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Note

Chemoselective hydrazine addition to diethyl 2-(2,3-dioxo-1,3-diarylpropyl)malonates and a tandem deesterification

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The structural features of the product of the chemoselective reaction of hydrazine on only one of the ketones in a gem diester system with two keto groups by hydrazinium sulfate and hydrazine hydrate are described. A tandem deesterification has also been noticed during the reaction with hydrazine hydrate.

Keywords: 1,2-Ketones, hydrazones, oxidation, chemoselectivity, deesterification, tandem reaction.

In continuation of our interest in diethyl 2-(2,3-dioxo-1,3-diarylpropyl)malonates **1** (ref.1) as precursors for construction of heterocyclic compounds, it is planned to introduce hetereo atoms in these compounds by reaction with nitrogen nucleophiles like hydroxylamine and hydrazine. Thus the reaction of diketone **1** (ref.1) with hydrazine has been investigated. The chemoselectivity observed during this reaction and the interesting structure analysis of the resultant compound are presented in this article.

In continuation of our search for potential precursors towards new set of heterocyclic compounds[2], it has been planned to prepare a new set of diketones, diethyl 2-(2,3-dioxo-1,3-diarylpropyl)-malonates [ArCOCOCH{CH(COOEt)$_2$}Ar][1] and to investigate the utility of these diketones possessing two carbonyl and carbethoxy functionalities as a synthon for heterocycles like diazepinone derivatives.

A mixture of diketones **1** (ref.1) and hydrazinium sulfate in the mole ratio 1:5 has been refluxed in ethanol for about 2 hr in the hope of functionalizing all the groups vulnerable for the attack of nuleophile. A single product **2** has been isolated and the unreacted diketone and hydrazinium sulfate are the remaining components of the reaction mixture. Compound **2** has been identified to be diethyl 2-(3-hydrazono-2-oxo-1,3-diarylpropyl) malonate from the IR and NMR spectral data (**Scheme I**). The same product is obtained quantitatively, when equimolar ratio of substrate and reactant are taken.

In the ^{13}C NMR speetrum of **2c**, one of the keto carbonyl signals has disappeared with a new carbon appearing at δ 142.7. It is clear that hydrazine addition has taken place with one of the carbonyl leaving the other undisturbed. The fact that benzoyl carbonyl carbon has undergone the reaction but not the other one has been confirmed by the HMBC relation between the signal at δ 7.07 with the carbon at δ 142.7. The signal at δ 6.27, which is due to NH_2 hydrogens, also has HMBC connection with this azomethine carbon.

Even in the presence of excess hydrazinium sulfate, only one product was obtained suggesting that only one of the carbonyl has undergone the reaction, while the other carbonyl and ester groups are not affected. Thus chemoselectivity has been noticed in the reaction. The other carbonyl may not be electrophilic enough due possibly to the enolic form involved in hydrogen bonding.

The structure of **2** has also been confirmed by single crystal X-ray analysis[3]. The results are summarized in **Table I** and the ORTEP and packing diagrams of **2c** are given in **Figure 1** and **Figure 2** respectively. In the solid state, one of the hydrogens of the NH_2 group (H22B) of one molecule is involved in inter molecular hydrogen bonding with the carbonyl oxygen of the other molecule (O3) thus forming a linear chain (N22–H22B = 0.860 Å, H22B–O3 = 2.116 Å, N22–O3 = 2.962 Å and N22–H22B–O3 = 167.9°; symmetry code: x, -y+1, z+1/2). The other hydrogen on the NH_2 group (H22A) of the molecule is involved in inter molecular hydrogen bonding with the carbonyl oxygen (O21) of the ester functionality (N22–H22A = 0.860 Å, H22A–O21 = 2.323 Å, N22–O21 = 3.100 Å and N22–H22A–O21 = 150.4°; symmetry code: x-1/2, y-1/2, z).

A significant chemoselectivity in the reaction of hydrazinium sulfate with diketone led to the study of this reaction with hydrazine hydrate instead of hydrazine sulfate. Thus a mixture of diketone **1a** and hydrazine hydrate in ethanol was refluxed for about 2 hr in a water bath. Upon working up, the crude reaction-mixture is found to contain two products

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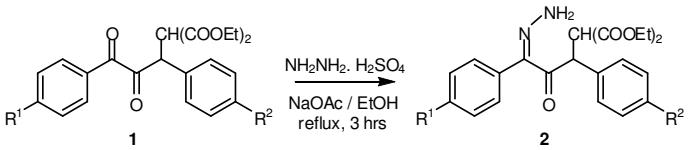


	R^1	R^2
a	H	H
b	H	CH_3
c	Cl	CH_3

Scheme I

Table I — Crystal data and structural refinement for **2c**

Parameters	**2c**
Empirical formula	$C_{23}\ H_{25}\ Cl\ N_2\ O_5$
Formula weight	444.90
Temperature	293 (2) K
Wavelength	0.71069 Å
Crystal system, Space group	Monoclinic, C c
Unit cell dimensions	a = 15.288(5) Å; α = 90.00°; b = 13.902(5) Å;
β = 94.942(5)°; c = 11.217(5) Å; γ = 90.00°	
Z, Volume	4, 2375.1(16) $Å^3$
Density (calculated)	1.244 Mg/m^3
Absorption coefficient	0.195 mm^{-1}
F(000)	936
Crystal size	0.20 x 0.17 x 0.15 mm
Theta range for data collection	2.61 to 24.97 deg.
Index ranges	0<=h<=18, -1<=k<=16, -13<=l<=13
Reflections collected	2367
Independent reflections	2177 [R_{int} = 0.0206]
Absorption correction	Psi-scans
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2177 / 2 / 282
Goodness-of-fit on F^2	1.043
Final R indices [I>2σ(I)]	R_1 = 0.0429, wR_2 = 0.1293
R indices (all data)	R_1 = 0.0570, wR_2 = 0.1308
Largest diff. peak and hole	0.190 and -0.244 e. $Å^{-3}$

along with the unreacted diketone (**1a** = 14%, **2a** = 40% and **3a** = 46%) as determined from ^{1}H NMR spectrum of crude reaction product (**Scheme II**). The two products have been isolated by column chromatography (pet.ether:ethyl acetate = 95:5). One of the products has been identified as **2a**.

The ^{1}H NMR spectrum of the other product, **3a**, has signals due to only one carbethoxy group. The presence of three doublets of doublets at δ 2.68, 3.30 and 5.42 clearly suggests a -CH_2CH- group. A two hydrogen singlet is noticed at δ 6.27 as observed in **2c** indicating the presence of NH_2 group. The ^{13}C NMR spectrum also supports the presence of -CH_2CH- group and here again, one of the carbonyls has been converted into azomethine carbon. As the aryl hydrogen has HMBC contour with the azomethine carbon and the methylene hydrogen has HMBC contour with the carbonyl carbon at δ 196.8, **3a** is assigned as ethyl 5-hydrazono-4-oxo-3,5-diphenyl-pentanoate unambiguously.

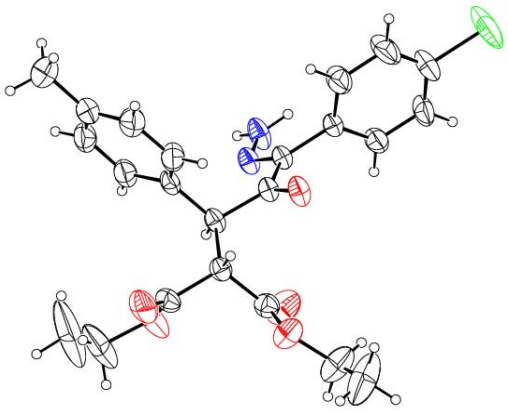


Figure 1 — ORTEP diagram of diethyl 2-[3-(4-chlorophenyl)-3-hydrazono-1-(4-methylphenyl)-2-oxopropyl]malonate (**2c**)

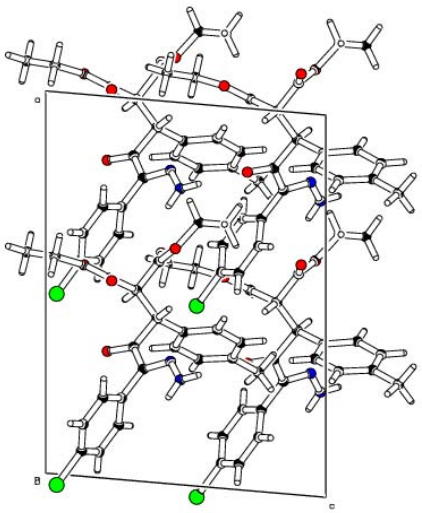


Figure 2 — Packing diagram of diethyl 2-[3-(4-chlorophenyl)-3-hydrazono-1-(4-methylphenyl)-2-oxopropyl]malonate (**2c**)

It is to be noted that the course of the reaction with hydrazine hydrate is different from that with hydrazinium sulfate. When hydrazinium sulfate is used, the initially formed hydrazone seems to have reacted with one of carbethoxy groups to give a seven-membered cyclic amide which have undergone hydrolysis to give **3a** as described speculatively in **Scheme III**. A similar deesterification has already been noticed[2b].

Thus a chemoselective hydrazine addition has been noticed during the reaction of diketone diethyl 2-(2,3-dioxo-1,3-diarylpropyl)malonates with hydrazinium sulfate. However, when hydrazine hydrate was employed, tandem deesterification has also taken place.

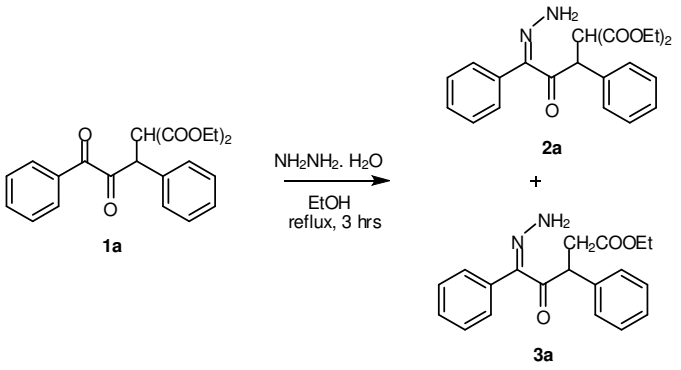
Experimental Section

Melting points are uncorrected. One and two dimensional NMR spectra were recorded on a Bruker 300 MHz instrument in $CDCl_3$ using TMS as internal standard. Chemical shifts are given in parts per million (δ-scale) and coupling constants are given in Hertz. IR spectra were recorded on a Jasco FT IR instrument (KBr pellet/$CHCl_3$ solution). The single crystal X-ray data were collected on a Nonius MACH3 kappa diffractometer with MoK_α radiation (λ = 0.71069 Å). The structure was solved by direct methods from SHELXS-97 and refined by full matrix least squares on F^2 by SHELXL-97.

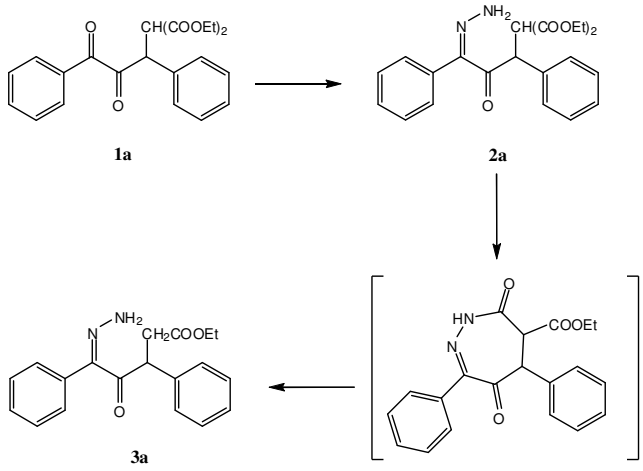
General procedure for the reaction of diethyl 2-(2,3-dioxo-1,3-diarylpropyl)malonate, 1, with hydrazinium sulphate. To a warm solution of 0.47 mmole of diethyl 2-(2,3-dioxo-1,3-diarylpropyl)-malonate[1] in 20 mL of ethyl alcohol, 0.30 g (2.35 mmoles) of hydrazinium sulphate and 0.19 g (2.35 mmoles) of anhydrous sodium acetate in 10 mL water was added dropwise. The reaction-mixture was refluxed on a water bath for 3 hr. The reaction-mixture was poured into crushed ice and extracted with chloroform. The product **2** was purified by column chromatography using silica gel (60-120 mesh) with pet. ether:ethyl acetate (90:10).

Diethyl 2-[3-hydrazono-2-oxo-1,3-diphenylpropyl]malonate, 2a. Colourless solid (78%) m.p. 88-89°C. IR ($CHCl_3$): 3408, 3278, 2987, 2933, 2875, 1730, 1655, 1556, 1319 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 3.92 (q, *J* = 7.2 Hz, 2H), 4.18* (q, *J* = 7.2 Hz, 2H), 4.39 (d, *J* = 12 Hz, 1H), 5.63 (d, *J* = 12 Hz, 1H), 6.29 (s, 2H), 7.08 (d, *J* = 7.5 Hz, 2H), 7.21-7.40 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 14.0, 50.2, 55.4, 61.2, 61.7, 127.4, 128.5, 128.9, 129.0, 129.1 , 131.4, 135.7, 143.8, 168.2, 168.4, 195.3. Anal. Calcd. for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.71; H, 6.15; N, 7.11%.

Diethyl 2-[3-hydrazono-1-(4-methylphenyl)-2-oxo-3-phenylpropyl]malonate, 2b. Colourless solid (61%) m.p. 83°C. IR ($CHCl_3$): 3409, 3280, 2985, 2925, 2873, 1747, 1732, 1653, 1556 cm^{-1}; ^1H NMR



Scheme II



Scheme III

(300 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 2.29 (s, 3H), 3.94 (q, *J* = 7.2 Hz, 2H), 4.20* (q, *J* = 7.2 Hz, 2H), 4.37 (d, *J* = 12 Hz, 1H), 5.60 (d, *J* = 12 Hz, 1H), 6.26 (s, 2H), 7.07-7.43 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 14.0, 21.1, 49.8, 55.4, 61.1, 61.6, 128.5, 128.9#, 129.0, 129.1, 129.2, 132.5, 137.0, 143.9, 168.2, 168.5, 195.5. Anal. Calcd. for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.37; H, 6.43; N, 6.85%.

Diethyl 2-[3-(4-chlorophenyl)-3-hydrazono-1-(4-methylphenyl)-2-oxopropyl] malonate, 2c. Colourless solid (67%) m.p. 131°C. IR ($CHCl_3$): 3384, 3209, 2987, 2925, 1732, 1641, 1539, 1487 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 2.30 (s, 3H), 3.94 (q, *J* = 7.2 Hz, 2H), 4.17* (q, *J* = 7.2 Hz, 2H), 4.36 (d, *J* = 12.0 Hz, 1H), 5.56 (d, *J* = 12.0 Hz, 1H), 6.27 (s, 2H), 7.07-7.09 (m, 4H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 14.0, 21.1, 49.8, 55.5, 61.2, 61.7, 127.3, 128.4, 128.9, 129.3, 129.4, 130.5, 132.4, 137.1, 142.7, 168.2, 168.5, 195.3. Anal. Calcd. for $C_{23}H_{25}ClN_2O_5$: C, 62.09; H, 5.66; N, 6.30. Found: C, 62.14; H, 5.71; N, 6.33%.

Reaction of diethyl 2-(2,3-dioxo-1,3-diphenylpropyl) malonate (1a) with hydrazine hydrate. A

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* Disturbed quartet.

mixture of 0.2 g (0.52 mmole) of diethyl 2-(2,3-dioxo-1,3-diphenylpropyl)malonate and 0.130 g (2.6 mmoles) of hydrazine hydrate in 20 mL of ethyl alcohol was refluxed on a water bath for 2 hr. The reaction-mixture was poured in to crushed ice and extracted with chloroform. The reaction-mixture was subjected to column chromatography using silica gel (60-120 mesh) with an eluent of pet. ether: ethyl acetate (95:5) to get two products, **2a** (40%) and **3a** (46%).

Ethyl 5-hydrazono-4-oxo-3,5-diphenylpentanoate 3a. Viscous liquid. IR ($CHCl_3$): 3477, 3315, 2983, 2939, 2906, 2873, 1745, 1730, 1674, 1564, 1369, 1313 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.2 Hz, 3H), 2.68 (dd, *J* = 16.8, 5.1 Hz, 1H), 3.30 (dd, *J* = 16.8, 10.2 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 5.42 (dd, *J* = 10.2, 5.1 Hz, 1H), 6.23 (s.2H), 7.09 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.21-7.45 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 37.8, 46.4, 60.5, 127.0, 128.4, 128.6, 128.9, 129.0, 129.1, 129.2, 139.0, 144.3, 172.3, 196.8.

Acknowledgements

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References

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3 Crystallographic data (excluding structure factors) for **2c** have been deposited with the Cambridge Crystallographic Data Centre (CCDC Number 614665). Copies of the data can be obtained, free of charge, by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK (email: data_request@ccdc.cam.ac.uk; fax: +44 1223 336033).

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