A CONVENIENT SYNTHESIS OF 4-OXO-4H-QUINOLIZINES

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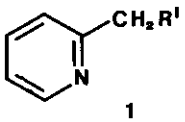
Abstract ——— By reacting α-substituted picolines (1) (or their synthetic equivalents) with ß,ß-dichloropropenals (4) (or their synthetic equivalents) substituted 1-(2-pyridyl)-4,4-dichloro-1,3-butadienes (6) were produced. Compounds (6) were smoothly cyclized to the corresponding 4-oxo-4H-quinolizines (8) bearing substituents in the 1 and/or 3 positions.

4-Oxo-4H-quinolizines are of general interest in view of the potential use of compounds containing their nucleus as biologically active compounds.[1] Several general routes leading to this heterocyclic system have been described in the literature [2-7] and some work had been done to clarify the behaviour of oxoquinolizines with respect to electrophilic reagents.[3,8,9] As a part of a work directed to the obtention of some substituted 4-oxo-4H-quinolizines we have developed a convenient synthetic procedure which involves the condensation of derivatives of 2-picoline with ß,ß-dichloroacroleins or their precursors and the cyclization of the condensation products.

RESULTS AND DISCUSSION

Reaction of ethyl (2-pyridyl)acetate (1a) and (2-pyridyl)acetonitrile (1b), respectively, with an equimolecular amount of 3-ethoxy-1,1,3-trichloropropene (3a) in 95% acetic acid at 0°C and reacting at room temperature for 12-20 h resulted in the formation of the corresponding ethyl 2-(2-pyridyl)-5,5-dichloro-2,4-pentadienoate (6b) and 2-(2-pyridyl)-5,5-dichloro-2,4-pentadienonitrile (6c), respectively. Starting from (3a) and 2-nitromethylpyridine (1c) a mixture of 1-(2-pyridyl)-4,4-dichloro-1-nitro-1,3-butadiene (6d) and its cyclization product (8c) was formed. Pure (6d) was obtained by chromatografic separation on



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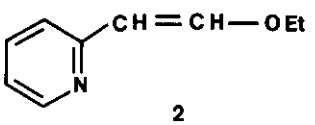


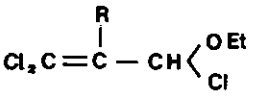
2

a: R^I = COOEt

b: R^I = CN

c: R^I = NO_2

d: R^I = H



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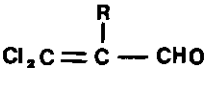
a: R = H

b: R = Et

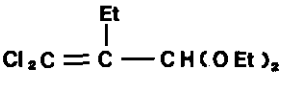


4

a: R = H

b: R = Me

c: R = Et



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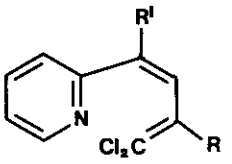

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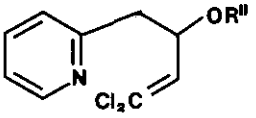
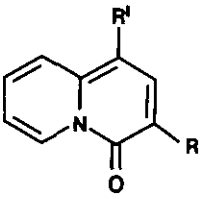


7

a: R^{II} = H

b: R^{II} = Et



8

a: R = H; R^I = CHO

b: R = NO_2; R^I = CHO

c: R = H; R^I = NO_2

d: R = NH_2; R^I = CHO

e: R = H; R^I = NH_2

f: R = H; R^I = COOEt

g: R = H; R^I = CN

h: R = Me; R^I = CN

i: R = Et; R^I = CN

j: R = R^I = H

a silica gel column. Similarly, by reacting a cis-trans mixture of 2-(2-ethoxyvinyl)-pyridine (2) with (3a) under the same conditions compound (6a) was formed in good yield. An identical result was obtained using 3,3-dichloropropenal (4a) instead of (3a). Obviously, the starting reactant (2) is hydrolyzed under the reaction conditions to 2-(2-pyridyl)-acetaldehyde. Compound (6e) was obtained by a similar procedure starting from (1b) and dichloromethacrolein (4b). This aldehyde was obtained through an extension of the known synthesis of (4a), i.e. by reacting 1-ethoxypropene with carbon tetrachloride in presence of azodiisobutyronitrile to obtain 1-ethoxy-1,3,3,3-tetrachloro-2-methylpropane which was then dehydrochlorinated and hydrolyzed. The analogous reaction of 1-ethoxybutene with CCl_4 as described above yielded, after dehydrochlorination of the reaction product, a mixture of (3b), (4c) and (5). Since both (3b) and (5) should give on hydrolysis the required (4c), this mixture was not separated and used directly for the reaction with (1b) affording the expected (6f). Products (6a-c) were easily identified through their analytical and spectroscopic data, as shown in the Table. Compounds (6a,c,e,f) were isolated as a single isomer, whereas products (6b) and (6d) were found to contain both the E and Z isomers. In the case of (6b) one isomer could be separated in a pure state by column chromatography. However, its stereochemistry could not be unambiguously determined. The formation of compounds (6a-f) is easily explained through an acid-catalyzed aldol-type condensation, followed by dehydration, between the active methylene of the α-substituted picoline (1) and the aldehyde group of the substituted acrolein. In agreement with this suggested mechanism, α-picoline itself (1d) did not react with (3a) or (4a) in acetic acid. However, by using butyl lithium as the condensation - promoting reagent and tetrahydrofuran as a solvent a mixture of (6g), (7a) and (7b) was formed starting from (3a). Only (7a) and (7b) could be isolated in a completely pure condition and fully characterized, whereas (6g) was identified by ^{1}H-NMR in an enriched mixture. The cyclization of (6a-f) to form the oxoquinolizines (8a,c,f-i) was smoothly accomplished by simple heating in aqueous dioxane for several hours. Good results were obtained also from unpurified (6) and this allows to use crude starting materials when only the final products are wanted. In the case of compounds (6g), (7a) and (7b), which all gave the unsubstituted 4-oxo-4H-quinolizine (8j), the cyclization required more severe conditions namely heating in 70% sulfuric acid for many hours. This is not surprising in view of the lower reactivity of the CCl_2 group owing to the lack of the electron-withdrawing group on the

diene system. Compounds (8a, f-j) were easily identified through their analytical and spectroscopic data and comparison of their properties with those reported in the literature (Table). The cyclization of (6) to form products (8) is probably to be ascribed to a partial hydrolysis of the dichloromethylene group to a chlorocarbonyl group which reacts with the pyridine nitrogen. Compounds (8a,c,f-j) have been already described in the literature (Table). However, our synthesis should be considered an useful alternative in many cases. E.g., compound (8a) can be obtained by Vilsmeier formylation of (8j). However, in this case a mixture of the 1-formyl- and 3-formyl derivative is produced.[9] Similarly, (8c) was obtained with a small yield besides its 3-nitro isomer and 1,3-dinitro compound by nitration of 4-oxo-4H-quinolizine.[8] When (8a) was nitrated with nitric acid, a 9:1 mixture of (8b) and (8c) was obtained. Both products were isolated and purified by column chromatography, and identified. The formation of (8c) is explained by a nitrodeformylation reaction of (8a). Other electrophilic displacements of substituents of the 4-oxo-4H-quinolizine nucleus have been thoroughly investigated.[3,8,9] Both (8b) and (8c) could be smoothly reduced with hydrogen and Pd/C to the corresponding amines (8d) and (8e), respectively.

Physical, Analytical and Spectroscopic Data for Compounds (6), (7) and (8)

Comp. N.	Purification: Column chrom.	Purification: Cryst. solvent	Yield [%]	Mp or bp °C	IR [cm^{-1}]	^{1}H-NMR [$CDCl_3$, δ]	Analysis: Formula	Analysis: Found (required) C	H	N
6a	AcOEt/PhH 1:4	iPr OH/ n-pentane	46	55	1690 (C=O)	7.15-7.95 (m, 5H, =CH-CH=, H-3, H-4, H-5); 8.67 (m, 1H, H-6); 9.75 (s, 1H, CHO)	$C_{10}H_7Cl_2NO$	52.34 (52.66)	3.20 (3.09)	5.96 (6.14)
6b	AcOEt/PhH 1:4	-	67	oil[a]	1630 (C=O)	[b] 1.40 (t, 3H, $-CH_2-\underline{CH_3}$); 4.37 (q, 2H, $-\underline{CH_2}-CH_3$); 7.15 (d, 1H, $\underline{CH} = CCl_2$); 7.55 (d, 1H, $-C = \underline{CH}$); 7.06-7.86 (m,3H, H-3, H-4, H-5); 8.50-8.76 (m, 1H, H6) [c] 1.45 (t,3H, $-CH_2-\underline{CH_3}$), 4.28 (q, 2H, $-\underline{CH_2}-CH_3$), 6.70 (d, 1H, $-CH=CCl_2$); 7.70 (d, 1H, $-C=CH$)	$C_{12}H_{11}Cl_2NO_2$	d		
6c	-	iPr OH	79	113-114	2200 (C≡N)	7.15 (d,1H, $-CH = CCl_2$); 7.65-8.56 (m, 3H, H3-H4-H5); 8.76-9.02 (m, 1H, H6), 9.20 (d, 1H, NC-C = CH)	$C_{10}H_6Cl_2N_2$	53.18 (53.36)	2.83 (2.69)	12.22 (12.44)
6d	AcOEt/PhH 1:2	-	65	oil[a]	1540, 1370 (NO_2)	[e] 6.73 and 6.85 (d, 1H, $CH = CCl_2$), 7.25-8.95 (m, 3H, H-3, H-4, H-5); 8.00 (d, 1H, $CH = CNO_2$); 8.65-8.86 (m, 1H, H-6)	$C_9H_6Cl_2N_2O_2$	43.91 (44.11)	2.63 (2.47)	11.20 (11.43)
6e	-	iPr OH	74	89	2210 (C≡N)	2.59 (s, 3H, CH_3); 7.18-7.43; 7.74-7.88 (2m, 3H, H-3, H-4, H-5); 8.57-8.74 (m, 1H, H-6); 8.75 (s, 1H, CH = CCN)	$C_{11}H_8Cl_2N_2$	54.82 (55.25)	3.28 (3.37)	11.58 (11.72)
6f	AcOEt/PhH 1:19	iPr OH	20	72	2220 (C≡N)	1.33 (t, 3H, $-CH_2-CH_3$); 3,05 (q, 2H, $-CH_2-CH_3$); 7.14-7.42; 7.60-7.83 (2 m, 3H, H3-H4-H5); 8.47 (s, 1H, NC-C = CH-) 8.52-8.70 (m, 1H, H6)	$C_{12}H_{10}Cl_2N_2$	56.77 (56.93)	3.85 (3.98)	10.96 (11.07)
7a	AcOEt/PhH 2:3	CH_2Cl_2/ iPr_2O	5	78-80	3600, 3290 (OH)	3.02 (d, 2H, $-CH_2-$); 4.86 (m, 1H, CH); 5.40-5.68 (1H, OH); 6.04 (d, 1H, -CH=) 6.98-7.40; 7.43-7.86 (2 m, 3H, H3-H4-H5); 8.34-8.64 (m, 1H, H6)	$C_9H_9Cl_2NO$	49.85 (49.56)	3.98 (4.16)	6.49 (6.42)

Physical, Analytical and Spectroscopic Data for Compounds (6), (7) and (8)

Comp. N.	Purification: Column chrom.	Purification: Cryst. solvent	Yield [%]	Mp or bp °C	IR [cm^{-1}]	^{1}H-NMR [$CDCl_3$, δ]	Analysis: Formula	Analysis: Found (required) C	H	N
7b	AcOEt/PhH 2:3	distilled	15	76-90/ 0.5 torr	-	1.21 (t, 3H, $-CH_2-CH_3$); 3.11 (dd, 2H, Pyr-CH_2-); 3.24-3.80 (m, 2H, $-CH_2-CH_3$) 4.75 (dt, 1H, -CH-) 5.87 (d, 1H, -CH=); 6.96-7.32; 7.38-7.78 (2 m, 3H, H3-H4-H5); 8.40-8.64 (m, 1H, H6)	$C_{11}H_{13}Cl_2NO$	53.84 (53.67)	5.18 (5.32)	5.71 (5.69)
8a	-	iPr OH	45	178 (176-177)[9]	1690 (CHO) 1640 (N-C=O)	6.70 (d, 1H, H3); 7.20-8.05 (m, 3H, H6 H7-H8); 8.05 (d, 1H, H2); 9.20-9.55 (m, 1H, H5); 9.95 (s, 1H, CHO)	$C_{10}H_7NO_2$	69.09 (69.36)	4.19 (4.07)	7.96 (8.09)
8b	AcOEt/PhH 1.5:1	CH_3CN	50	243	1710 (CHO) 1670 (N-C=O)	7.70-8.05; 8.30-8.65, 9.30-9.75 (3m, 4H, H5-H6-H7-H8); 9.20 (s, 1H, H2); 10.02 (s, 1H, CHO)	$C_{10}H_6N_2O_4$	54.79 (55.05)	2.98 (2.77)	12.68 (12.84)
8c	AcOEt/PhH 1.5:1	PhH/ petroleum ether	22 (from 8a) 38 (from 6d)	153 (150-152)[8]	1670 (N-C=O)	6.52 (d, 1H, H3); 8.75 (d, 1H, H2); 7.20-7.62; 7.82-8.18; 9.14-9.54 (3m, 4H, H5-H6-H7-H8)	$C_9H_6N_2O_3$	56.77 (56.84)	3.09 (3.18)	14.59 (14.73)
8d	PhH/THF 1.5:1	CH_2Cl_2/ n-pentane	70	174	3320; 3420 (NH_2) 1630 (CHO) 1575 (N-C=O)	3.36-4.05 (NH_2); 7.45 (s, 1H, H2); 6.80-7.42; 8.70-9.20 (2m, 4H, H5-H6-H7-H8); 10.05 (s, 1H, CHO)	$C_{10}H_8N_2O_2$	63.67 (63.82)	4.22 (4.28)	15.03 (14.89)
8e	-	CH_2Cl_2 / n-pentane	47	decomp.	3600; 3690 (NH_2) 1650 (N-C=O)	6.42 (d, 1H, H3); 7.85 (d, 1H, H2); 6.83-7.61 (m, 3H, H6-H7-H8); 8.72-8.98 (m, 1H, H5)	$C_9H_8N_2O$	66.56 (67.48)	5.35 (5.03)	16.95 (17.49)
8f	-	iPr OH	21	115 (117-118)[2]	1630 (C=O) 1700 (-N-C=O)	1.49 (t, 3H, $-CH_2-CH_3$); 4.44 (q, 2H, $-CH_2-CH_3$); 6.55 (d, 1H, H3); 8.40 (d, 1H, H2); 7.01-7.36, 7.47-7.87; 9.14-9.4 (3m, 4H, H5-H6-H7-H8)	$C_{12}H_{11}NO_3$	67.27 (65.59)	5.48 (5.29)	6.35 (6.45)
8g	-	CH_3CN	75	213 (211-212)[7]	2200 (CN) 1680 (N-C=O)	6.55 (d, 1H, H3); 7.80 (d, 1H, H2); 7.12-7.48; 7.58-8.13 (2m, 3H, H6-H7-H8); 9.11-9.32 (m, 1H, H5)	$C_{10}H_6N_2O$	70.28 (70.58)	3.73 (3.55)	16.15 (16.46)

Physical, Analytical and Spectroscopic Data for Compounds (6), (7) and (8)

Comp. N.	Purification: Column chrom.	Purification: Cryst. solvent	Yield [%]	Mp or bp °C	IR [cm^{-1}]	^{1}H-NMR [$CDCl_3$, δ]	Formula	Analysis: Found (required) C	H	N
8h	-	iPr OH	94	184 (183-184)[7]	2200 (CN) 1660 (N-C=O)	2.36 (s, 3H, $-CH_3$); 7.73 (s, 1H, H2); 7.00-7.32, 7.43-8.07 (2m, 3H, H6-H7-H8); 9.06-9.31 (m, 1H, H5)	$C_{11}H_8NO_2$	71.47 (71.72)	4.26 (4.37)	14.97 (15.21)
8i	-	iPr OH	69 (from 6f) 6 (from 1b)	124 (125-126)[7]	2210 (CN) 1660 (N-C=O)	1.37 (t, 3H, $-CH_2$ $-CH_3$); 2.82 (q, 2H, $-CH_2$ $-CH_3$); 7.70 (s, 1H, H2); 6.98-7.31, 7.40-8.06 (2m, 3H, H6-H7-H8); 9.07-9.31 (m, 1H, H5)	$C_{12}H_{10}N_2O$	72.38 (72.71)	5.24 (5.09)	13.99 (14.13)
8j	-	n-pentane	36 (from 7a) 38 (from 7b)	70-71 (72-73)[2]	1660 (N-C=O)	6.46-6.80 (m, 2H, H1-H3); 6.82-7.64 (m, 3H, H6-H7-H8); 7.66-7.88 (m, 1H, H2); 8.99-9.25 (m, 1H, H5)	C_9H_7NO	74.19 (74.48)	4.91 (4.86)	9.49 (9.65)

[a] Not distillable without decomposition

[b] One stereoisomer

[c] Important signals of the second stereoisomer

[d] Unsatisfactory analysis due to the impossibility to distillate the product

[e] Mixture of cis and trans isomers

EXPERIMENTAL

Mps are not corrected. Tlc was run on ready-to-use silica gel plates (60F-254 Merck) with benzene:ethyl acetate mixtures (1:0 to 0:1). Column chromatographies were performed on silica gel with the eluants indicated. ^{1}H-nmr spectra were taken in deuterochloroform solutions at 60 MHz on a A-360 Varian instrument. Chemical shifts are given in ppm from TMS. Ir spectra were recorded on a Perkin Elmer 197 spectrometer.

Materials. ----- (2-Pyridyl)acetonitrile (1b) and 2-picoline were commercial products. According to described procedures were prepared ethyl 2-pyridylacetate (1a)[10], 2-nitromethylpyridine (1c)[11], 2-(2-ethoxyvinyl)-pyridine (2)[12] and 3-ethoxy-1,1,3-trichloropropene (3a)[13]. 2-Methyl-3,3-dichloropropenal (4b) was prepared by the same procedure used to obtain (3a) followed by hydrolysis of the intermediate 3-ethoxy-1,1,3-trichloro-2-methylpropene (44% yield, bp$_{15}$ 49°C, Lit.[14] bp$_{15}$ 47-49°C). The mixture of (3b), (4c) and (5) was prepared by the same method used for (3a) starting from 1-butenyl-ethyl ether.

Reaction of (2) with (3a). ----- 2-(2-Ethoxyvinyl)-pyridine (2) (20 g, 0.13 mol) was dissolved in acetic acid (26 ml) and cooled to 0°C. 3-Ethoxy-1,3,3-trichloropropene (3a) (30 g, 0.16 mol) in acetic acid (30 ml) was added dropwise. Water (3.2 ml) was added, the temperature was brought to 25°C and the reaction mixture was stirred for 16 h. Water (100 ml) was added and the reaction mixture was extracted with ethyl ether. The ethereal layer was washed with a saturated $NaHCO_3$ solution, then dried over Na_2SO_4 and evaporated. The residue was purified (Table) yielding (6a). A similar result was obtained by using 3,3-dichloropropenal (4a) (17.4 g, 0.16 mol) instead of (3a).

Reaction of (1a) with (3a). ----- Ethyl 2-pyridylacetate (1a) (2.0 g, 12 mmol) reacted with (3a) (2.55 g, 13 mmol) as described above. The crude reaction product was purified as described in the Table yielding pure (6b).

Reaction of (1b) with (3a). ----- (2-Pyridyl)acetonitrile (1b) (1.0 g, 8.5 mmol) reacted with (3a) (1.8 g, 9.0 mmol) as described above. A solid precipitate was formed during the reaction. It was filtered and purified (Table) yielding pure (6c). The reaction solution was diluted with water (10 ml) and extracted with ether. The ethereal layer was separated, washed with $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated yielding another crop of (6c).

Reaction of (1c) with (3a). ----- 2-Nitromethylpyridine (1c) (1.0 g, 7.2 mmol) reacted with (3a) (1.65 g, 8.7 mmol) as described above. The crude reaction product was chromatographed (Table) yielding two main fractions containing (6d) and (8c), respectively.

Reaction of (1b) with (4b). ----- (2-Pyridyl)acetonitrile (1b) (1.0 g, 8.5 mmol) reacted with 2-methyl-3,3-dichloropropenal (4b) (1.3 g, 9.4 mmol) as described above. By adding water (10 ml) to the reaction mixture a precipitate of (6e) was formed, filtered and purified as described in the Table.

Reaction of (1b) with (3b + 4c + 5). ----- (2-Pyridyl)acetonitrile (1b) (1.0 g, 8.5 mmol) was reacted with the mixture of (3b), (4c) and (5) (3.0 g) as described above. The reaction mixture was diluted with water (10 ml) and extracted with ether. The ethereal layer was washed with $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated affording a mixture of (6f) and (8i) which were separated by column chromatography (Table).

Reaction of (1d) with (3a). ----- 2-Picoline (2.8 g, 30 mmol) was dissolved in anhydrous tetrahydrofuran (15 ml) under N_2 atmosphere. Butyl lithium (30 mmol) (as a 1.6 M solution in hexane) was added dropwise at -5°C. The lithium picolinate prepared in this way was dropped in 3-ethoxy-1,3,3-trichloropropene (3a) (5.7 g, 30 mmol) dissolved in tetrahydrofuran (10 ml). The reaction temperature was kept to -5°C and N_2 atmosphere was mantained during the addition. The reaction mixture was warmed to room temperature and water (100 ml) was dropped in. The organic layer was evaporated under reduced pressure and the aqueous layer was extracted with ether. The extract was dried over Na_2SO_4 and evaporated affording a crude mixture of (6g), (7a) and (7b) which was separated by column chromatography (Table).

Cyclization reactions of (6) and (7). -----

a.--- Compound (6b) (0.5 g, 1.8 mmol) was dissolved in dioxane: water, 1:1 (20 ml) and refluxed for 6 h. The reaction solution was extracted with ethyl ether and the ethereal layer was dried over Na_2SO_4, and evaporated to afford the crude (8f) which was purified as described in the Table.

b. --- Compound (6a) (2.0 g, 8.7 mmol) was cyclized and isolated as described in a, affording (8a).

c. --- Compound (6c) (0.3 g, 1.33 mmol) was dissolved in acetic acid (20 ml) and refluxed for 4 h. The reaction solution was diluted with water (40 ml) and extracted with ethyl ether. The ethereal solution was washed with $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated affording crude (8g) which was purified (Table).

d. --- Compound (6e) (0.5 g, 2.1 mmol) was dissolved in acetic acid (40 ml) and reacted as described in c. The product (8h) was isolated and purified as described above.

e. --- Compound (6f) (0.3 g, 1.2 mmol) was dissolved in acetic acid (30 ml) and reacted and isolated as described in c yielding (8i).

f. --- Compound (6d) (0.3 g, 1.2 mmol) was dissolved in dioxane: water, 1:1 (20 ml) and reacted and isolated as described in a, affording (8c).

g. --- Compound (7a) (0.4 g, 1.8 mmol) was dissolved in 70% sulfuric acid (10 ml) and refluxed for 3 h. Water (20 ml) was added, the solution was neutralized with sodium bicarbonate and extracted with ethyl ether. The ethereal layer was dried and evaporated yielding crude (8j) which was purified as described in the Table.

h. --- Compound (7b) (1.0 g, 4.0 mmol) was reacted as described above for (7a) yielding (8j).

i. --- A mixture containing mainly (6g) besides (7a) and (7b) (0.4 g) was cyclized as described for (7a), affording (8j).

Nitration of (8a). ----- The aldehyde (8a) (2.0 g, 12 mmol) was dissolved in acetic acid (20 ml) and cooled with an ice bath. Nitric acid (d = 1.40 , 6 ml) was added dropwise with vigorous stirring. After 7 min. the reaction mixture was poured on ice (50 g) and the precipitate was filtered. The filtrate was made neutral with sodium hydrogencarbonate and extracted several times with ethyl ether. The ethereal layer was dried (Na_2SO_4) and evaporated. The residue was added to the precipitate and chromatographed (Table) yielding (8b) and (8c).

Hydrogenation Reactions of (8b) and (8c). -----

a. --- The nitro compound (8b) (0.6 g, 2.7 mmol) was suspended in methanol (70 ml) and palladium on carbon (5%, 120 mg) was added. The reaction mixture was hydrogenated at room temperature and pressure until consuming of the theoretical amount of hydrogen. The catalyst was filtered and the clear solution was evaporated. The residue was purified by column chromatography and recrystallization, yielding pure (8d) (Table).

b. --- Compound (8c) (0.5 g, 2.63 mmol) was suspended in methanol (70 ml) and hydrogenated as described in a, yielding (8e).

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