REACTION OF DICHLOROCARBENE WITH SUBSTITUTED 3,4-DIHYDROISOQUINOLINES AND 1-METHYLENE-1,2,3,4-TETRAHYDROISOQUINOLINES

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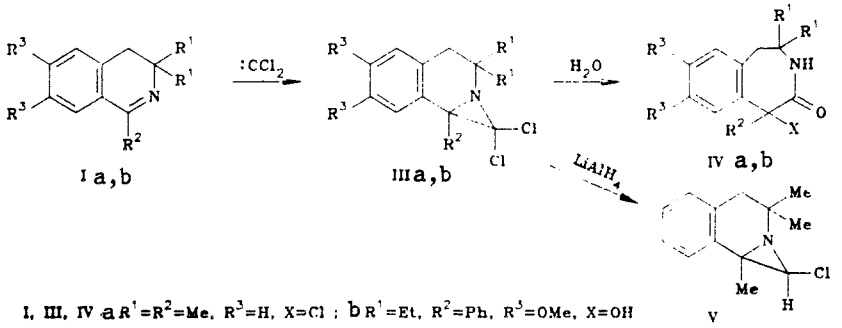
Reaction of dichlorocarbene with 3,3-dialkyl-3,4-dihydroisoquinolines results in the formation of gem-dichloroazirino[2,1-a]isoquinolines, which are in turn converted to 3-benzazepinones upon hydrolysis. Reaction of dichlorocarbene with the ethyl ester or amide of (3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)acetic acid is accompanied by rearrangement of the intermediate carbene adducts at the enamine C=C bond and results in the formation of a 1-azadiene, 3-(3,3-dimethyl-3,4-dihydroisoquinolin-1-yl)-3-chloroacrylic acid ethyl ester, and a spirolactam, 3,3-dimethyl-3-chlorospiro[1,2,3,4-tetrahydroisoquinoline-1,2'-pyrrole]-5'(2'H)-one, respectively.

Dichlorocarbene addition to the multiple bond in enamines and azomethines leads to the formation of gem-dichlorocyclopropanes and aziridines, respectively [1-3].

In the present paper we have examined the reaction of dichlorocarbene with 3,3-dialkyl-3,4-dihydroisoquinolines, which can exist in either azomethine (Ia-c) or enamine (IIa, b) forms, as well as with enamines having structures IIc, d. The structures of the reaction products were established based on spectral methods (Table 1), and also on the basis of their chemical reactions. Dichlorocarbene was generated by action of base (caustic) on chloroform in the presence of a phase transfer catalyst, benzyltriethylammonium chloride.

Reaction of dichlorocarbene with dihydroisoquinolines Ia, b gave the following gem-dichloroazirinoisoquinolines IIIa, b in high yields.



I, III, IV a $R^1=R^2=Me$, $R^3=H$, X=Cl ; b $R^1=Et$, $R^2=Ph$, $R^3=OMe$, X=OH

The PMR spectra of compounds IIIa, b contained appropriate signals for the alkyl groups, an AB spin system for the methylene group protons in the tetrahydroisoquinoline ring, as well as aromatic proton signals (Table 1). In the case of compound Ic dichlorocarbene reacted with both the C=N bond to form an aziridine ring product, and with the amine nitrogen atom to give an N-formylation product (cf. [4]), giving compound IIIc in addition.

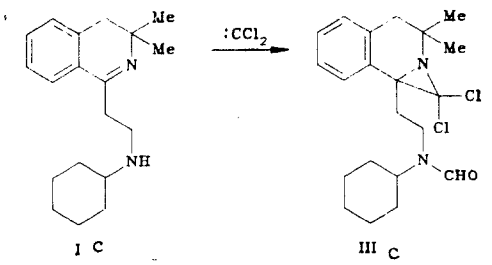


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TABLE 1. Spectral Characteristics of Newly Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}*	PMR spectrum, δ, ppm (J, Hz) †
IIb	1630, 3200, 3240, 3410, 3525	1,22 (6H, s, Me); 2,80 (2H, s CH_2); 5,10 (3H, =CH—, NH_2CO); 7,08...7,80 (4H, m, arom.); 9,71 (1H, s, NH)
IIc	1610, 3170, 3250, 3410, 3523	1,08 (9H, s, *t*-Bu); 4,45 (1H, s, =CH—); 5,15 (2H, br.s, NH_2CO); 7,48 (5H, s, Ph); 9,38 (1H, b s, NH)
IId	1630, 3405, 3520	2,95 (4H, t, *J*=5, CH_2N); 3,72 (4H, *J*=5, CH_2O); 5,05 (3H, =CH—, NH_2CO); 7,32...7,68 (5H, m, Ph)
IIIa		1,12, 1,57 and ,85 (3H, s, Me); 2,51 and 3,05 (1H, d, CH, *J*=17); 6,98...7,72 (4H, arom)
IIIb		0,93 and 1,10 (3H, t, Me, *J*=7,5); 1,79 and 1,97 (2H, d, *J*=7,5); 2,56 and 2,88 (1H, d, CH, *J*=17); 3,55 and 3,74 (3H, s MeO); 6,43 and 6,61 (1H, s, 4-H, 7-H); 7,25...7,49 (5H, m, Ph)
IIIc	1670	Cyclohexane ring: 1,08 m; 1,32 m 1,44 m 1,68 m, 1,81 m 3,22, 4,04 m 1,17 and 1,59 (3H, s Me); C—CH_2—C: 1,93 (t.d. *J*=13,4); *2,16* (d.d.d. *J*=14,5; *J*=12,5; *J*=5,0); 2,99 (d.d. *J*=13,4); *2,75* (d.d.d. *J*=14,0; *J*=12,5; *J*=5,0); C—CH_2—N: 2,93 (t.d. *J*=12,5, *J*=4,0); 3,09 (d.d.d *J*=14,5, *J*=12,5; *J*=5,0); 3,17 (d.d.d. , *J*=14,5; *J*=12,5; *J*=5,0); *3,41* (t.d. *J*=12,5; *J*=4,0); CH_2: 2,55 (d *J*=17,0); *2,57* (d *J*=17,0); 3,02 (d, *J*=17,0); arom., 7,04, 7,09 (d *J*=8,5); 7,25, 7,34 (t *J*=8,5); *7,52*, 7,78 (d *J*=8,5); CHO: 8,03, 8,13 (s)
IVa	1655, 3215, 3295, 3410	0,98, 1,48 and 2,33 (3H, s Me); 2,65 (1H, d.d CH, *J*=15,0; *J*=2,0); 4,68 (1H, d CH, *J*=15,0); 6,25 (1H, br.s, NH); 7,25...7,95 (4H, m, arom)
IVb	1640, 3360 m, 3365	0,76 (6H, t, *J*=7,0, Me); 1,29 and 1,36 (3H, q *J*=7,0, CH_2), 2,18 and 2,81 (1H, d, *J*=15,0, CH); 3,93 and 3,87 (3H, s MeO); 6,38 (1H, br.s OH); 6,57 and 7,72 (1H, s 6-H, 9-H); 7,06...7,29 (6H, m Ph, NH);
V		0,98, 1,32 and ,70 (3H, s Me); 2,43 (2H, s CH_2); 4,08 (1H, s, CH); 6,88...7,58 (4H, m, arom)
VII‡	1625, 1640, 1730	1,08, *1,28* (t, *J*=7,0, Me); 1,20 (s Me); *2,72*, 2,75 (s, CH_2); 4,01, *4,25* (q *J*=7,0, CH_2); 6,41, *6,47* (s, =CH—); 7,11...7,47 (m, arom)
VIIIa‡	1715, 3350, 3440	1,17 and 1,31 (3H, s Me); 1,73 (1H, s NH); 2,59 and 2,90 (1H, d. *J*=15,0, CH); 6,05 (1H, d *J*=1,7, =CH—); 7,02 (1H, CONH); 7,09...7,32 (4H, m, arom)
VIIIa**		1,09 and 1,21 (3H, s, Me); 2,56 and 2,69 (1H, d *J*=15,0, CH); 2,88 (1H, s NH); 6,22 (1H, d, *J*=1,7, =CH—); 6,94...7,28 (4H, m arom); 8,86 (1H, s CONH)
VIIIb	1715, 3200, 3360, 3438	1,19 (9H, s *t*-Bu); 1,65 (1H, s NH); 5,90 (1H, d *J*=1,7, =CH—); 7,21...7,35 and 7,55...7,71 (5H, m Ph); 8,14 (1H, br.s, NHCO)
VIIIb**		1,15 (9H, s *t*-Bu); 2,45 (1H, s, NH); 6,12 (1H, d *J*=1,7, =CH—); 7,26...7,65 (5H, m Ph); 8,88 (1H, s NHCO)
IX	2215	3,05 (4H, t *J*=5, CH_2N); 3,72 (4H, t *J*=5, CH_2O); 4,32 (1H, s =CH—); 7,55 (5H, s Ph)

*Spectra were recorded for 2% solutions of compounds IIb-d, IIIc, IVb, and VIIIa, b in chloroform, a 2% solution of VII in CCl_4, and for IVa in the form of a KBr pellet.

† The signals for the minor isomers in compounds IIIc and VII are given separately in italics.

‡ ^{13}C-NMR spectrum. Compound VII: 13.33 (Me), 26.55 (2Me), 37.53 (CH_2), 54.49 (C), 60.02 (OCH_2), *120.45* and 122.31 (=CH–), 124.48 ($C_{(4a)}$), 125.00, *126.05*, 126.42, 127.84, 131.05 ($C_{(5)}$–$C_{(8)}$), 135.69 and *136.28* ($C_{(8a)}$), *142.71* and 145.10 (=CCl–), 160.63 (C=N), 162.28 and 162.80 ppm (C=O). Compound VIIIa: 27.36 and 31.47 (Me), 42.76 ($C_{(4)}$), 48.95 ($C_{(3)}$), 79.15 ($C_{(1)}$), 121.38 ($C_{(4')}$), 125.78, 126.94, 128.80, and 129.60 ($C_{(5)}$–$C_{(8)}$), 130.33 ($C_{(4a)}$), 136.18 ($C_{(8a)}$), 159.89 ($C_{(5')}$), 169.74 ppm (C=O).

** In DMSO-D_6 solution.

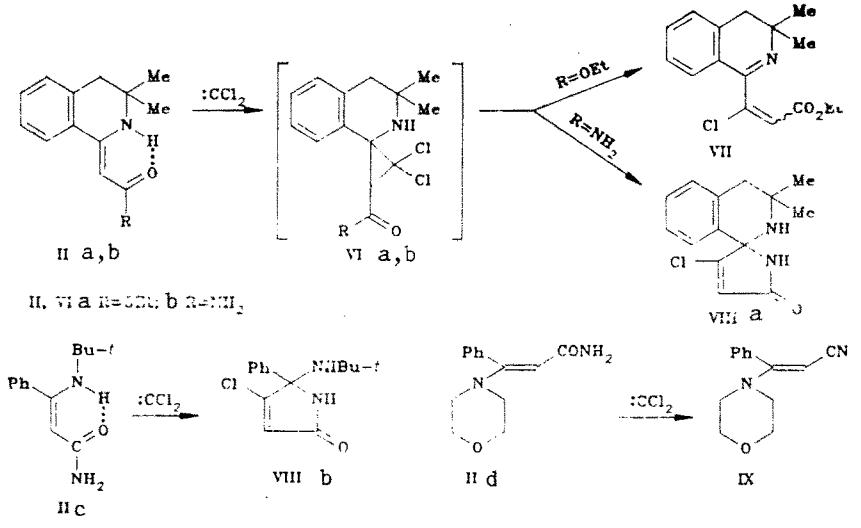
The PMR spectrum of compound IIIc exhibits a double set of proton signals, due to the existence of two conformational isomers relative to the C–N formamide group bond. Hydrolysis of the gem-dichloroaziridine derivatives IIIa, b results in cleavage of the C–N bond located opposite the gem-dichloromethylene group (cf. [5-7]). The products of this reaction of

TABLE 2. Physical Characteristics of Compounds II-V, VIII, and IX

Compound	mp, °C	Solvent	Molecular formula	Yield, %
II c	135...137	Ether–hexane	$C_{13}H_{18}N_2O$	45
II d	148...154	Ether–chloroform	$C_{13}H_{16}N_2O_2$	73
III a	54...55	Hexane	$C_{13}H_{15}Cl_2N$	81
III c	138...140	Ether	$C_{21}H_{28}Cl_2N_2O$	30
IV a	173...174	Ethanol	$C_{13}H_{16}ClNO$	49
IV b	197...199	Ethanol–water	$C_{22}H_{27}NO_4$	61
V	37...38	Ether–CH_2Cl_2	$C_{13}H_{16}ClN$	26
VIII a	172...174 (dec.)	Ether–CH_2Cl_2	$C_{14}H_{15}ClN_2O$	50
VIII b	150 (dec.)	Ether–CH_2Cl_2	$C_{14}H_{17}ClN_2O$	25
IX	71...72	Ether–hexane	$C_{13}H_{14}N_2O$	30

compounds IIIa, b are 1-chloro- and 1-hydroxy-3-benzazepinones IVa, b, respectively. The IR spectra of compounds IVa, b contain C=O stretching vibration bands for the amide group at 1655 and 1640 cm^{-1}, as well as N–H and O–H bond stretching vibration bands in the 3200-3400 cm^{-1} region. Appropriate alkyl group signals, an AB spin system for the methylene group protons, and a broad signal for the NH group proton are all observed in the PMR spectra of azepinones IVa, b. Reduction of dichloroaziridine IIIa with lithium aluminum hydride gives the monochloroaziridine V (Tables 1 and 2).

In the case of the reaction of substituted 1-methylenetetrahydroisoquinolines IIa, b with dichlorocarbene, the intermediate aminodichlorocyclopropane products VIa, b were not isolated, but rather were obtained in the form of their further conversion products. Thus, reaction of enamine IIa with dichlorocarbene resulted in the formation of azadiene VII, which based on its PMR spectral data exists as a ~3:1 mixture of cis- and trans-isomers. The ^{13}C-NMR spectrum (Table 1) corresponds to the proposed structure for compound VII, although several of the carbon atom signals (CH=CCl, $C_{(8a)}$, C=O) are doubled. Several multiple bond vibrational bands (1625, 1640, and 1730 cm^{-1}) are present in the IR spectrum of azadiene VII.



Reaction of compound IIb with dichlorocarbene gave γ-lactam VIIIa, the product of rearrangement of the intermediate aminodichlorocyclopropane VIb. The IR spectrum of compound VIIIa contains bands for the amide group C=O stretching vibration at 1715 cm^{-1} and N–H bond stretching bands at 3350 and 3440 cm^{-1}. The PMR spectrum of spirolactam VIIIa exhibits singlets for the methyl groups, broadened signals for the amino and amide group protons at 1.73 and 7.02 ppm, respectively, an AB spin system for the methylene group protons, and a doublet for the vinyl proton ($J_{1,4}$ = 1.7 Hz with the CONH proton). The signals for the NH group protons are shifted downfield in DMSO-D_6. The ^{13}C-NMR spectrum of this compound is also consistent with the assigned structure for VIIIa. These results indicate that compound IIb, which contains several potentially reactive groups, namely secondary amine, primary amide, and enamine groups, which can react with dichlorocarbene to give a formamide [4], nitrile [8, 9], and cyclopropane [1, 2] product, respectively, reacts at only one site, i.e., as the enamine. The low reactivity of the amino site is apparently due to steric hindrance to dichlorocarbene attack at the unshared electron pair of the nitrogen atom. The absence of dehydration of the amide group to a nitrile functional group upon reaction with dichlorocarbene, which would occur via formation of an intermediate carbonyl ylide [9], can probably be at-

tributed to reduced nucleophilicity of the carbonyl oxygen atom due to the existence in compound IIb of strong intramolecular hydrogen bond formation between the cis-oriented carbonyl and amide groups, respectively (see its IR and NMR spectra). This conclusion is also supported by the observed difference in the chemical behavior of enamines IIc, d relative to dichlorocarbene; enamines IIc, d were synthesized from phenylpropiolic acid amide and tert-butylamine or morpholine, respectively. Thus, compound IIc, which like compound IIb also contains hydrogen bonding between the amine and carbonyl groups [as evidenced by the low-field resonance position of the amine proton (9.38 ppm)], reacts with dichlorocarbene at the C=C bond, resulting in the formation of lactam VIIIb as the final product; in contrast, amide IId undergoes dehydration to its nitrile derivative IX upon treatment with dichlorocarbene. Comparison of the chemical shift for the vinyl group proton in nitrile IX (4.32 ppm) with the calculated values, based on an additivity scheme, for the E- and Z-IX isomers (4.22 and 4.56 ppm, respectively), suggests that nitrile IX, and by analogy amide IId, exist in the E-configuration.

It has therefore been shown that substituted 3-benzazepines can be prepared from 3,4-dihydroisoquinolines via azirino[2,1-*a*]isoquinoline derivatives, just as the reaction of 1,2-dihydroisoquinolines with dichlorocarbene permits the synthesis of substituted 2-benzazepines via intermediate cyclopropa[c]isoquinolines [10-12]. In the reaction of dichlorocarbene with (3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)acetic acid derivatives only the enamine double bond is attacked; the spirocyclic cyclopropane intermediates formed in this manner undergo rearrangement under the reaction conditions, via a novel amino-gem-dihalocyclopropane pathway (cf. [1, 2]), to give a 1-azadiene or spirolactam.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer, NMR spectra on Tesla BS-567A, Bruker WM-400, and M-500 spectrometers using 10% solutions in CCl_4 (IIIa, b, V, VII) or $CDCl_3$ (IIb-d, IIIc, IVa, b, VIIIa, b). Column chromatography was performed on 100-160 μm silica gel. The analytical characteristics of all newly synthesized compounds agreed with calculations.

(Z)-3-(tert-Butylamino)-3-phenylprop-2-enoic Acid Amide (IIc). A mixture of 3.3 g (23 mmoles) phenylpropiolic acid amide and 3.3 ml tert-butylamine in a sealed ampul was heated for 31 h at 100°C. The unreacted amine was evaporated and the residue was subjected to column chromatography (hexane–ether–dioxane 4:2:1 eluent) to give 2.24 g of amide IIc.

(E)-3-Morpholino-3-phenylprop-2-enoic Acid Amide (IId). A mixture of 2.05 g (14 mmoles) phenylpropiolic acid amide and 2 ml morpholine was heated for 4 h at 100°C, cooled, and 20 ml absolute ether was added; the reaction mixture was allowed to stand for 2 days at 5°C for crystallization to occur, after which the crystals were separated, washed with absolute ether, and recrystallized from chloroform–ether to give 2.4 g of amide IId.

3,3,8b-Trimethyl-1,1-dichloro-1,3,4,8b-tetrahydroazirino[2,1-*a*]isoquinoline (IIIa). A solution of 1.7 g (9.8 mmoles) isoquinoline Ia in 4.8 g chloroform was cooled to 0°C, 23 mg (0.1 mmole) benzyltriethylammonium chloride and 3.2 g 50% aqueous NaOH solution were added, and the mixture was vigorously stirred for 15 min at 0°C, followed by another 3 h at 15°C. After the addition of another 6 ml chloroform the reaction mixture was filtered through a 1-cm layer of silica gel, washed with hexane, and the filtrate was evaporated under vacuum; recrystallization of the residue from hexane gave 2.1 g of aziridine IIIa.

6,7-Dimethoxy-8b-phenyl-1,1-dichloro-3,3-diethyl-1,3,4,8b-tetrahydroazirino[2,1-*a*]isoquinoline (IIIb). To a solution of 0.4 g (1.2 mmoles) isoquinoline Ib and 50 mg (0.2 mmoles) benzyltriethylammonium chloride in a mixture of 5 ml hexane and 5 ml chloroform was added 2 g (50 mmoles) powdered NaOH, and the mixture was cooled to 10-12°C and stirred for 3 h; an additional 0.5 g (12 mmoles) NaOH was added and the mixture stirred for 1 h at 20°C. The reaction mixture was diluted with 50 ml hexane, filtered through a Schott filter, and the precipitate washed with hexane; the filtrate was washed with water, dried over sodium sulfate, and evaporated to give 0.5 g of an oil, yield of aziridine IIIb about 100%.

3,3-Dimethyl-8b-[2-(N-formyl-N-cyclohexylamino)ethyl]-1,1-dichloro-1,3,4,8b-tetrahydroazirino-[2,1-*a*]isoquinoline (IIIc). To a solution of 0.91 g (3.2 mmoles) isoquinoline Ic and 30 mg (0.13 mmole) benzyltriethylammonium chloride in 10 ml chloroform was added 3 g 50% aqueous NaOH solution, and the mixture was stirred for for 40 min; an additional 3 g 50% NaOH solution was added and the reaction mixture stirred for 5.5 h. The reaction mixture was washed with water, dried over sodium sulfate, and evaporated to give a residue, which was subjected to column chromatography to yield 0.38 g aziridine IIIc.

1,4,4-Trimethyl-1-chloro-2,3,4,5-tetrahydro-1H-3-benzazepin-2-one (IVa). A suspension of 0.22 g (0.9 mmole) aziridine IIIa in 5 ml water was stored for 8 days, and the resulting precipitate was removed by filtration, washed with water, dried over vacuum, and recrystallized to give 0.1 g of amide IVa.

1-Hydroxy-7,8-dimethoxy-4,4-diethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-2-one (IVb). A mixture of 0.2 g (0.5 mmole) aziridine IIIb in 3 ml water was refluxed with a condenser for 5 h, cooled, and the resulting crystals were removed by filtration and recrystallized to give 0.11 g of amide IVb.

3,3,8b-Trimethyl-1-chloro-1,3,4,8b-tetrahydroazirino[2,1-*a*]isoquinoline (V). A solution of 0.88 g (3.4 mmoles) aziridine IIIa in 10 ml absolute ether was added to a solution of 0.38 g lithium aluminum hydride in 60 ml absolute ether, and the resulting mixture was refluxed for 2.5 h, cooled, and 0.4 ml 15% NaOH solution; 1.1 ml water were added sequentially; the mixture was filtered and the filtrate evaporated and subjected to column chromatography (ether–hexane, 1:2, eluent) to give 0.2 g of aziridine V.

3-(3,3-Dimethyl-3,4-dihydroisoquinolin-1-yl)-3-chloroacrylic Acid Ethyl Ester (VII). To a solution of 1.23 g (5 mmoles) isoquinoline IIa and 20 mg (0.1 mmole) benzyltriethylammonium chloride in 5 ml chloroform at 0°C was added 2 g 50% aqueous NaOH solution, and the reaction mixture was stirred vigorously for 0.5 h at 0°C, followed by another 1 h at 25°C. The reaction mixture was washed with water, dried over $MgSO_4$, and evaporated; column chromatography (of the residue) (with 1:4 hexane–ether eluent) gave 1.0 g (69%) of ester VII.

3,3-Dimethyl-3'-chlorospiro[1,2,3,4-tetrahydroisoquinoline-1,2'-pyrrole]-5'(2'H)-one (VIIIa). To a mixture of 3.24 g (15 mmoles) amide IIb, 0.15 g (0.7 mmole) benzyltriethylammonium chloride, and 40 ml chloroform (purified to remove alcohol) was added 10 g of 50% aqueous NaOH solution; the mixture was vigorously stirred under an Ar atmosphere at 15°C for 1 h. The reaction mixture was washed with water, dried over $MgSO_4$, and subjected to column chromatography (with 10:20:3 hexane–ether–dioxane eluent) to give 2.0 g of lactam VIIIa.

5-tert-Butylamino-5-phenyl-4-chloropyrrol-2(5H)-one (VIIIb). To a solution of 1.24 g (5.7 mmoles) amide IIc, 75 ml (0.3 mmole) benzyltriethylammonium chloride in 20 ml chloroform (purified to remove alcohol) which was vigorously stirred under argon at 25°C was added in portions over a 3-h period 1.8 g (32 mmoles) powdered KOH; the mixture was stirred an additional 0.5 h, filtered, evaporated, and subjected to column chromatography (1:1 hexane–ether eluent) to give 0.38 g of pyrrolone VIIIb.

(E)-3-Morpholino-3-phenylacrylonitrile (IX). To a solution of 1.08 g (4.6 mmoles) amide IId and 50 ml (0.2 mmole) benzyltriethylammonium chloride in 10 ml chloroform was added 4 g 50% aqueous NaOH solution, and the mixture was stirred for 40 min at 25°C. The reaction mixture was washed with water and dried over $MgSO_4$, and 0.30 g of nitrile IX was isolated after column chromatography (with 1:1 ether–hexane eluent).

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