio)propionyl chloride (obtained from acid 2 with thionyl chloride in dry benzene) gave the 3,1-benzoxazinone derivative 5.

β-Aroylacrylic acid[13,14] are Michael acceptors. Here, we examined the behavoir of 1with active methylene compounds.

The study involves the reaction of 1 with 2-cyanomethyl-thiazolidin-4-one[15], methyl-N-acetylglycinate and dimethylhomophthalate.

1 reacted with 2-cyanomethyl thiazolidin-4-one in the presence of sodium ethoxide to give 10, the Michael adduct (intermediate) was not isolated.

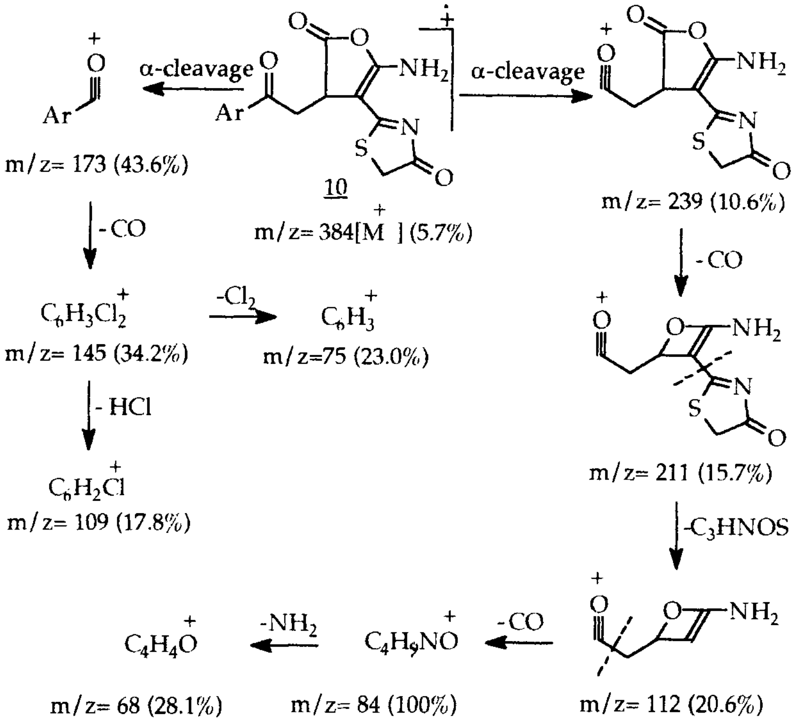


When the acid 1 was allowed to react with methyl-N-acetylglycinate in the presence of sodium hydride, the Michael adduct 11 was formed. The Michael adduct 12 was obtained upon treatment of 1 with dimethyl homophthalate in the presence of sodium ethoxide.

Structures 10-12 are based on data of elementary analysis, IR, ^{1}H-NMR and MS.

EXPERIMENTAL

M.P's are not corrected. IR spectra were measured on a unicam SP 1200 spectrophotometer using KBr Wafer technique. All mass spectra were determined with A.E.I.M.S., 12 single focussing mass spectrophotometer.

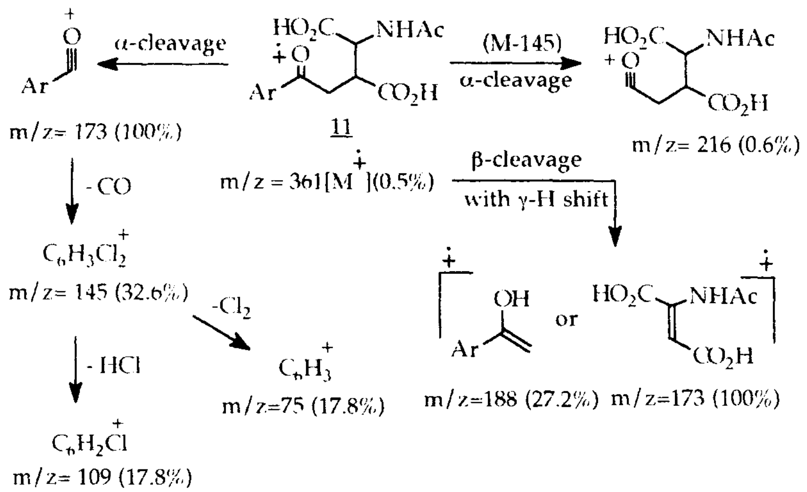


SCHEME 2 Tentative MS fragmentation of 10

The ^{1}H-NMR spectra were taken on a Varian EM 390 instrument operating at 90 MHz in $CDCl_3$

β-(3,4-Dichlorobenzoyl)-α-(phenylthio)propionic acid (2)

A mixture of 1 (2.5 g, 0.01 mol), thiopenol (1.2 g, 0.01 mol) and piperidine (0.5 ml) in dry benzene (50 ml) was stirred for 24 h at room temperature and left overnight. The solvent was evaporated in vacuo and the solid that separated was filtered off, washed with light petroleum ether, dried and recrystallized from a mixture of light petroleum ether (b.p.60–80°C) – benzene (3:1) as colourless crystals (1.92g, 53.3%),m.p. 87–89°C – IR (KBr): 3540 (br.OH), 1704 (CO acid), 1688 (aryl ketone) cm^{-1} – Anal: Calcd. for $C_{16}H_{12}Cl_2O_3S$: C,54.24; H,3.39; S,9.04; Cl,19.77. Found: C,



SCHEME 3 Tentative MS fragmentation of 11

54.36; H, 3.08; S, 8.37; Cl, 20.1 – MS : m/z (%) = 354 [M$^+$, 2%], 336 [M$^+$-H$_2$O ; 13.1 %], 310 [M$^+$-CO2, 2.3%], 173 [Ar-C=-O$^+$, 91.7], 145 [C6H3Cl$_2$$^+$, 30.7%], 110 [PhSH; 100%] and 77 [C$_6$H$_5$$^+$, 13.8%] beside the M+2 and M+4 peaks – ^{1}H-NMR : δ 10.93 (s, 1H COOH), 8.0–7.0 (m, 8H, arom. H), 4.4 (m, 1H), 3.7–3.9 (d,d, 1H) and 3.15–3.25 (d,d, 1H).

3-(3,4-Dichlorophenyl)-pyrazole-5-carboxylic acid (3)

A mixture of 2 (1.9 g, 0.005 mol) and hydrazine hydrate (0.25 g, 0.005 mol, 80%) in absolute ethanol (30 ml) was refluxed for 3h (TLC). After concentration and cooling, the solid that deposited was collected and recrystallized from ethanol as white crystals (0.8g, 58.3%), m.p. 248–250°C – Anal : Calcd. for $C_{10}H_6Cl_2N_2O_2$: C, 46.87; H, 2.34; N, 10.94. Found: C, 47.16, H, 2.56; N, 11.34 – IR (KBr): νc=o (acid) at 1698 cm^{-1}, νC=N at 1628 cm^{-1}, νNH at 3280 cm^{-1} and νOH at 3500–3600 cm^{-1}.

4-(3,4-Dichlorophenyl)-4-hydroxyimino-2-(phenylthio)butanoic acid (4)

A mixture of 2 (1.9g, 0.005 mol), hydroxylamine hydrochloride (0.6g, 0.007 mol) and anhydrous sodium acetate (0.83 g, 0.007 mol) was heated on oil bath with stirring for 3h. The reaction mixture was poured into water and stirred for 0.5h. The solid deposited was filtered off, washed with hot water, dried and recrystallized from ethanol to give 4 as colourless crystals (1.13 g, 62.9%), m.p. 183–6°C – IR (KBr): 3200–3533 (br. OH), 1704 (CO acid), 1631 (C=N) cm^{-1} – ^{1}HNMR($CDCl_3$) : 10.8 (s, 1H, COOH), 9.2 (s, 1H, NOH), 7.6–7.2 (m, 8H, arom.H) 4.3 (m, 1H, CH), 3.1 (d,d, 1H), 2.9 (d,d, 1H, CH_2) – MS:325 [M^+- CO2] – Anal : Calcd. for $C_{16}H_{13}Cl_2NO_3S$: C, 52.03; H, 3.52; N, 3.79; S, 8.67; Found : C, 51.83; H, 3.91; N, 4.22; S, 8.80.

β-(4-Oxo-3,1-benzoxazin-2-yl)-β-phenylthio-3,4-dichloropropiophenone(5)

To a solution of 2 (3.5g, 0.01 mol) in dry benzene (50 ml) thionyl chloride (10 ml) was added dropwise with stirring. The reaction mixture was refluxed for 3h. The excess of thionyl chloride was evaporated with the solvent in vacuo and the crude mixture was dissolved in dry benzene (50 ml) and added to a solution of anthranilic acid (1.4g, 0.001 mol) in dry benzene (20ml), then refluxed for 6h (TLC). The reaction mixture was poured into ice water and extracted with ether. Evaporation of ether left a crude solid product which recrystallized from light petroleum (b.p. 80–100°C) to give 5 as brown crystals (1.93 g, 42.9%),m.p. 263–5°C – IR(KBr): 1762 (CO δ-lactone), 1693 (CO) cm^{-1} – ^{1}HMNR($CDCl_3$) : δ 7.6–6.8 (m, 12H, arom.H), 4.3 (m, 1H), 3.4 (d,d,2H) – MS: 455 [M^+; 0.7%], 411 [M^+-CO_2, 43%], 110 [$PhSH^+$, 100%], 145 [$C_6H_3Cl_2^+$, 33.7%] – Anal: Calcd. for $C_{23}H_{15}Cl_2NO_3S$: 60.66; H, 3.3; N, 3.3; S, 7.03; Found : C, 60.07; H, 3.35; N 3.01; S, 7.33 .

5-(3,4-Dichlorophenyl)-3-phenylthio-2,3-dihydrofuran-2-one(6)

A mixture of 2 (3.54g, 0.01 mol) and freshly distilled acetic anhydride (30 ml) containing fused sodium acetate (2g, 0.025 mol)was heated on a steam bath for 6h (TLC). The reaction mixture was poured into water and the solid deposited was filtered off, washed several times with water, dried and recrystallized from a mixture of light Pertoleum ether (b.p. 40–60°C) – benzene (3:1) to give 6 as orange crystals (1.2g, 35.7%). m.p. 137–9°C – IR(KBr): 1782(5-membered γ-lactone), 1605 (C=C) cm^{-1} – ^{1}HNMR (CDC13):δ 7.6–7.3(m, 8H arom.H),6.3(s, 1H, C-4), 5.1 (s, 1H, C-3) –

Anal : Calcd. for $C_{16}H_{10}Cl_2O_2S$: C, 57.14; H, 2.98; S, 9.5; Cl, 20.83. Found: C, 57.18; H, 3.31; S, 9.0; Cl, 20.46.

β-(3,4-Dichlorobenzoyl)-N-(2-furomethyl)-α-(phenythio)propionamide (7)

A mixture of 6 (1 g, 0.002 mol) and furfurylamine (0.2g, 0.002 mol) in absolute ethanol (30ml) was refluxed for 6h. The excess solvent was removed and the solid that separated was filtered off, dried and recrystallized from ethanol to give 7 as buff crystals (0.72 g, 55.8%), m.p. 210–12°C – IR (KBr): 3312 (NH), 1689 (CO), 1642 (CO amide) cm^{-1} ^{1}HNMR (CDCl3): δ 8.1–7.6 (m, 8H, aryl H), 7.33 (s, 1H), 6.3 (s, 1H) furyl H, 4.0 (m, 1H), 3.8 (d,d, 2H), 3.1 (s,2H), 1.53, (s, 1H) – Anal: Calcd. for $C_{21}H_{17}Cl_2NO_3S$: C, 58.19; H, 2.9; N, 3.23; S, 7.39.Found : C, 58.38; H, 3.13, N, 3.16; S, 7.49.

β-(3,4-Dichlorobenzoyl)-α-(phenylthio)propionohydrazide (8)

To a solution of 6 (2.1 g, 0.006 mol) in absolute ethanol (30 ml) hydrazine hydrate (0.3 g, 0.006 mol, 80%) was added and the mixture was refluxed for 2h (TLC). Evaporation of ethanol left a solid product which was collected and recrystallized from ethanol to give 8 as colourless crystals (1.4 g, 60.8%), m.p. 189–190°C – IR (KBr) :3270–3312–3410 (NH), 1690 (CO arylketone), 1671 (CO hydrazide) cm^{-1} – MS : 368 [M^+, 11.2%] – Anal: Calcd.for $C_{16}H_{14}Cl_2N_2O_2S$: C, 52.17; H, 3.8; N, 7.6; S, 8.69. Found: C, 52.62; H, 3.73; N, 8.08; S, 8.14.

3-(3,4-Dichlorobenzoyl)-5-phenylthio-1,4,5,6-tetrahydropyridazin-6-one (9)

A mixture of 8 (1.3g, 0.003 mol) and acetic anhydride (15ml) was heated on a steam bath for 2h. The cooled mixture was poured into ice-water and the solid deposited was filtered off, washed several times with water, dried and recrystallized from ethanol to give 9 as pale yellow crystals (0.6g, 50%), m.p. 240–2°C – IR (KBr): 3210–3360 (br. NH), 1733 (CO), 1636 (C=N) cm^{-1} – MS: 350 [M^+, 16%], 307 [M±HCNO, 37.7%], 110, [$PhSH^+$, 100%] – Anal: Calcd. for $C_{16}H_{12}Cl_2N_2OS$: C, 54.86; H, 3.43; N, 8.0; S, 9.14. Found: C, 54.72; H, 3.3; N, 7.7; S, 8.78.

Michael adducts

To a suspension of 1 (2.5g,0.01 mol) and 2-cyanomethyl thiazolidin-4-one[15], methyl N-acetylglycinate or dimethylhomophthalate (0.01 mol) in absolute ethanol (50ml), soduim ethoxide and/or sodium hydride (0.03 mol) was added. The whole mixture was stirred at room temperature for 30 min, then reflux for 6h, poured into hydrochloric acid. The solid that separated was filtered off, dried and recrystallized from proper solvent to give 10-12 .

5-Amino-3-(3,4-dichlorobenzoylmethyl)-4-(4-oxo-thiazolidin-2-yl)-2,3-dihydrofuran-2-one (10)

recrystallized from ethanol as orange crystals (1.72g, 43.7%), m.p. 60–62°C – IR (KBr): 3237–3350 (NH), 1776 (CO δ-lactone), 1742 (CO thiazolidinone), 1672 (CO aryl ketone) cm^{-1} – Anal : Calcd. for $C_{15}H_{10}Cl_2N_2O_4S$: C, 46.87; H, 2.6; N, 7.29; S, 8.33. Found : C, 47.16; H, 3.0; N, 7.23; S. 8.21 – MS: (cf. scheme 2).

2-Acetylamino-3-carboxy-4-(3,4-dichlorobenzoyl)butanoic acid (11)

recrystallized from benzene as colourless crystals (2.3g, 62.3%), m.p. 176–8°C – Anal: Caled for $C_{14}H_{13}Cl_2NO_6$:C,46.53; H,3.6:N,3.88 Cl, 19.39 Found : C, 46.35; H, 3.62; N, 4.27; Cl, 18.91-IR (KBr) 1702 (CO acid), 1684 (CO ketone), 1646 (CO amide), 3396–3528 (br-NH, OH) cm^{-1} ^{1}. MS: (cf. Scheme 3).

2-o-Carbomethoxyphenyl-3-carboxy-4-(3.4-dichlorobenzoyl)-butanoic acid (12)

recrystallized from ethanol as buff crystals (2g, 43.5%), m.p.212–4°C – Anal: Calcd. for $C_{20}H_{16}Cl_2O_7$: C, 54.79; H, 3.65; Cl,15.98. Found: C, 54.32; H, 4.07; Cl 16.13 -IR(KBr): 1719 (CO ester), 1708–1700 (CO acid), 1688 (CO Ketone), 3447 (br. OH) cm^{-1} – MS : 396 [M^+-CO_2].

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