THE REACTION OF ISATIN WITH ALKOXYCARBONYLMETHYLENE(TRIPHENYL)PHOSPHORANES IN ACETIC ANHYDRIDE

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Abstract : Isatin (**1**) reacted with alkoxycarbonylmethylene(triphenyl)phosphoranes (**2**) in acetic anhydride as a solvent at room temperature for 1 h to form a mixture consisting mainly of orange yellow crystalline products of alkyl (1,2-dihydro-2-oxo-3H-indol-3-yl)acetates (**3**) together with a small amount of alkyl (1-acetyl-1,2-dihydro-2-oxo-3H-indol-3-yl)acetates (**5**) as yellow crystals. Heating compounds **3** in acetic anhydride for 4 h at 110°C afforded N-acetyl derivatives **5** with unexpected products of structure **6**. The structural assignments of the new compounds are based on the spectroscopic results.

Introduction

In a previous paper (1), we have reported that the reaction of isatin (**1**) with alkoxycarbonylmethylene (triphenyl)phosphoranes (**2**) in the usual solvents such as benzene and ethanol led to the formation of alkyl (1,2-dihydro-2-oxo-3H-indol-3-yl)acetates (**3**) in good yields. In the present article, we describe the behaviour of dione **1** towards its reaction with ylides **2**, using acetic anhydride as a solvent.

Results and Discussions

We have found that isatin (**1**) reacted with stabilized methylenephosphoranes (**2**) in acetic anhydride as a solvent at room temperature for 1 h to form a mixture consisting mainly of compounds **3** together with a small amount of yellow crystalline products of alkyl (1-acetyl-1,2-dihydro-2-oxo-3H-indol-3-yl)acetates (**5**) as (*E*)-isomer (Scheme 1).

These compounds were separated by column chromatography on silica gel. Triphenylphosphine oxide was also isolated and identified. The identity of compounds **3** was proved by comparison with authentic samples (1) (mp, mixed mp and comparative IR spectra). The assigned structure of the products **5** was established from the elemental analyses, IR, ^{1}H NMR and mass spectra. The IR spectra of compounds **5** showed the presence of two strong absorption bands appeared at 1760 cm^{-1}, due to the carbonyl of the ester (2) and at 1710 cm^{-1}, for both carbonyl of the acetyl group and amidic carbonyl (2). The ^{1}H NMR spectrum of **5a**, taken as an example, revealed the presence of two singlets at δ 2.72 and 3.89 ppm, corresponding to the protons of acetyl and methoxy groups, respectively. Another singlet appeared at δ 6.92 ppm, denoting the exocyclic vinyl proton (=CH-). The phenyl protons at C-5 and C-6 appeared as two triplets of doublets, due to the di-*ortho/meta* coupling (J_{HH} = 7.8 and 1.2 Hz) with chemical shift values δ 7.24 and 7.45 ppm. The

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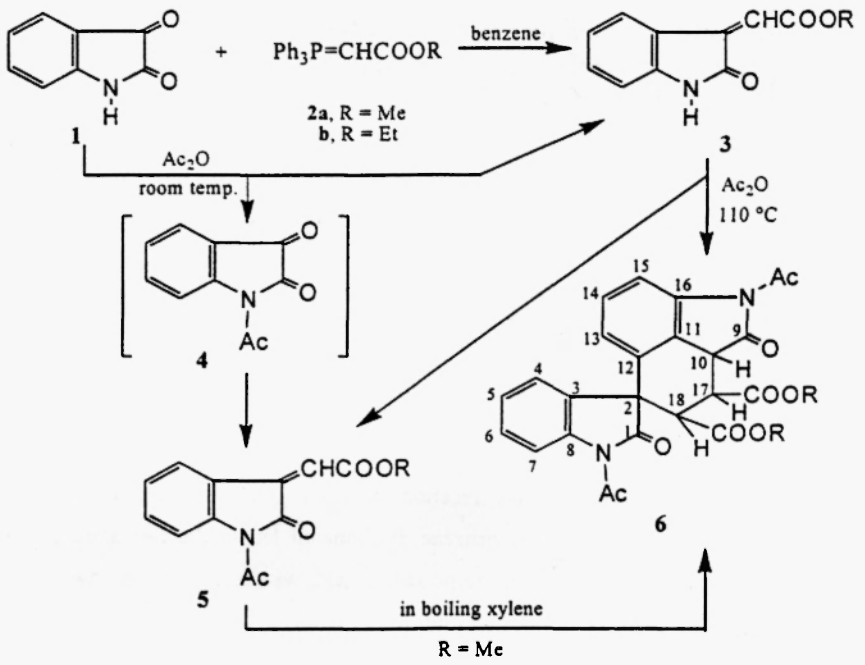
other two phenyl protons at C-4 and C-7 exhibited two doublets of doublets at δ 8.69 and 8.30 ppm which are characteristic for *ortho/meta* coupling (J_{HH} = 8.2 and 1.2 Hz).

Compounds **5** were also obtained in good yields by stirring N-acetylisatin (**4**) with ylides **2** in benzene solution or acetic anhydride.

Furthermore, we studied the reaction of alkyl (1,2-dihydro-2-oxo-3H-indol-3-yl)acetates (**3**) with acetic anhydride. At room temperature no reaction takes place, however, when the same mixture was heated under reflux in an oil bath at



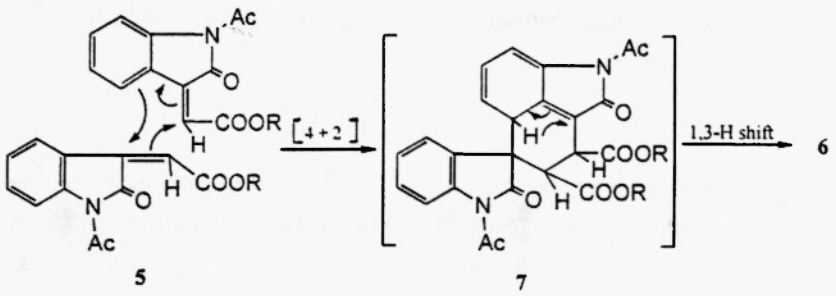
Scheme 1

110°C for about 4 h afforded N-acetyl derivatives **5** with unexpected products 6 (Scheme1).

In another experiment, compounds **6** were formed in quantitative yields by heating alkyl (1-acetyl-1,2-dihydro-2-oxo-3H-indol-3-yl)acetates (**5**) in boiling xylene for 20 h.

Correct elemental analyses, molecular weight determination (MS) and compatible spectroscopic results supported the identity of the dimeric spiro-products 6.

The IR spectra exhibit two strong absorption bands at 1770 cm^{-1}, corresponding to the carbonyl-ester and at 1717 cm^{-1}, due to the carbonyl-acetyl and amidic carbonyl. The ^1H NMR spectrum of **6a**, taken as an example, reveals the presence of two singlets at δ 2.66 and 2.74 ppm, for the protons of the two acetyl groups (6H), and another two singlets at δ 3.15 and 3.90 ppm, attributable to protons of two methoxy groups in the esters. It also shows a triplet centered at δ 3.22 ppm with coupling constant J_{HH} = 11.8 Hz, for a proton at C-17 which is vicinal to both other two protons at C-18 and C-10, appeared as two doublets at δ 4.05 ppm (J_{HH} = 11.7 Hz) and at δ 4.13 ppm (J_{HH} = 11.8 Hz). These coupling constant values indicate that the three vicinal protons are in position axial-axial configuration (3). The phenyl region in the spectrum shows the resonance of seven aromatic protons as four doublets at δ 6.37, 6.80, 7.99, 8.31 ppm and three triplets at δ 7.06, 7.16, 7.35 ppm. These data were supported by ^{13}C NMR results (Experimental).



Scheme 2

The proposed mechanism for the formation of the dimeric structure **6** illustrated in Scheme 2 shows the N-acetyl derivatives **5** initially undergo Diels-Alder cyclization with another molecule to give [4+2] cycloadducts **7** which are followed by 1,3-H shift to form compounds **6**. From the above results which are summarized in Table 1, it seems logical to consider that the conversion of small amount of dione **1** into *mono*-alkenes **5** by its reaction with ylides **2** in acetic anhydride at room temperature *via* the formation of N-acetylisatin intermediate (**4**) as shown in Scheme 1. This is correlated to the heat released from the reaction (exothermic).

Table 1

Reaction conditions and the products of the reaction of diones **1** and **4** with stabilized ylides **2** and the effect of acetic anhydride on compounds **3**.

Reactants	Solvent	Reaction temperature (°C)	Reaction time (h)	Reaction products (%)					
				3a	3b	5a	5b	6a	6b
1 + 2a	Acetic anhydride	R[a]	1	67	-	11	-	-	-
1 + 2b	Acetic anhydride	R[a]	1	-	65.3	-	14.7	-	-
4 + 2a	Benzene	R[a]	6	-	-	73	-	-	-
	Benzene	R[b]	1	-	-	68	-	-	-
	Acetic anhydride	R[a]	2.5	-	-	76	-	-	-
4 + 2b	Acetic anhydride	R[a]	2.5	-	-	-	78	-	-
3a	Acetic anhydride	R[a]	24	no reaction					
	Acetic anhydride	110	4	-	-	17.8	-	18.5	-
3b	Acetic anhydride	110	4	-	-	-	21	-	19.7

[a] Room temperature
[b] Reflux temperature

Conclusion

The reaction of compound **1** and **2** in acetic anhydride was examined and afforded at room temperature a mixture

consisting mainly of compounds **3** with a small amount of N-acetyl derivatives **5**, while at 110°C gave compounds **5** with unexpected products of structure **6**.

Experimental

Melting points were determined on electrothermal digital-melting-point apparatus and are uncorrected. The IR spectra were recorded in KBr disks, on a Jasco Fourier Transform Infrared spectrophotometer Model FT/IR-3000E. The ^1H and ^{13}C NMR spectra were measured in $CDCl_3$, on a Varian Gemini 200 MHz spectrometer, using tetramethylsilane as an internal reference. The mass spectra (MS) were determined at 70 eV on a finnigan MAT SSQ 7000 spectrometer.

Reaction of Isatin (1) with Methoxycarbonylmethylene(triphenyl)phosphorane (2a).

A mixture of **1** (0.29 g, 2.0 mmole) and ylide **2a** (4) (0.67 g, 2.0 mmole) in acetic anhydride (15 ml) was stirred at room temperature for 1 h. The orange yellow precipitate, thus formed, was filtered off and identified as methyl (1,2-dihydro-2-oxo-3H-indol-3-yl)acetate (**3a**) (0.20 g) (mp and mixed mp with an authentic sample) (1). The filtrate was poured into water (20 ml) and extracted with chloroform (4 x 20 ml). The extract solution was dried over anhydrous sodium sulfate and evaporated to dryness in the presence of silica gel. The mixture was subjected to column chromatography on silica gel, using petroleum ether (bp 60-80°C) and ethyl acetate. The first fraction (95-90 % petroleum ether) yielded yellow crystalline product (0.05 g, 11% yield), identified as methyl (1-acetyl-1,2-dihydro-2-oxo-3H-indol-3-yl)acetate (**5a**), recrystallized from benzene-petroleum ether (bp 40-60°C), mp 135-136°C. Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 63.66; H, 4.52; N, 5.72. Found: C, 63.54; H, 4.48; N, 5.81 %. IR cm^{-1}: 1760 (C=O, ester); 1705 (C=O, acetyl and C=O, amide); 1594 (C=C). ^1H NMR : δ 2.72 (s, 3H, acetyl CH_3); 3.89 (s, 3H, ester CH_3); 6.92 (s, 1H, =CH-); 7.24 (dt, J_{HH} = 7.8 and 1.2 Hz, 1H, ArH at C-5); 7.45(dt, J_{HH} = 7.8 and 1.2 Hz, 1H, ArH at C-6); 8.30 (dd, J_{HH} = 8.4 and 1.2 Hz, 1H, ArH at C-7); 8.69 (dd, J_{HH} = 8.2 and 1.2 Hz, 1H, ArH at C-4). MS: m/z (relative intensity) 245 (M^+, 17 %), 203 (100), 172 (44), 144 (52), 116 (23), 89 (15), and 43 (75). The second fraction (85-80 % petroleum ether) gave an additional amount of **3a** (0.10 g) (the total yield 0.30 g, 67%). The third fraction (75-50% petroleum ether) afforded triphenylphosphine oxide (0.50 g, 90 % yield).

Reaction of Isatin (1) with Ethoxycarbonylmethylene(triphenyl)phosphorane(2b).

A mixture of **1** (0.29 g, 2 mmole) and ylide **2b** (4) (0.69 g, 2 mmole) in acetic anhydride (15 ml) was stirred for 1 h at room temperature. The precipitated solid material was isolated by filtration and crystallized from benzene to give orange yellow crystals (0.18 g), proved to be ethyl (1,2-dihydro-2-oxo-3H-indol-3-yl)acetate (**3b**) (mp and mixed mp, comparative IR and ^1H NMR spectra with an authentic sample) (1). The acetic anhydride filtrate was added into water (20 ml) and extracted with chloroform (4 x 20 ml). The extract was dried over anhydrous sodium sulfate. Then, the solvent was removed under reduced pressure and the residue chromatographed on silica gel. Elution with ethyl acetate-petroleum ether (bp 60-80°C) afforded three fractions. The first fraction yielded yellow crystalline product, identified as ethyl (1-acetyl-1,2-dihydro-2-oxo-3H-indol-3-yl)acetate (**5b**) (0.07 g, 14.7% yield), recrystallized from benzene-petroleum ether (bp 40-60°C), mp 93-94°C. Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.84; H, 5.06; N, 5.41. Found: C, 64.61; H, 5.15; N, 5.30%. IR cm^{-1}: 1747 (C=O, ester); 1712 (C=O, acetyl and C=O, amide); 1596 (C=C). ^1H NMR: δ 1.38 (t, J_{HH} = 7.2 Hz, 3H, ester CH_3); 2.72 (s, 3H, acetyl CH_3); 4.35 (q, J_{HH} = 7.2 Hz, 2H, ester CH_2); 6.93(s,1H, =CH-); 7.23(dt, J_{HH} = 7.8 and 1.2 Hz, 1H, ArH at C-5); 7.43 (dt, J_{HH} = 7.8 and 1.2 Hz, 1H, ArH at C-6); 8.30 (d, J_{HH} = 7.8Hz, 1H, ArH at C-7); 8.69 (d, J_{HH} = 7.8 Hz, 1H, ArH at C-4). MS: m/z (relative intensity) 259 (M^+, 74%), 218 (20), 217 (100), 172 (46), 161 (6), 145 (46), 115 (30), 89 (9), and 63 (5). The second fraction gave an additional amount of **3b** (0.13g) (the

total yield 0.31g, 65.3%). The last fraction gave colourless crystalline product of triphenylphosphine oxide (0.4 g, 72% yield) (mp and mixed mp with an authentic sample).

Preparation of N-Acetylisatin (4)

A solution of isatin (**1**) (5 g, 34 mmole) in acetic anhydride (10 ml) was heated at 110°C for about 3 h. After cooling to room temperature, the yellow precipitate that separated, was collected by filtration and washed with dry ether. Recrystallization from benzene gave yellow crystalline product of N-acetylisatin (4) (6.2 g, 96% yield). mp 143°C (lit.(5) 142-143.5°C). IR cm^{-1}: Strong absorption bands at 1781, 1747, 1714 (3 C=O for ketone, amide and acetyl);1593 (C=C). ^1H NMR: δ 2.73 (s, 3H, acetyl CH_3); 7.34 (t, J_{HH} = 7.6 Hz, 1H, ArH, at C-5); 7.70 (dd, J_{HH} = 8.2 and 1.4 Hz, 1H, ArH at C-4); 7.76 (dt, J_{HH} = 7.4 and 1.4 Hz, 1H, ArH at C-6); 8.41 (d, J_{HH} = 8.2 Hz, 1H, ArH at C-7).

Reaction of N-Acetylisatin (4) with Methoxycarbonylmethylene(triphenyl)phosphorane (2a).

a) In benzene solution: To a solution of **4** (0.19 g, 1 mmole) in dry benzene (10 ml), ylide **2a** (0.33 g, 1 mmole) was added and the mixture was stirred at room temperature for about 6 h. Then, the solution was evaporated on silica gel and separated by column chromatography using ethyl acetate/*n*-hexane as eluent. The first fraction gave yellow crystalline product of methyl (1-acetyl-1,2-dihydro-2-oxo-3H-indol-3-yl)acetate (**5a**) (0.18 g, 73% yield) which identified by its mp and mixed mp with an authentic sample previously obtained from the reaction of isatin (**1**) with **2a** in acetic anhydride as a solvent. The second fraction yielded triphenylphosphine oxide (0.23 g, 83% yield). When the above reaction was carried out in boiling benzene for 1 h gave **5a** in 68% yield.

b) In acetic anhydride: To a stirred solution of **4** (0.50 g, 2.7 mmole) in acetic anhydride (10 ml) at room temperature, ylide **2a** (0.90 g, 2.7 mmole) was added. After 30 minutes, the yellow crystals began to appear. Stirring was continued for 2 h and the precipitated product was isolated by filtration to give **5a** (0.28 g) (mp and mixed mp). The filtrate was poured on 10 ml of water and extracted with chloroform (3 x 15 ml). The extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate/*n*-hexane as eluent to afford two fractions. The first fraction gave an additional amount of **5a** (0.22 g) (the total yield 0.50 g, 76%). The second fraction yielded colourless crystals of triphenylphosphine oxide (0.60 g, 80 % yield).

In a similar manner, compound **5b** was obtained in good yield (78%) along with triphenylphosphine oxide by stirring N-acetylisatin (**4**) with ylide **2b** in benzene solution or acetic anhydride.

Action of Acetic Anhydride on Methyl (1,2-dihydro-2-oxo-3H-indol-3-yl)acetate (3a)

Formation of Compounds 5a and 6a.

A solution of compound **3a** (1.3 g, 6.4 mmole) in acetic anhydride (10 ml) was heated at 110°C for about 4 h. Then, the yellow solution was poured into water (20 ml) and extracted with chloroform. The extract dried over anhydrous sodium sulfate and the solvent was evaporated in a rotary evaporator. The residue was chromatographed on silica gel with ethyl acetate/*n*-hexane as eluent to give two fractions. The first fraction (95% *n*-hexane) yielded yellow crystalline product (0.28 g, 17.8% yield), identified as methyl (1-acetyl-1,2-dihydro-2-oxo-3H-indol-3-yl)acetate (**5a**) (mp and mixed mp with an authentic sample previously obtained). The second fraction (75% *n*-hexane) gave colourless crystals of compound **6a** (0.29 g, 18.5% yield), recrystallized from benzene/*n*-hexane, mp 254-256°C. Anal. Calcd. for $C_{26}H_{22}N_2O_8$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.51; H, 4.47; N, 5.78 %. IR cm^{-1}: 1767 (C=O, ester); 1716 (C=O, acetyl and C=O, amide). ^1H NMR: δ 2.66, 2.74 (2s, 6H, acetyl CH_3); 3.15 (s, 3H, ester CH_3); 3.22 (t, J_{HH} = 11.8 Hz, 1H, H at C-17); 3.90 (s, 3H, ester CH_3); 4.05 (d, J_{HH} = 11.7 Hz, 1H, H at C-18); 4.13 (d, J_{HH} = 11.8 Hz, 1H, H at C-10); 6.37 (d, J_{HH} = 8 Hz, 1H, ArH at C-13); 6.80 (d, J_{HH} = 7.6 Hz, 1H, ArH at C-4); 7.06, 7.16 (2t, J_{HH} = 8 Hz, 2H, ArH at C-5, C-14); 7.35 (t, J_{HH} = 8 Hz, 1H, ArH at C-6); 7.99 (d, J_{HH} = 8 Hz, 1H, ArH at C-15); 8.31 (d, J_{HH} = 8 Hz, 1H, ArH at C-7).

^{13}C NMR: δ 26.1, 26.6 (2 CH_3, acetyl); 41.2 (C-17); 45.4 (C-18); 52.1 (CH_3, ester); 52.8 (C-10); 53.3 (CH_3, ester); 54.9 (C-2); 116.1 (C-7); 116.6 (C-15); 122.5 (C-6); 123.4 (C-12); 123.9 (C-14); 125.9 (C-4); 129.6 (C-5); 130.3 (C-13); 131.0 (C-3); 131.8 (C-11); 139.0 (C-8); 139.9 (C-16); 169.5 (C-1); 170.4, 170.9 (2 C=O, acetyl); 172.4 (C-9); 174.3, 178.4 (2 C=O, ester). MS: m/z (relative intensity) 490 (M^+, 40%), 448 (3), 430 (19), 388 (21), 360 (13), 328 (48), 287 (100), 269 (27), 229 (21), 214 (15), 204 (11), 176 (4), 113 (1), and 59 (5).

Action of Acetic Anhydride on Ethyl (1,2-dihydro-2-oxo-3H-indol-3-yl)acetate (3b)

Formation of Compounds 5b and 6b

A solution of **3b** (0.6 g, 2.76 mmole) in acetic anhydride (5 ml) was heated at 110°C. After 4 h, the solution was poured into water and then extracted with chloroform. The solution was dried, evaporated on silica gel and separated by column chromatography using ethyl acetate/*n*-hexane as eluent. The first fraction (95% *n*-hexane) gave ethyl (1-acetyl-1,2-dihydro-2-oxo-3H-indol-3-yl)acetate (**5b**) (0.15 g, 21% yield) (mp and mixed mp with an authentic sample). The second fraction (75 % *n*-hexane) yielded colourless crystals of compound **6b** (0.14 g, 19.7% yield), recrystallized from benzene/*n*-hexane, mp 246-247°C. Anal. Calcd. for $C_{28}H_{26}N_2O_8$: C, 64.86; H, 5.06; N, 5.40. Found: C, 64.79; H, 5.01; N, 5.33 %. IR cm^{-1}: 1770 (C=O, ester); 1718 (C=O, acetyl and C=O, amide). ^{1}H NMR: δ 0.75, 1.35 (2t, J_{HH} = 7.0 Hz, 6H, ester CH_3); 2.64, 2.72 (2s, 6H, acetyl CH_3); 3.20 (t, J_{HH} = 11.8 Hz, 1H, H at C-17); 3.61 (m, 2H, ester CH_2); 4.03 (d, J_{HH} = 11.8 Hz, 1H, H at C-18); 4.09 (d, J_{HH} = 11.8 Hz, 1H, H at C-10); 4.33 (m, 2H, ester CH_2); 6.35 (d, J_{HH} = 8 Hz, 1H, ArH at C-13); 6.81 (d, J_{HH} = 7.6 Hz, 1H, ArH at C-4); 7.07, 7.13 (2t, J_{HH} = 8 Hz, 2H, ArH at C-5 and C-14); 7.32 (t, J_{HH} = 7.8 Hz, 1H, ArH at C-6); 7.95 (d, J_{HH} = 8 Hz, 1H, ArH at C-15); 8.29 (d, J_{HH} = 8 Hz, 1H, ArH at C-7). ^{13}C NMR: δ 13.2, 14.1 (2 CH_3, ester); 26.1, 26.6 (2 CH_3, acetyl); 41.3 (C-17); 45.4 (C-18); 53.0 (C-10); 54.8 (C-2); 61.5, 61.8 (2 CH_2, ester); 115.9 (C-7); 116.6 (C-15); 122.4 (C-6); 123.5 (C-12); 124.0 (C-14); 125.9 (C-4); 129.5 (C-5); 130.2 (C-13); 131.2 (C-3); 131.9 (C-11); 139.0 (C-8); 140.1 (C-16); 169.0 (C-1); 170.4, 170.9 (2 C=O, acetyl); 171.9 (C-9); 174.3, 178.5 (2 C=O, ester). MS: m/z (relative intensity) 518 (M^+, 86%), 473 (10), 444 (45), 401 (38), 359 (33), 328 (73), 287 (100), 269 (22), 258 (17), 241 (15), 217 (11), 127 (3) and 99 (2).

Effect of Heat on Methyl (1-acetyl-1,2-dihydro-2-oxo-3H-indol-3-yl)acetate (5a).

Formation of Compound 6a.

A yellow solution of **5a** (1.23 g, 5 mmole) in dry xylene (10 ml) was heated under reflux for about 20 h. Then, the solvent was removed under reduced pressure and the residue was triturated with dry ether to give a colourless crystalline product, identified as **6a** (1.12 g, 91 % yield) (mp, mixed mp and comparative ^{1}H NMR spectrum with an authentic sample previously obtained)

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