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CONDENSATION OF N-3-SUBSTITUTED 5-PYRAZOLONES WITH ESTERS OF β-KETO ACIDS. SYNTHESIS OF PYRANO[2,3-*c*]PYRAZOL-6-ONES

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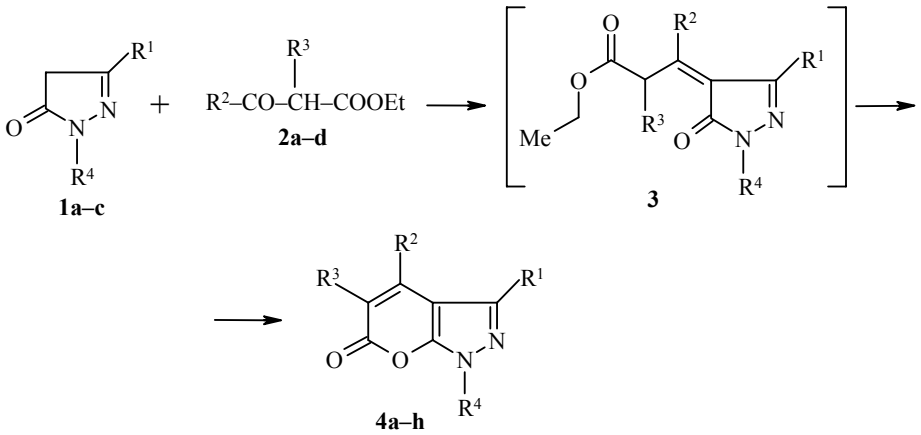
N-Substituted 5-pryazolones undergo thermal condensation with esters of β-keto acids, losing water and alcohol molecules, to form N-substituted pyrano[2,3-c]pyrazol-6-ones. The pyran ring in these products is readily cleaved by the action of alkali to give the corresponding salts of unsaturated acids.

Keywords: 5-pyrazolones, pyrano[2,3-*c*]pyrazol-6-ones, esters of β-keto acids.

In previous work [1], we found that the condensation of β-keto acids with 5-pyrazolones unsubstituted at the nitrogen atom leads to pyrano[2,3-*c*]pyrazol-6-ones, which are heteroanalogs of coumarin. The high analgesic and anti-inflammatory activity found for these compounds [2] led us to study the behavior of N-substituted 5-pyrazolones with esters of β-keto acids. As early at 1905, Stolle [3] showed that the first step in the condensation of 3-methyl-1-phenyl-5-pyrazolone (**1a**) with ethyl acetoacetate (**2a**) proceeds even at 100°C with the loss of water and formation of **3**, which is the product of condensation at $C_{(4)}$. Ester **3** then loses an ethanol molecule at 140°C to give pyrano[2,3-*c*]pyrazol-6-one (**4a**).



1 a R^1 = Me, R^4 = Ph, **b** R^1 = R^4 = Me, **c** R^1 = Me, R^4 = CH_2CH_2OH; **2 a** R^2 = Me, R^3 = H, **b** R^2 = Me, R^3 = Et, **c** R^2 = Ph, R^3 = H, **d** α-acetylbutyrolactone; **4 a-h** R^1 = Me, **a** R^2 = Me, R^3 = H, R^4 = Ph, **b** R^2 = R^4 = Ph, R^3 = H, **c** R^2 = Me, R^3 = Et, R^4 = Ph, **d** R^2 = R^4 = Me, R^3 = H, **e** R^2 = R^4 = Me, R^3 = CH_2CH_2OH, **f** R^2 = Me, R^3 = H, R^4 = $CH_2CH_2OCOCH_2COMe$, **g** R^2 = Me, R^3 = H, R^4 = CH_2CH_2OH, **h** R^2 = Me, R^3 = CH_2CH_2OH, R^4 = Ph

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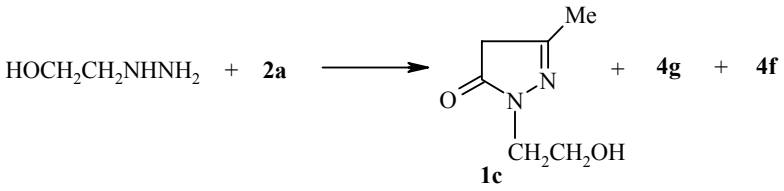
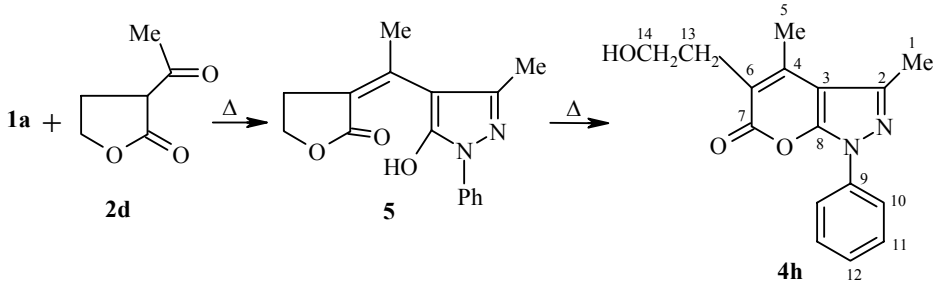
After using **1a** in this reaction, we also studied 1,3-dimethyl-5-pyrazolone (**1b**) and 1-(β-hydroxyethyl)-3-methyl-5-pyrazolone (**1c**). The β-keto esters examined were ethyl acetoacetate (**2a**), ethyl ethylacetoacetate (**2b**), ethyl benzoylacetate (**2c**), and α-acetylbutyrolactone (**2d**). We should note that N-alkyl-5-pyrazolones undergo condensation with subsequent cyclization even at 90-100°C. Thus, for example, Elguero et al. [4] studied the reaction of methylhydrazine and ethyl acetoacetate (**2a**) in an attempt to prepare 5-pyrazolone but found that this compound was not obtained at 100°C but rather **4d**. The preparation of 5-pyrazolone required lowering the reaction temperature to 70°C. The low yields of N-alkyl-5-pyrazolones in the condensation of alkylhydrazines with β-keto esters may specifically be related to this side-condensation. We have found that the reaction should be carried out in methanol without excess β-keto ester by slowly adding the β-keto ester to a solution of the hydrazine in methanol at reflux (see Experimental). Further complications arise in the preparation of pyranopyrazole **4g**. Transesterification of ethyl acetoacetate present in excess occurs already in the synthesis of starting 1-(β-hydroxyethyl)-3-methyl-5-pyrazolone (**1c**) in addition to the side-condensation to give a pyran ring and leads to a mixture of products (see Scheme).



The reaction of hydrazine with a three-fold excess of ethyl acetoacetate gives only acylated pyranopyrazolone **4f** in satisfactory yield. Acid hydrolysis of **4f** gives pure hydroxyethylpyranopyrazolone **4g** (see also the work of Kuo et al. [2]).

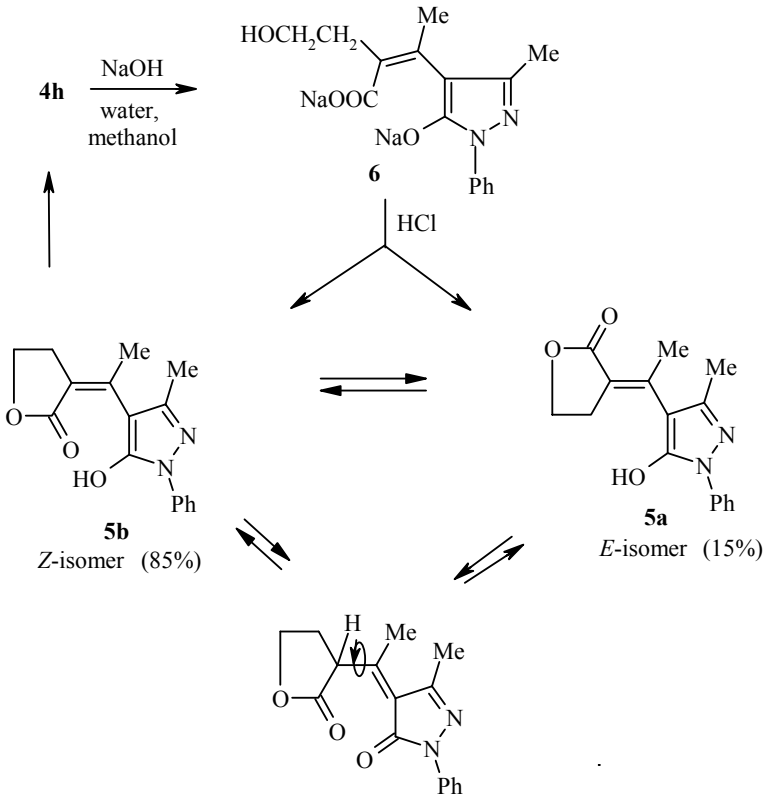
All pyrano-6-pyrazolones do not give a positive test with $FeCl_3$, while 5-hydroxypyrazoles, which are tautomers of 5-pyrazolones, turn dark brown upon adding $FeCl_3$.

The reaction between **1a** and **2d** gives the product of the usual condensation as well as about 15% of an impurity, which proved difficult to isolate. ^{1}H NMR spectroscopy indicated that this impurity was uncyclized lactone **5**.



The ^{1}H and ^{13}C NMR spectra of **4h** correspond to the structure presented and the ^{13}C NMR spectra of pyrano-6-pyrazolones [5] (see Experimental).

As heteroanalogs of coumarin, pyranopyrazolones undergo opening of the pyran ring by the action of alkali to give salts of unsaturated acids, which partially recyclize upon acidification. However, complete cyclization required heating to 160-180°C. Treatment of **4h** with alkali in 1:1 water–methanol leads to opening of the pyran ring and formation of an unsaturated acid salt **6**. Contrary to expectation, cyclization to restore the pyran ring dos not occur upon acidification of the salt solution. Instead, a 15:85 mixture of *E*-butyrolactone **5a** and *Z*-butyrolactone **5b** is obtained. However, we should note that the conversion of the *Z*-isomer to the *E*-isomer and *vice versa* may occur upon tautomeric transformations through an oxo form by means of rotation about the C–C axis.



The mass spectrum of **5b** shows a strong $[M - CH_2OH]^+$ (M - 31) peak, which is not characteristic for lactones. At high temperatures (up to 300°C) upon direct inlet into the ionization chamber, lactone **5b** rearranges to pyranopyrazole **4h**, which decomposes, giving the $[M - CH_2OH]^+$ ion characteristic of aromatic alcohols Ar–CH_2CH_2OH.

EXPERIMENTAL

The ^1H NMR spectra (in DMSO-d_6) and ^{13}C NMR spectra (in $CDCl_3$) were taken on a Bruker AM-300 spectrometer at 300 and 75 MHz, respectively. The UV spectra were taken on a Specord M-40 spectrometer in ethanol. The IR spectra were taken on a Perkin–Elmer spectrometer for KBr pellets.

1,3-Dimethyl-5-pyrazolone (1b). A sample of methylhydrazine sulfate (14.4 g, 100 mmol) was added to a stirred solution of NaOH (8 g, 100 mmol) in a mixture of water (10 ml) and methanol (100 ml). Then, ethyl acetoacetate (13 g, 100 mmol) was added dropwise slowly over 1 h with stirring and heating to 50°C on a water bath. The mixture was stirred for an additional 6 h at this temperature and then evaporated to dryness in vacuum. The residue was extracted with ethyl acetate in a Soxhlet apparatus. The solvent was evaporated off and the residue recrystallized from 3:1 ethyl acetate–hexane to give 9.3 g (83%) **1b**; mp 116°C (mp 118°C [4]).

Pyrano[2,3-*c*]pyrazol-6-ones (4) (General Method). A mixture of N-substituted 5-pyrazolone (50 mmol) and corresponding β-keto ester (55 mmol) was heated on a metal bath at 150-190°C for 2-4 h, distilling off the eliminated water and alcohol. After cooling, ethyl acetate (20 ml) was added and the mixture was heated at reflux for 15 min. The mixture was cooled. The precipitate formed was filtered off and recrystallized from a suitable solvent.

3,4-Dimethyl-1-phenylpyrano[2,3-*c*]pyrazol-6-one (4a). Heating a mixture of pyrazolone **1a** and ester **2a** at 160-165°C for 3 h gave **4a** in 72% yield; mp 146°C (1:4 benzene–hexane) (mp 145°C [5]). IR spectrum, ν, cm^{-1}: 1615, 1755 (C=O). UV spectrum, λ_{max}, nm (log ε): 239 (4.08), 250 (4.10), 317 (3.98). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 2.47 (3H, d, 4-CH_3); 2.51 (3H, s, 3-CH_3); 5.84 (1H, q, *J* = 1.1, H-5); 7.41 (1H, m, *p*-H_{Ph}); 7.58 (2H, m, *m*-H_{Ph}); 7.85 (2H, m, *o*-H_{Ph}).

3-Methyl-1,4-diphenylpyrano[2,3-*c*]pyrazol-6-one (4b). Heating a mixture of pyrazolone **1a** and ethyl benzoylacetate at 150°C for 3 h gave **4b** in 48% yield, mp 136°C (after heating, the mixture was heated at reflux in 2:1 hexane–ethyl acetate and then recrystallized from this mixed solvent) (mp 140°C [5]). IR spectrum, ν, cm^{-1}: 1525, 1595, 1730 (C=O). UV spectrum, λ_{max}, nm (log ε): 232 (4.27), 254 (4.44), 330 (4.03). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 2.11 (3H, s, 3-CH_3); 5.94 (1h, s, H-5); 7.54 (5H, m, 4-C_6H_5); 7.42 (1H, m, *p*-H, 1-C_6H_5); 7.26 (2H, m, *m*-H, 1-C_6H_5); 7.83 (2H, m, *o*-H, 1-C_6H_5).

5-Ethyl-3,4-dimethyl-1-phenylpyrano[2,3-*c*]pyrazol-6-one (4c). Heating a mixture of pyrazolone **1a** and ethyl ethylacetoacetate at 175-180°C for 4 h gave **4c** in 30% yield; mp 144°C (ethyl acetate) (mp 142°C [3]). IR spectrum, ν, cm^{-1}: 1515, 1605, 1725 (C=O). UV spectrum, λ_{max}, nm (log ε): 232 (4.13), 240 sh (4.12), 258 (4.13), 319 (4.12). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 1.12 (3H, t, *J* = 7.8, 5-CH_3); 2.40 (3H, s, 4-CH_3); 2.52 (3H, s, 3-CH_3); 2.56 (2H, m, 5-CH_2); 7.36 (1H, m, *p*-H, 1-C_6H_5); 7.56 (2H, m, *m*-H, 1-C_6H_5); 7.80 (2H, m, *o*-H, 1-C_6H_5).

1,3,4-Trimethylpyrano[2,3-*c*]pyrazol-6-one (4d). Heating a mixture of pyrazolone **1b** and ester **2a** at 150°C for 2 h gave **4d** in 80% yield; mp 170°C (ethyl acetate) (mp 167-168°C [4]). IR spectrum, ν, cm^{-1}: 1520, 1600, 1720 (C=O). UV spectrum, λ_{max}, nm (log ε): 225 (3.89), 314 (4.17). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 2.40 (3H, s, 4-CH_3); 2.44 (3H, s, 3-CH_3); 3.69 (3H, s, 1-CH_3); 5.74 (1H, s, H-5).

5-(β-Hydroxyethyl)-1,3,4-trimethylpyrano[2,3-*c*]pyrazol-6-one (4e). Heating a mixture of pyrazolone **1b** and α-acetylbutyrolactone **2d** at 165°C for 3 h gave **4e** in 88% yield; mp 189°C (5:1 ethyl acetate–hexane and then methanol). IR spectrum, ν, cm^{-1}: 1630, 1720 (C=O). UV spectrum, λ_{max}, nm (log ε): 227 (3.88), 237 sh (3.84), 311 (3.93). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 2.40 (3H, s, 4-CH_3); 2.50 (3H, s, 3-CH_3); 2.64 (2H, t, *J* = 7.9, 5-$\underline{CH_2}CH_2OH$); 3.45 (2H, m, 5-$CH_2\underline{CH_2}OH$); 3.70 (3H, s, 1-CH_3); 4.43 (1H, m, 5-OH). Found, %: C 59.8; H 6.6; N 12.1. $C_{11}H_{14}N_2O_3$. Calculated, %: C 59.4; H 6.3; N 12.6.

1-(β-Acetoacetoxyethyl)-3,4-dimethylpyrano[2,3-*c*]pyrazol-6-one (4f) was obtained in 76% yield from β-hydroxyethylhydrazine (50 mmol) and ester **2a** (180 mmol) upon heating at 150°C for 2 h; mp 120°C (2:1 ethyl acetate–hexane) (mp 120-122°C [2]). IR spectrum, ν, cm^{-1}: 1705 (C=O), 1725 (C=O). UV spectrum, λ_{max}, nm (log ε): 225 (3.83), 314 (4.16). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 2.12 (3H, s, $COCH_3$); 2.34 (3H, s, 4-CH_3); 2.36 (3H, s, 3-CH_3); 3.48 (2H, s, $COCH_2$); 4.29 (2H, t, *J* = 7.6, N–CH_2); 4.42 (2H, t, *J* = 7.7, O–CH_2); 5.77 (1H, s, H-5).

1-(β-Hydroxyethyl)-3,4-dimethylpyrano[2,3-*c*]pyrazol-6-one (4g). Crude condensation product **4f** obtained in the above procedure was hydrolyzed by heating with concentrated hydrochloric acid (35 ml) for 90 min at 50°C with vigorous stirring. The reaction mixture was evaporated in vacuum to dryness maintaining the external bath temperature at 60°C. The residue was heated with water (12 ml) to 60°C and cooled. The crystalline precipitate was filtered off washed with water (3 ml), and dried to give 3.5 g (31%) **4g**; mp 158°C (mp 158-160°C [2]). IR spectrum, ν, cm^{-1}: 1715 (C=O), 2600-3200. UV spectrum, λ_{max}, nm (log ε): 26 (3.70), 315 (4.01). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 2.38 (6H, s, 3,4-CH_3), 3.70 (2H, t, *J* = 7.7, 1-$\underline{CH_2}CH_2OH$); 3.98 (2H, m, 1-$CH_2\underline{CH_2}OH$); 4.78 (1H, br. s, OH); 5.76 (1H, s, H-5).

5-(β-Hydroxyethyl)-3,4-dimethyl-1-phenylpyrano[2,3-*c*]pyrazol-6-one (4h). A mixture of pyrazolone **1a** (8.7 g, 50 mmol) and α-acetylbutyrolactone **4h** (6.5 g) was heated at 195°C for 4 h. After cooling, ethyl acetate (40 ml) and activated charcoal (1 g) were added. The mixture was heated at reflux for 15 min and filtered while hot. After cooling, the crystalline precipitate was filtered off and dried to give 10.4 g crude product with mp 140-146°C. The ^{1}H NMR spectrum showed the presence of about 15% unsaturated lactone impurity (see text). The product was purified by repeated crystallization from benzene, from ethyl acetate, and,

finally, from methanol to give 2.4 g pure **4h**; mp 157°C. IR spectrum, ν, cm^{-1}: 1740 (C=O), 2900, 3200. UV spectrum, λ_{max}, nm (log ε): 233 (3.98), 241 (3.97), 258 (3.98), 319 (3.97). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 2.40 (3H, s, 3-CH_3); 2.49 (3H, s, 4-CH_3); 2.80 (2H, t, *J* = 7.8, 5-$\underline{CH_2}CH_2OH$); 3.78 (2H, m, 5-$CH_2\underline{CH_2}OH$); 7.30 (1H, m, *p*-H_{Ph}); 7.46 (2H, m, *m*-H_{Ph}); 7.81 (2H, *o*-H_{Ph}). ^{13}C NMR spectrum, δ, ppm: 15.1 (C-1), 149.5 (C-2), 102.6 (C-3), 136.9 (C-4), 19.2 (C-5), 113.6 (C-6), 169.3 (C-7), 161.6 (C-8), 144.4 (C-9), 120.3 (C-10), 129.3 (C-11), 126.9 (C-12), 30.3 (C-13); 6.1.3 (C-14) (numbering of the atoms given in the text). Found, %: C 67.8; H 5.3; N 10.0. $C_{16}H_{16}N_2O_3$. Calculated, %: C 67.6; H 5.6; N 9.9.

3-[1-(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)ethylidene]dihydro-2-furanone (5) (Mixture of *E*- and *Z*-isomers). A sample of pyranopyrazolone **4h** (3.5 g, 12.3 mmol) was added to a solution of KOH (1.5 g) in a mixture of water (20 ml) and methanol (20 ml) and stirred for 30 min. The solution was filtered and acidified by adding a mixture of acetic acid (4 ml) and concentrated hydrochloric acid (2 ml). The mixture was evaporated in vacuum to half volume and cooled. The crystalline precipitate was filtered off, washed with water (4 ml), and dried. Recrystallization from benzene–ethanol gave 1.4 g (40%) mixture of **5a** and **5b**; mp 124-127°C, which gives a positive test with $FeCl_3$. IR spectrum, ν, cm^{-1}: 1750 (C=O), 2700, 3300. UV spectrum, λ_{max}, nm (log ε): 247 (4.02), 288 sh (3.76). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 2.16 (3H, s, 3-CH_3); 2.38 (3H, s, α-CH_3); 2.78 (2H, t, *J* = 7.9, $\underline{CH_2}CH_2O$); 4.22 (2H, t, *J* = 7.8, $CH_2\underline{CH_2}O$); 7.22 (1H, m, *p*-H, 1-C_6H_5); 7.45 (2H, m, *m*-H, 1-C_6H_5); 7.72 (2H, m, *o*-H, 1-C_6H_5).

Repeated crystallization from benzene–ethanol gave pure *Z*-isomer **5b**; mp 129°C. The IR and UV spectra and elemental analysis were identical to those described for the mixture. ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 2.02 (3H, s, 3-CH_3); 2.09 (3H, s, α-CH_3); 3.00 (2H, t, *J* = 7.7, $\underline{CH_2}CH_2O$); 4.22 (2H, t, *J* = 7.8, $CH_2\underline{CH_2}O$); 7.22 (1H, m, *p*-H, 1-C_6H_5); 7.45 (2H, m, *m*-H, 1-C_6H_5); 7.72 (2H, m, *o*-H, 1-C_6H_5). Mass spectrum, *m/z* (I_{rel}, %): 284 $[M]^+$ (75), 269 (31), 253 $[M^+ - CH_2OH]$ (81), 255 (47), 91 (70), 77 (100). Found, %: C 67.3; H 5.7; N 9.6. $C_{16}H_{10}N_2O_3$. Calculated, %: C 67.6; H 5.6; N 9.9.

Heating 500 mg **5b** at 180°C for 30 min and subsequent recrystallization from methanol gave 310 mg pure **4h**, identical in all characteristics to the sample described above.

Reaction of 3,4-Dimethyl-1-phenylpyrano[2,3-*c*]pyrazol-6-one with Alkali. A sample of pyranopyrazolone **4** (3.6 g, 15 mmol) in was dissolved in a solution of NaOH (1.4 g, 35 mmol) in a mixture of water (20 ml) and methanol (20 ml) and stirred for 30 min. The solution was filtered and methanol was distilled off in vacuum. The residue was acidified by adding formic acid (3 ml). The semicrystalline mass was separated, washed with water, and dried in vacuum. The crude product was recrystallized from 1:2 ethyl acetate–hexane to give 2.6 g brown crystals with a broad melting range from 96 to 110°C. Chromatography using 5:1 benzene–acetone as the eluent showed three spots with R_f 0.55 (starting pyranopyrazole); 0.37 and 0.76 (*E*-isomer **5a** and *Z*-isomer **5b**). Heating 1.5 g of this product for 30 min at 180°C gave a crystalline mass, which was recrystallized from 1:2 benzene–hexane to give 1.1 g pure **4h** identical to the sample described above.

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