Notes

A Synthesis of Progesterone from Dehydroepiandrosterone

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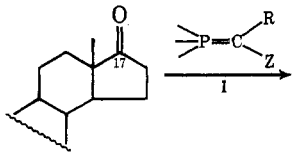
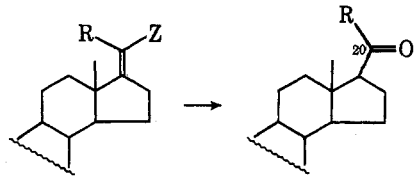
A direct two-carbon homologation of 17-keto androstanes to 20-keto pregnanes using the Wittig reaction would require a phosphorous reagent **1** bearing a masked carbonyl group Z as well as a methyl group (R = CH_3).[1] Alternative approaches



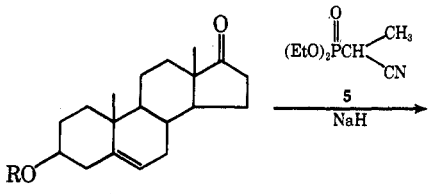


to this problem have utilized Wittig reagents bearing only a methyl group[2] (R = CH_3, Z = H) or only a masked carbonyl group[3] (R = H, Z = OCH_3). Further elaboration of the products of these Wittig reactions to 20-keto pregnanes has excluded the presence of a double bond elsewhere in the steroid[2] or has required an expensive reagent.[3] We wish to report an efficient solution to these problems as illustrated by the synthesis of progesterone (**2**) from dehydroepiandrosterone (**3**) using the phosphonate Wittig reaction.[4]

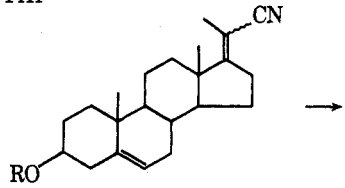
The condensation of the tetrahydropyranyl ether of dehydroepiandrosterone[5] (**4**) with the anion of 2-(diethylphosphono)-propionitrile (**5**) afforded the α,β-unsaturated nitrile (**6b**) in 77% yield as a mixture of *E* and *Z* isomers. The magnesium in methanol reduction[6] of **6b** provided the 17β-oriented side chain stereoselectively, and the subsequent hydrolysis of the tetrahydropyranyl protecting group furnished the hydroxynitrile **7** in 85% yield.[7] An alternative synthesis of **7** using pregnenolone and tosylmethyl isocyanide[8] afforded **7** in low yield.

The oxidation of **7** to the enone **8** using chromium reagents proceeded in low yield[9a] as a result of concomitant oxidation of **8** at C-6. The Oppenauer oxidation of **7** using aluminum isopropoxide and cyclohexanone[9b] circumvented this difficulty but presented the annoying problem of separating **8** from excess cyclohexanone[9b] by recrystallization or chromatography. Our inability to resolve this separation problem completely led us to substitute 4-methyl-1-piperidone (**9**) for cyclohexanone in the Oppenauer oxidation of **7**. This convenient modification of the Oppenauer oxidation afforded **8** in 90% yield following extraction of the acidified reaction mixture. As shown in Table I, this modification may prove useful in other small-scale oxidations of 3-hydroxy-Δ^5-steroids.

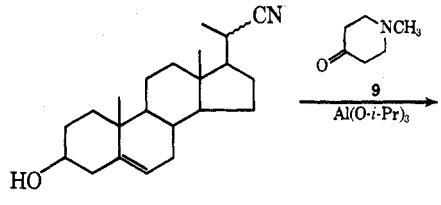
The ketalization of **8** with ethylene glycol furnished the ketal nitrile **10** in 62% yield. The oxidative decyanation[10] of **10** via the intermediate α-hydroperoxynitrile[11] **11** and the acid hydrolysis of the ethylene ketal protecting group furnished progesterone (**2**) in 69% yield. This synthesis illustrates a viable procedure for the introduction of a C-17β acetyl moiety



3, R = H
4, R = THP



6a, R = H
b, R = THP



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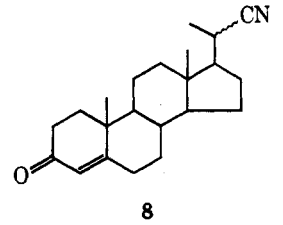

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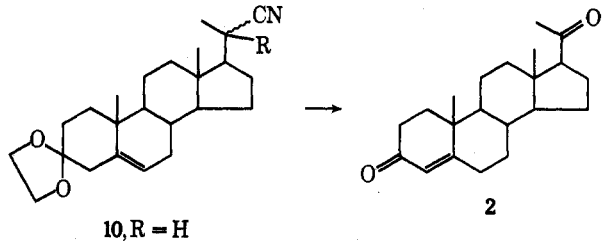

10, R = H
11, R = OOH

2

in steroids which (1) utilizes available or readily synthesized reagents and (2) is compatible with an isolated double bond elsewhere in the steroid.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Infracord spectrophotometer. NMR spectra were determined on a Varian A-60A spectrometer. Mass spectra were determined on a Varian MAT CH5 mass spectrometer. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected.

2-(Diethylphosphono)-propionitrile (5). To 200 ml of thionyl chloride (2.8 mol, 1.4 equiv) under reflux was added 148 g (2.0 mol) of propionic acid dropwise over 0.5 h. The solution was refluxed for an additional 1 h. To the propionyl chloride solution was added 336 g (2.1 mol, 1.05 equiv) of bromine dropwise over 0.5 h. The dark red solution was refluxed for an additional 24 h.[12] To 1 l. of concentrated ammonium hydroxide at 0 °C in a 2-l. flask equipped with a Hirshberg stirrer was added the crude 2-bromopropionyl halide[13] solution dropwise over 1 h. The mixture was stirred for an additional 0.5 h at 0 °C, and the brown precipitate was collected in a large Buchner

Table I. Oppenauer Oxidation of Steroids Using Aluminum Isopropoxide and 1-Methyl-4-piperidone

Starting material	Product	Isolated yield, %
7	8	90
Pregnenolone	Progesterone	85
Cholesterol	Cholest-4-en-3-one	84
β-Sitosterol	24-Ethylcholest-4-en-3-one	71
Methyl 3β-hydroxy-5-cholenate	Methyl 3-keto 4-cholenate	67
3	Androst-4-ene-3,17-dione	81

funnel, washed with ca. 200 ml of water, and allowed to air dry. The crude product was recrystallized from reagent grade acetone[14] to afford 144 g (47%) of 2-bromopropionamide: mp 121–122.5 °C (lit.[15] mp 123 °C); ir ($CHCl_3$) 5.92 μ (C=O); NMR ($CDCl_3$) δ 2.02 (d, J = 7 Hz, 3, $CHCH_3$), 4.54 (q, J = 7 Hz, 1, $CHCH_3$), and 6.4 (broad s, 2, $CONH_2$).

A three-necked 500-ml round-bottomed flask equipped with a Hirshberg stirrer and connected to a high vacuum line via a dry ice–acetone trap was charged with 92.3 g (0.61 mol) of 2-bromopropionamide and 115 g (0.81 mol, 4.0 equiv) of phosphorus pentoxide. An oil bath at 180 °C was applied to the mixture. After approximately 10 min, the liquid was distilled into the trap under high vacuum. The liquid was subsequently distilled from ca. 1 g of phosphorus pentoxide to afford 49.7 g (61%) of 2-bromopropionitrile: bp 57.5–58.5 °C (25 mm) [lit.[16] 59 °C (24 mm)]; ir (TF) 4.55 μ (C≡N); NMR ($CDCl_3$) δ 2.00 (d, J = 7 Hz, 3, $CHCH_3$) and 4.40 (q, J = 7 Hz, 1, $CHCH_3$). In the same fashion, the above procedure was applied to other carboxylic acids to afford the α-bromo amides and α-bromonitriles in the following yields: butyric acid, 49, 76%; isovaleric acid, 31, 87%; octanoic acid, 36, 70%; and 3-phenylpropionic acid, 30, 44%.

A mixture of 74.5 g (0.56 mol) of 2-bromopropionitrile and 186 g (1.12 mol, 2.0 equiv) of triethyl phosphite was heated at 140–150 °C for 8.5 h under a slow stream of nitrogen. Ethyl bromide (95% yield) was collected in a dry ice–acetone trap. The product was distilled to afford 74.6 g (70%) of **5**: bp 103–107 °C (1.0 mm); ir (TF) 4.55 μ (C≡N); NMR ($CDCl_3$) δ 1.20–1.75 (m, 9, CH_2CH_3 and $CHCH_3$), 2.50–3.45 (m, 1, $CHCH_3$), and 3.90–4.50 (m, 4, CH_2CH_3).

20-Carbonitrile-3β-hydroxypregna-5,17(20)-diene Tetrahydropyranyl Ether (6b). To 120 mg (5.0 mmol) of sodium hydride in 8 ml of anhydrous DME[17] under a nitrogen atmosphere was added 955 mg (5.0 mmol) of **5** in 3 ml of DME. The mixture was refluxed for 10 min at which time gas evolution had ceased. To the white precipitate was added 372 mg (1 mmol) of **4** as a slurry in 4 ml of DME. The solution was refluxed for 24 h, cooled, and diluted with 50 ml of ether and 25 ml of cold water. The product was extracted with an additional 25 ml of ether. The combined ether solutions were washed consecutively with 25 ml of water and 25 ml of brine and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the product was chromatographed on a 20 × 20 cm preparative layer Merck silica gel F254 plate in 1:1 ether–hexane.

A band (R_f 0.37) was eluted to afford 59 mg (16%) of unreacted **4**.

A band (R_f 0.47) was eluted to afford 315 mg (77%) of **6b**: ir ($CHCl_3$) 4.54 (C≡N) and 6.12 μ (C=C); NMR ($CDCl_3$) δ 0.94 and 1.03 (two s, 6, angular CH_3), 1.83 (broad s, 3, vinyl CH_3), 4.71 (m, 1, OCHO), 5.39 (m, 1, vinyl H); mass spectrum (70 eV) m/e (rel intensity) 308 (12, P − $C_5H_9O_2$), 307 (33), 105 (6), 91 (5), 86 (6), and 85 (100). The product is presumably a mixture of E and Z isomers as evidenced by the broad melting point (185–194 °C after three recrystallizations from ether).

Repetition of this reaction starting with 10 g of **4** afforded after column chromatography 7.9 g (72%) of **6b**.

In order to characterize **6b** further, 102 mg (0.25 mmol) of **6b** was hydrolyzed in 10 ml of methanol containing ca. 10 mg of p-toluenesulfonic acid monohydrate to afford 81 mg (100%) of 20-carbonitrile-3β-hydroxypregna-5,17(20)-diene (**6a**): mp 227–229 °C (lit.[18] mp 176–177 °C); ir ($CHCl_3$) 2.92 (OH), 4.52 (C≡N), 6.12 and 6.27 μ (C=C); NMR ($CDCl_3$) δ 0.95 and 1.03 (two s, 6, angular CH_3), 1.83 (broad s, 3, vinyl CH_3), and 5.39 (m, 1, vinyl H); mass spectrum (70 eV) m/e (rel intensity) 325 (54), 310 (17), 308 (20), 307 (72), 293 (16), 292 (60), 240 (13), 231 (11), 214 (37), 213 (58), and 105 (100). The discrepancy in melting points may reflect a different E/Z isomer ratio in **6a** prepared by two different routes.

20-Carbonitrile-3β-hydroxypregn-5-ene (7). The reduction[6] of 409 mg (1.0 mmol) of **6b** using 960 mg (40 mmol) of magnesium in 20 ml of methanol followed by hydrolysis with 30 ml of 6 N hydrochloric acid afforded, after recrystallizing twice from methanol and drying at 80 °C (0.2 mm), 277 mg (85%) of **7**: mp 170–173 °C; ir ($CHCl_3$) 4.49, 4.52 (C≡N), and 6.28 μ (C=C); NMR ($CDCl_3$) δ 0.76 and 1.03 (two s, 6, angular CH_3), 1.31 and 1.36 (two d, J = 7 Hz, 3, CH_3CH) and 5.37 (m, 1, vinyl H); mass spectrum (70 eV) m/e (rel intensity) 327 (43), 309 (42), 294 (39), 242 (27), 216 (39), 161 (38), and 119 (100).

20-Carbonitrilepregn-4-en-3-one (8). A solution of 327 mg (1.0 mmol) of **7** in 19 ml of toluene and 1 ml of 1-methyl-4-piperidone (**9**) was refluxed under a Dean-Stark trap until ca. 2 ml of distillate had collected. To the solution was added 306 mg (1.5 mmol) of aluminum isopropoxide. The mixture was refluxed for 6 h, cooled, diluted with 50 ml of ether, washed with two 25-ml portions of 1 M hydrochloric acid and 25 ml of brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on two 20 × 20 cm preparative layer Merck silica gel F254 plates in ether to afford 294 mg (90%) of **8**: R_f 0.60; ir ($CHCl_3$) 4.49, 4.52 (C≡N), 6.01 (C=O), and 6.20 μ (C=C); NMR ($CDCl_3$) δ 0.80 and 1.22 (two s, 6, angular CH_3), 1.31 and 1.35 (two d, J = 7 Hz, 3, CH_3CH) and 5.76 (m, 1, vinyl H); mass spectrum (70 eV) m/e (rel intensity) 325 (84), 284 (91), 240 (29), 229 (14), 202 (17), 147 (25), 135 (25), and 124 (100).

20-Carbonitrilepregn-5-en-3-one Ethylene Ketal (10). A solution of 325 mg (1.0 mmol) of **8**, 310 mg (5.0 mmol) of ethylene glycol, and ca. 2 mg of p-toluenesulfonic acid monohydrate in 20 ml of benzene was refluxed under a Dean-Stark trap for 17 h. The product was diluted with 50 ml of ether, washed with 25 ml of saturated sodium bicarbonate solution and 25 ml of brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on two 20 × 20 cm preparative layer Merck silica gel F254 plates in ether to afford 227 mg (62%) of **10**: R_f 0.85; ir ($CHCl_3$) 4.49 and 4.52 μ (C≡N); NMR ($CDCl_3$) δ 0.77 and 1.05 (two s, 6, angular CH_3), 1.31 and 1.36 (two d, J = 7 Hz, 3, CH_3CH), 3.96 (s, 4, OCH_2CH_2O), and 5.36 (m, 1, vinyl H); mass spectrum (70 eV) m/e (rel intensity) 369 (5), 341 (3), 100 (6), and 99 (100).

Progesterone (2). To a lithium diisopropylamide solution prepared from 111 mg (1.1 mmol) of diisopropylamine and 0.42 ml of 2.60 M n-butyllithium in 2.0 ml of hexane–THF at −78 °C under a nitrogen atmosphere was added 369 mg (1.0 mmol) of **10** in 2.0 ml of 50% hexamethylphosphoramide–THF. Dry oxygen gas was bubbled into the yellow solution (250 ml/min) at −78 °C for 30 min to afford a pale yellow solution which was quenched with 2 ml of 1 M sodium sulfite solution. The solution was stirred for 5 h at 25 °C, diluted with 25 ml of water, and extracted with 50 ml of 20% dichloromethane–ether. The product was washed with 25 ml of 1 M sodium hydroxide solution and 25 ml of brine and dried over anhydrous $MgSO_4$. To the crude white solid in 2 ml of THF was added 1.0 ml of glacial acetic acid and 0.5 ml of 1 M hydrochloric acid. The solution was stirred for 2.5 h, diluted with 25 ml of water, and extracted with 50 ml of 20% dichloromethane–ether. The product was washed with 25 ml of water, 25 ml of saturated sodium bicarbonate solution, and 25 ml of brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on two 20 × 20 cm preparative layer Merck silica gel F254 plates in 10% dichloromethane–ether to afford 215 mg (69%) of **2** (R_f 0.54) which was identical with an authentic sample.

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Registry No.—**2**, 57-83-0; **4**, 19637-35-5; **5**, 29668-61-9; (*E*)-**6a**, 58449-01-7; (*Z*)-**6a**, 58449-02-8; (*E*)-**6b**, 58449-03-9; (*Z*)-**6b**, 58449-04-0; **7** isomer 1, 58449-05-1; **7** isomer 2, 50303-63-4; **8**, 58462-91-2; **9**, 1445-73-4; **10**, 58462-92-3; 2-bromopropionamide, 5875-25-2; phosphorus pentoxide, 1314-56-3; 2-bromopropionitrile, 19481-82-4; triethyl phosphite, 122-52-1; ethylene glycol, 107-21-1; lithium diisopropylamide, 4111-54-0.

References and Notes

(1) Approaches not requiring a Wittig reaction have also been recorded: (a) A. Butenandt and J. Schmidt-Thome, *Chem. Ber.*, **72**, 112 (1939); (b) A. Butenandt, J. Schmidt-Thome, and H. Paul, *ibid.*, **72**, 182 (1939); (c) J. S. Mills, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6118 (1958).
(2) (a) A. Krubiner and E. Olivetto, *J. Org. Chem.*, **31**, 24 (1966); (b) A. Krubiner, G. Saucy, and E. Olivetto, *ibid.*, **33**, 3548 (1968).
(3) S. Danishefsky, K. Nagasawa, and N. Wang, *J. Org. Chem.*, **40**, 1989 (1975).
(4) J. Boutagy and R. Thomas, *Chem. Rev.*, **74**, 87 (1974).
(5) A. C. Ott, M. F. Murray, and R. L. Pederson, *J. Am. Chem. Soc.*, **74**, 1239 (1952).
(6) J. A. Profitt, D. S. Watt, and E. J. Corey, *J. Org. Chem.*, **40**, 127 (1975).
(7) The hydroxynitrile **7** was a mixture of diastereomers (at C-20) as evidenced by the NMR and ir spectra.

(8) O. H. Oldenziel and A. M. van Leusen, *Tetrahedron Lett.*, 1357 (1973). The low yield was, in part, the result of the extensive purification necessary to free **7** from unreacted pregnenolone.
(9) (a) For example, the yield of **8** using Jones reagent was 39% and using Collins reagent was 56%. (b) The use of a volatile ketone such as acetone required long reaction times and furnished **8** in low yield (44% after 60 h).
(10) S. J. Selikson and D. S. Watt, *J. Org. Chem.*, **40**, 267 (1975).
(11) The intermediacy of **11** was confirmed by isolating the acetate derivative.
(12) E. Schwenk and D. Papa, *J. Am. Chem. Soc.*, **70**, 3626 (1948).
(13) Distillation of the product at this stage afforded a mixture of 2-bromopropionyl chloride and bromide.
(14) Filtration of the hot acetone solution was often necessary in order to remove small amounts of ammonium salts.
(15) C. A. Bischoff, *Chem. Ber.*, **30**, 2303 (1897).
(16) C. Moureu and R. L. Brown, *Bull. Soc. Chim. Fr.*, **27**, 901 (1920).
(17) THF is a suitable solvent but required longer reaction times than DME.
(18) L. H. Sarett, *J. Am. Chem. Soc.*, **70**, 1454 (1948).

Synthesis of 1,4-Disubstituted Tetrazoline-5-thiones

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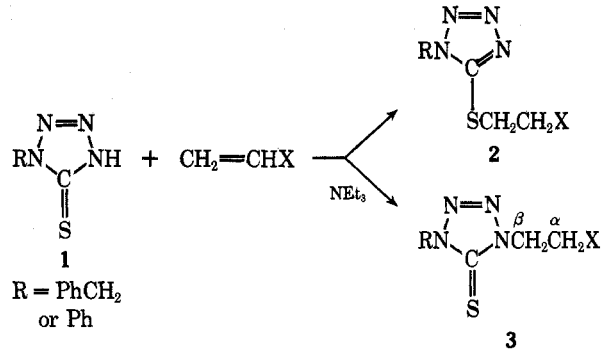
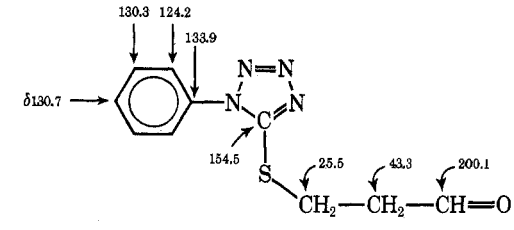
1,4-Disubstituted tetrazoline-5-thiones (**3**) may be considered as potential precursors for the hitherto unknown diaziridinethiones[1] which are of current interest in our laboratory.[2] We have already reported that alkylation, acylation, and sulfonylation of 1-benzyl-4*H*-tetrazoline-5-thione (**1**, R = $PhCH_2$) in the presence of triethylamine resulted in S-substitution in all cases except with phenylacetyl chloride, which furnished the N derivative.[3] Sulfenylations of 1-substituted 4*H*-tetrazoline-5-thiones in the presence of pyridine also occurred at sulfur as was shown by Stajer et al.[4]

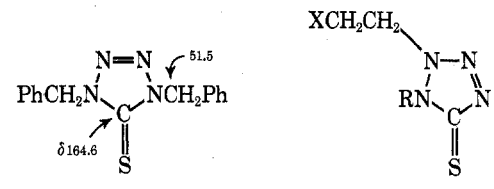
Very recently, Lippmann and Reifegerste[5] carried out Michael additions of 1-phenyl-4*H*-tetrazoline-5-thione onto α,β-unsaturated aldehydes, maleic anhydride, and methyl acrylate in the absence of base and concluded (correctly) from their ^1H NMR spectra that S-addition products (**2**) were formed. Independently, we have carried out Michael additions with 1-benzyl- (or phenyl-) 4*H*-tetrazoline-5-thione (**1**) under slightly modified experimental conditions (THF/NEt_3) which resulted in the formation of N derivatives (**3**) in all cases (see Table I). The structures of **3a–f** are fully supported by the ^{13}C NMR data recorded in Table II. That N-addition occurred instead of S-addition is apparent from the absorptions at δ 164 and 42–44 ppm which are attributed to the C=S and the β-CH_2 carbon atoms. If addition would have occurred at sulfur to give **2**, the C=N and β-CH_2 carbon resonances would be found at δ 154 and 25 ppm, respectively. This is shown below for structure **2a** prepared by the method of Lippmann and Reifegerste.[5] The assignment of the absorption peak at δ 164





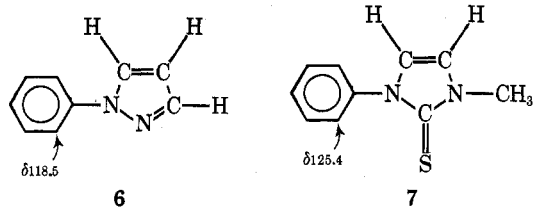
2a

ppm to the C=S carbon atom[3] is confirmed by the ^{13}C NMR spectrum of 1,4-dibenzyltetrazoline-5-thione (**4**) (C=S at δ 164.6 ppm). This compound was obtained in our laboratory



4 **5**

from the corresponding ketone[6] upon treatment with P_2S_5. Thus far, we have only interpreted our results in terms of S vs. N_4 addition. The alternative structure for the N adduct, namely **5**, can be excluded on the basis of the position of the ortho phenyl carbon absorption in compounds **3a,c,e**. According to Begtrup[7] the chemical shift value of this ortho carbon atom is strongly dependent on the extent of interannular conjugation between the two rings, resulting in a downfield shift as the steric hindrance increases. This is illustrated for three compounds, **6**, **7**, and **8**, taken from the work of Begtrup.[7] In our phenyl substituted compounds **3a,c,e** (as well as in **2a**) the ortho phenyl carbon absorptions are found at ca. δ 124 ppm in accordance with the value noted on model compound **7** which has only one neighboring sub-



6 **7**

Table I. 1,4-Disubstituted Tetrazoline-5-thiones

Compd	R	X	Yield, %	^1H NMR, δ values[a]		
				$PhCH_2N$	NCH_2CH_2X	X
3a	Ph	CHO	43		4.60, 3.18	9.84
3b	$PhCH_2$	COMe	85	5.38	4.45, 3.07	2.14
3c	Ph	COMe	76		4.56, 3.18	2.24
3d	$PhCH_2$	CO_2Me	70	5.56	4.56, 2.92	3.61
3e	Ph	CO_2Me	57		4.70, 3.10	3.70
3f	$PhCH_2$	CN	72.5	5.43	4.50, 2.98	

[a] All the spectra were recorded in $CDCl_3$ with Me_4Si as internal reference. The aromatic proton absorptions are omitted.