

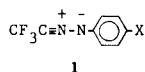
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The cycloadditions of *N*-aryl-*C*-(trifluoromethyl)nitrilimines **1**, generated *in situ* from various precursors, with dimethyl fumarate and maleate are described. *N*-Aryltrifluoroacetohydrazonoyl bromides **2** reacted with fumarate in the presence of triethylamine to give the *trans*-4,5-dimethoxycarbonylpyrazolines **4** whereas the reactions with maleate afforded the 4,5-dimethoxycarbonylpyrazoles **5** as well as **4**. In the reactions with the chloride **6** under the more drastic conditions, both fumarate and maleate gave the pyrazole **5a**. From thermolysis of the oxadiazaphosphole **8**, the *trans*-pyrazoline **4a** was formed in both cases of fumarate and maleate. The preparation of the *cis*-pyrazoline **9** was attempted from **8** and maleic anhydride but **9** was found to be so unstable as to be epimerized under the mild conditions.

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As part of research on the reactivity of the fluorinated β , β -dipolar compounds, we previously reported the reactions of *N*-phenyl-*C*-(trifluoromethyl)nitrilimine with various olefins and acetylenes which provided the novel route to 3-trifluoromethylpyrazolines and -pyrazoles [1]. In a continuation of these studies, the cycloadditions of *N*-aryl-*C*-(trifluoromethyl)nitrilimines (**1**) with dimethyl fumarate and maleate are now investigated to obtain the information regarding the stereoselectivity of the cycloadditions [2].



N-Aryltrifluoroacetohydrazonoyl bromides **2a**, **2b**, and **2d**, the precursors of the nitrilimines **1** (X = H, Me, and NO₂), were prepared by bromination of the corresponding trifluoroacetaldehyde arylhydrazones **3a**, **3b**, and **3d** with *N*-bromosuccinimide (NBS), respectively. The bromide **2c** was obtained by the reaction of **3a** with 2 equivalents of

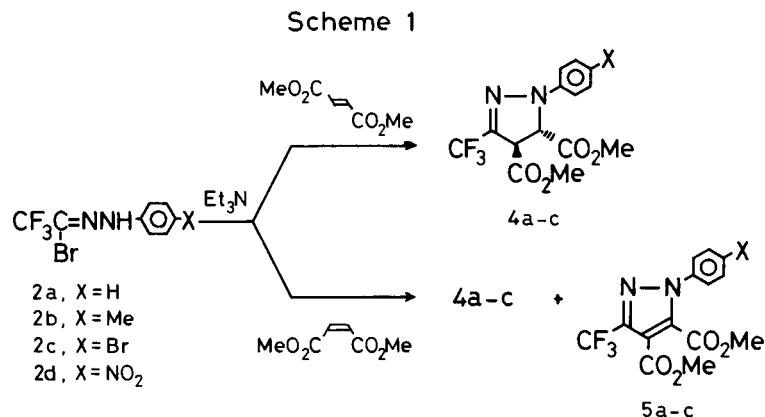
bromine [3] and the chloride **6** was prepared by chlorination of **3a** with *N*-chlorosuccinimide (NCS). The results are summarized in Table 1.

The reaction of the bromide **2a** with dimethyl fumarate in the presence of triethylamine was carried out in toluene at room temperature for 4 hours and gave *trans*-4,5-dimethoxycarbonyl-1-phenyl-3-trifluoromethyl-2-pyrazoline (**4a**) in moderate yield. On the other hand, the reaction with dimethyl maleate under the similar conditions gave not only **4a** but also its dehydrogenated pyrazole, 4,5-dimethoxycarbonyl-1-phenyl-3-trifluoromethylpyrazole (**5a**), where the *cis*-4,5-dimethoxycarbonylpyrazoline (**9**) was not detected at all. The ratio of **4a** and **5a** was determined to be 84/16 by ¹H nmr analysis. The structure of the products was determined by their elemental analyses and spectral data. The pyrazole **5a** was consistent with the sample which was produced from **2a** with dimethyl acetylenedicarboxylate. Similarly, the bromides **2b** and **2c** were allowed to react with fumarate to give only the *trans*-pyrazolines

Table 1
Preparation of Trifluoroacetohydrazonoyl Halides **2** and **6**

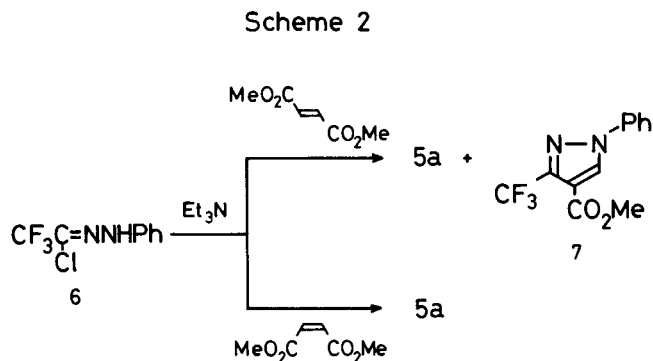
Halide	Yield (%) [a]	Bp (°C/mm Hg) or [Mp (°C)]	NH	IR (cm ⁻¹) C=N and Ar	CF ₃	Formula	Analysis, % Found/(Calcd.)		
							C	H	N
2a	74	84-87/3	3325	1600	1140	C ₈ H ₆ BrF ₃ N ₂	35.70 (35.98)	2.10 (2.26)	10.35 (10.49)
2b	67	116-122/10	3316	1606	1146	C ₈ H ₆ BrF ₃ N ₂	38.95 (38.46)	2.71 (2.87)	10.03 (9.97)
2c	72	114-120/4.5	3350	1610	1126, 1092	C ₈ H ₅ Br ₂ F ₃ N ₂	28.00 (27.78)	1.31 (1.46)	8.12 (8.10)
2d	84	[153-154]	3254	1585	1126, 1092	C ₈ H ₅ BrF ₃ N ₃ O ₂	30.50 (30.79)	1.50 (1.61)	13.57 (13.47)
6	71	72-73/2	3340	1600	1150, 1130	C ₈ H ₆ ClF ₃ N ₂	43.05 (43.17)	2.69 (2.72)	12.66 (12.58)

[a] Isolated yield based on the corresponding hydrazone.



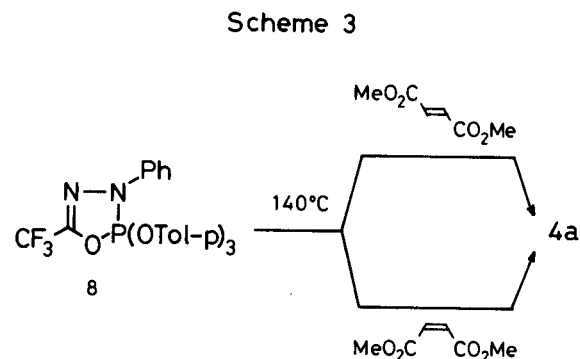
4b and **4c**, respectively, whereas the reactions with maleate necessarily gave the corresponding pyrazoles **5b** and **5c** as well as the *trans*-pyrazolines **4b** and **4c**, respectively (Scheme 1 and Table 2). Particularly, the pyrazole **5c** was produced in substantial quantity and its product ratio was almost equal to that of **4c**. The bromide **2d**, the more electron-deficient bromide, was expected to give more significant amounts of the pyrazole in the reaction with maleate but the reaction only resulted in a tar-like matter.

The similar reactions with the chloride **6** were moreover investigated. These reactions were so sluggish as to be carried out under the more drastic conditions. The reaction with fumarate at 110° afforded the pyrazole **5a** in 15% yield, accompanying a 7% yield of 4-methoxycarbonyl-1-phenyl-3-trifluoromethylpyrazole (**7**). The pyrazole **7** was found to be obtained in 32% yield on the similar treatment at 110° of the isolated **5a**. On the other hand, the reaction with maleate at room temperature for 6 days gave only **5a** in 23% yield (Scheme 2). When the isolated *trans*-pyrazoline **4a** was treated with triethylamine for 24 hours, the pyrazole **5a** was formed in 57% yield. For this conversion, both air and triethylamine are found to be needed because the pyrazole **5a** was not formed at all without either air or triethylamine. From these results, the exclusive formation of the pyrazole is interpreted by the conver-



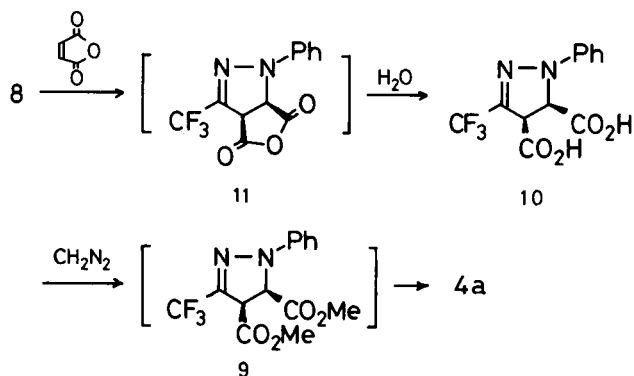
sion of the once formed *trans*-pyrazoline to the pyrazole on prolonged stirring or heating.

Next, the cycloadditions under neutral conditions were investigated. The nitrilimine **1** (X = H) was generated *in situ* by the thermal decomposition of the oxadiazaphosphole **8** [2]. In both cases of fumarate and maleate, only the *trans*-pyrazoline **4a** was found to be produced in 44 and 30% yields, respectively (Scheme 3).

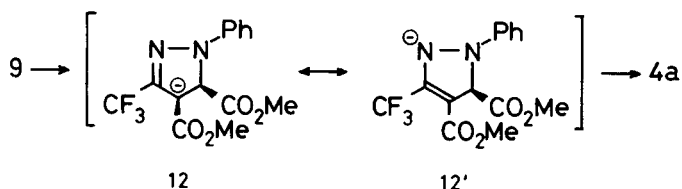


To obtain the *cis*-pyrazoline **9**, the following procedures were attempted using maleic anhydride as starting material. The oxadiazaphosphole **8** was cleaved in the presence of maleic anhydride and the resulting product was recrystallized from chloroform to give a 22% yield of 1-phenyl-3-trifluoromethylpyrazoline-*cis*-4,5-dicarboxylic acid (**10**). The initial cycloadduct **11** is seen to be hydrolyzed during the work-up. The *cis*-configuration of **10** was determined on the basis of the coupling constant ($J = 14$ Hz) between the 4- and 5-methine protons in ¹H nmr [4]. Methylation of **10** was subsequently performed with diazomethane to give not the *cis*-pyrazoline **9** but the *trans*-isomer **4a** (Scheme 4). These results indicate that the *cis*-pyrazoline **9** is extremely unstable and easily epimerized to the *trans*-isomer **4a**. This instability is characteristic of 3-trifluoromethylpyrazolines since 3-phenyl analogues are stable under the

Scheme 4



similar conditions as reported in the literature [5]. According to the previously reported explanation [5], the epimerization is conducted through the anion **12** and its meso-meric isomer **12'**. In the case of **9**, this type of anion is thought to be more easily formed, compared with the 3-phenyl analogue, because of the strong electron-withdrawing effect of the trifluoromethyl group.



In conclusion, the *cis*-pyrazoline **9** was found to be so unstable as to be epimerized to the *trans*-isomer under mild conditions. The instability does not allow a definite conclusion of the stereoselectivity of the cycloadditions. However, the reactions of the bromides **2** with maleate in the presence of triethylamine give substantial amounts of the pyrazoles **5** along with the *trans*-pyrazolines **4** and this fact is in contrast to that with fumarate giving only the *trans*-pyrazolines **4**. Such results may suggest the forma-

Table 2

Yield and Ratio of **4** and **5** in the Reaction of **2**

Bromide	Dimethyl Fumarate (F) or Maleate (M)	Yield (4 + 5), % [a]	Ratio (4/5) [b]
2a	F	71	100/0
	M	56	84/16
2b	F	77	100/0
	M	67	87/13
2c	F	56	100/0
	M	33	48/52

[a] Yield of a mixture of **4** and **5**. [b] Determined by ¹H nmr analysis.

tion of some unstable intermediates such as *cis*-pyrazolines in the cases of maleate; that is, the initially formed *cis*-pyrazolines seem to be not only epimerized but also oxidized to the pyrazoles.

EXPERIMENTAL

All melting and boiling points are uncorrected. The ir spectra were recorded on a JASCO IRA-1 spectrometer. The ¹H nmr spectra were measured with a JEOL JNM-PMX 60 using tetramethylsilane as an internal standard, the chemical shifts being given in δ ppm downfield.

Preparations of *N*-Aryltrifluoroacetylhydrazonoyl Bromides **2** and *N*-Phenyltrifluoroacetylhydrazonoyl Chloride (**6**).

Trifluoroacetaldehyde hydrate was prepared by reduction of trifluoroacetic acid with lithium aluminum hydride as reported in our previous paper [6]. A mixture of 4.1 g of thus-obtained trifluoroacetaldehyde hydrate and 2.8 g of phenyl hydrazine was stirred at 100° for 1 hour. After cooling, the precipitated solid was collected on a filter, washed with water, and dried at the pump overnight to give 3.7 g (62% yield based on trifluoroacetic acid) of pale yellow solid of trifluoroacetaldehyde phenylhydrazone (**3a**) which was further purified by recrystallization from hexane, mp 69-73°; ¹H nmr (carbon tetrachloride): δ 6.5-7.3 (m, 6H), 7.6 (br s, 1H); ir (potassium bromide): 3300 (NH), 1610 cm⁻¹ (C=N).

Anal. Calcd. for C₈H₇F₃N₂: C, 51.07; H, 3.75. Found: C, 50.95; H, 3.73.

Similarly, trifluoroacetaldehyde 4-methylphenylhydrazone (**3b**) was obtained in 40% yield, mp 84.5-85° (recrystallized from hexane); ¹H nmr (deuteriochloroform): δ 2.28 (s, 3H), 6.7-7.3 (m, 5H), 7.8 (br s, 1H); ir (potassium bromide): 3290 (NH), 1607 cm⁻¹ (C=N).

Anal. Calcd. for C₉H₉F₃N₂: C, 53.47; H, 4.49; N, 13.86. Found: C, 53.18; H, 4.20; N, 13.58.

To a solution of **3a** (5.34 g, 28.4 mmoles) in 45 ml of *N,N*-dimethylformamide (DMF) was added NBS (5.31 g, 29.8 mmoles) over a period of 2 hours and the mixture was stirred for an additional 1.5 hours. The mixture was poured into water and extracted with diethyl ether. The extracts were washed with water and brine, dried over magnesium sulfate, and distilled to give 5.59 g (74%) of *N*-phenyltrifluoroacetylhydrazonoyl bromide (**2a**). In a similar manner, *N*-(4-methylphenyl)- and (4-nitrophenyl)trifluoroacetylhydrazonoyl bromides (**2b** and **2d**) were obtained from the corresponding trifluoroacetaldehyde arylhydrazones **3b** and **3d**.

A solution of bromine 5.99 g (37.4 mmoles) in 30 ml of acetic acid was dropped into a solution of 3.55 g (18.9 mmoles) of **3a** in 80 ml of acetic acid and the mixture was stirred at room temperature for 28 hours. After the solvent was evaporated under reduced pressure, the resulting oil was distilled to give 4.72 g (72%) of *N*-(4-bromophenyl)trifluoroacetylhydrazonoyl bromide (**2c**).

To a solution of 4.76 g (25.3 mmoles) of **3a** in 25 ml of DMF was added about one-third of 3.38 g (25.3 mmoles) of NCS. Into the DMF solution was bubbled 5 ml of gas collected from the head space of concentrated hydrochloric acid reagent bottle. Once the reaction began, the rest of NCS was added to the mixture holding the temperature below 35° [7]. After the mixture was stirred at room temperature for an additional 20 hours, the similar procedures as described above were performed to give 4.00 g (71%) of **6**.

Yields and physical and spectral data of the products are collected in Table 1.

Reaction of **2a** with Dimethyl Fumarate.

Triethylamine (3 ml) was added dropwise to a solution of **2a** (1.50 g, 5.6 mmoles) and dimethyl fumarate (0.97 g, 6.7 mmoles) in 20 ml of toluene. After stirring at room temperature for 4 hours, 100 ml of diethyl ether was added to the reaction mixture. The mixture was washed with water and brine and dried over magnesium sulfate. The solvent was evaporated. The residue was then placed on a column (silica gel) and eluted with hexane-chloroform (3:1) to give 1.32 g (71%) of *trans*-4,5-dimethoxycarb-

onyl-1-phenyl-3-trifluoromethyl-2-pyrazoline (**4a**) which was further purified by recrystallization from hexane, mp 62-63°; ¹H nmr (deuteriochloroform): δ 3.74 (s, 3H), 3.80 (s, 3H), 4.36 (dq, J = 6 and 1 Hz, 1H), 5.31 (d, J = 6 Hz, 1H), 6.8-7.5 (m, 5H); ir (potassium bromide): 1740 (C=O), 1152 and 1116 cm⁻¹ (CF₃).

Anal. Calcd. for C₁₄H₁₃F₃N₂O₄: C, 50.92; H, 3.97; N, 8.48. Found: C, 51.37; H, 3.90; N, 8.85.

Reaction of **2a** with Dimethyl Maleate.

In a similar manner, from 1.50 g of **2a** and 0.97 g of dimethyl maleate, 1.04 g (56% total yield) of a mixture of **4a** and 4,5-dimethoxycarbonyl-1-phenyl-3-trifluoromethylpyrazole (**5a**) was obtained (**4a/5a** ratio of 84/16). Each product was purified by column chromatography (silica gel, hexane-chloroform, 1:1) followed by recrystallization from hexane; **4a**, mp 61-63°; spectral data are consistent with those obtained above; **5a**, mp 83-84°; ¹H nmr (deuteriochloroform): δ 3.84 (s, 3H), 3.89 (s, 3H), 7.47 (s, 5H); ir (potassium bromide): 1737 (C=O), 1166 and 1130 cm⁻¹ (CF₃).

Anal. Calcd. for C₁₄H₁₁F₃N₂O₄: C, 51.23; H, 3.38; N, 8.53. Found: C, 51.35; H, 3.33; N, 8.53.

In a similar manner to the above, the reaction of **2b** or **2c** with dimethyl fumarate or maleate was performed. Melting points and spectral data of the products are as follows; *trans*-4,5-dimethoxycarbonyl-1-(4-methylphenyl)-3-trifluoromethyl-2-pyrazoline (**4b**), mp 70.5-72°; ¹H nmr (deuteriochloroform): δ 2.24 (s, 3H), 3.74 (s, 3H), 3.79 (s, 3H), 4.31 (dq, J = 7 and 1 Hz, 1H), 5.22 (d, J = 7 Hz, 1H), 6.8-7.2 (m, 4H); ir (potassium bromide): 1763 and 1750 (C=O), 1126 cm⁻¹ (CF₃).

Anal. Calcd. for C₁₅H₁₅F₃N₂O₄: C, 52.33; H, 4.39; N, 8.14. Found: C, 52.24; H, 4.35; N, 8.13.

4,5-Dimethoxycarbonyl-1-(4-methylphenyl)-3-trifluoromethylpyrazole (**5b**).

This compound had mp 105.5-107°; ¹H nmr (deuteriochloroform): δ 2.41 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 7.2-7.5 (m, 4H); ir (potassium bromide): 1737 (C=O), 1165 and 1127 cm⁻¹ (CF₃).

Anal. Calcd. for C₁₅H₁₃F₃N₂O₄: C, 52.64; H, 3.83; N, 8.18. Found: C, 52.43; H, 3.72; N, 8.17.

1-(4-Bromophenyl)-*trans*-4,5-dimethoxycarbonyl-3-trifluoromethyl-2-pyrazoline (**4c**).

This compound had mp 81-83°; ¹H nmr (deuteriochloroform): δ 3.75 (s, 3H), 3.81 (s, 3H), 4.36 (dq, J = 6 and 1 Hz, 1H), 5.24 (d, J = 6 Hz, 1H), 7.15 (A₂X₂, 4H); ir (potassium bromide): 1749 (C=O), 1180 and 1121 cm⁻¹ (CF₃).

Anal. Calcd. for C₁₄H₁₂BrF₃N₂O₄: C, 41.10; H, 2.96; N, 6.85. Found: C, 41.17; H, 2.93; N, 6.83.

1-(4-Bromophenyl)-4,5-dimethoxycarbonyl-3-trifluoromethylpyrazole (**5c**).

This compound had mp 117-117.5°; ¹H nmr (deuteriochloroform): δ 3.88 (s, 3H), 3.92 (s, 3H), 7.50 (A₂X₂, 4H); ir (potassium bromide): 1743 and 1733 (C=O), 1129 cm⁻¹ (CF₃).

Anal. Calcd. for C₁₄H₁₀BrF₃N₂O₄: C, 41.30; H, 2.48; N, 6.88. Found: C, 41.04; H, 2.29; N, 6.98.

Preparation of **5a** from **2a** with Dimethyl Acetylenedicarboxylate.

Triethylamine (3 ml) was added dropwise to a solution of **2a** (1.50 g, 5.6 mmoles) and dimethyl acetylenedicarboxylate (2.39 g, 16.8 mmoles) in 10 ml of toluene. After stirring at room temperature for 2 hours, 100 ml of diethyl ether was added to the reaction mixture. The mixture was washed with water and brine and dried over a magnesium sulfate. After the solvent was removed, the residue was chromatographed to give 1.42 g (77%) of **5a** which was further purified by recrystallization from hexane, mp 81-83°; ¹H nmr and ir spectra are consistent with those above.

Reaction of **6** with Dimethyl Fumarate.

A solution of **6** (1.00 g, 4.5 mmoles) and dimethyl fumarate (0.78 g, 5.4

mmoles) in 10 ml of toluene was refluxed for 14 hours to the reaction mixture was added 100 ml of diethyl ether. The mixture was washed with water and brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was placed on a column (silica gel) and eluted with hexane-chloroform (3:1) to give 0.22 g (15%) of **5a** and 0.08 g (7%) of 4-methoxycarbonyl-1-phenyl-3-trifluoromethylpyrazole (**7**). Each pyrazole was recrystallized from hexane; **5a**, mp 83-84°; **7**, mp 109-111° (lit 112° [1]); ¹H nmr (carbon tetrachloride): δ 3.85 (s, 3H), 7.3-7.9 (m, 5H), 8.46 (s, 1H); ir (potassium bromide): 1707 (C=O) 1126 cm⁻¹ (CF₃).

Similar procedures were carried out for the reaction of **6** with dimethyl maleate and gave 23% of **5a**, mp 83-84°.

Thermolysis of 3-phenyl-5-trifluoromethyl-2,2,2-tris(4-methylphenoxy)-2,3-dihydro-1,3,4,2-oxadiazaphosphole (**8**) in Dimethyl Fumarate.

A mixture of 1.00 g (1.8 mmoles) of **8** and 0.52 g (3.6 mmoles) of dimethyl fumarate in 20 ml of xylene was refluxed for 6 hours and the solvent was removed. The resulting oily matter was placed on a column (silica gel) and eluted with hexane-chloroform (1:3) to give 0.26 g (44%) of **4a** and 0.39 g (59%) of tris(4-methylphenyl) phosphate. The pyrazoline **4a** was further purified by recrystallization from hexane, mp 60-63°.

A similar thermolysis of **8** in dimethyl maleate gave 30 and 90% yields of **4a** and tris(4-methylphenyl) phosphate, respectively.

Thermolysis of **8** in Maleic Anhydride.

A mixture of 1.50 g (2.7 mmoles) of **8** and 0.53 g (5.4 mmoles) of maleic anhydride in 30 ml of xylene was refluxed for 6 hours. After the solvent was evaporated, the residue was dissolved in 30 ml of chloroform. The chloroform solution was allowed to stand for 24 hours and the deposited white crystals 1-phenyl-3-trifluoromethylpyrazoline-*cis*-4,5-dicarboxylic acid (**10**) were collected on a filter, 0.18 g (22%), mp 143° dec; ¹H nmr (deuteriochloroform-DMSO-d₆): δ 4.64 (dm, J = 14 Hz, 1H), 5.25 (d, J = 14 Hz, 1H), 6.8-7.5 (m, 5H), 8.6 (br s, 2H); ir (potassium bromide): 3060 (OH), 1746 and 1724 (C=O), 1186 and 1155 cm⁻¹ (CF₃).

Anal. Calcd. for C₁₂H₅F₃N₂O₄: C, 47.69; H, 3.00; N, 9.27. Found: C, 47.50; H, 2.89; N, 9.20.

Methylation of **10** with Diazomethane.

An excess ethereal solution of diazomethane was added dropwise to a solution of 70 mg of **10** in 5 ml of diethyl ether cooled in a freezing mixture of common salt and crushed ice. After stirring for 20 minutes, the solvent was removed. The residue was chromatographed on a silica gel column to give 60 mg (78%) of **4a** which was recrystallized from hexane, mp 60-61°. The ¹H nmr and ir spectra are consistent with those obtained above.

REFERENCES AND NOTES

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