Synthesis and Stereochemical Assignments of Some Trifluoromethylphenylcyclopropanes

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Stereochemical assignments of a series of substituted *cis*- and *trans*-1-trifluoromethyl-2-phenylcyclopropanes (unsubstituted, bromide, carbonitrile, and carboxamide) based on a detailed analysis of the n.m.r. spectra and on the ten-fold difference in rates in the reaction of *cis*- and *trans*-1-trifluoromethyl-2-phenylcyclopropyl carbonitrile with basic hydrogen peroxide are presented.

Des attributions de stéréochimie pour une série de trifluorométhyl-1 phényl-2 cyclopropanes substitués (non-substitué, bromo, carbonitrile, et carboxamide) *cis* et *trans* sont présentées; les conclusions sont basées sur analyse détaillée des spectres r.m.n. et sur le fait que le rapport des vitesses de réaction des trifluorométhyl-1 phényl-1 cyclopropylcarbonitriles *cis* et *trans* avec le peroxyde d'hydrogène en milieu basique est de 10/1.

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In connection with our work on the configurational stability of the α-trifluoromethylcyclopropyl radical (1), it was necessary to synthesize and assign the stereochemistry of a number of trifluoromethylphenylcyclopropanes. The stereochemical assignments are based to a large part on analysis of the n.m.r. spectra of these compounds. We present here the results of the analyses.

The synthesis of the compounds **1***a–c* and **2***a–c* was accomplished through a 1,3-dipolar addition (2) of phenyldiazomethane to an electron deficient olefin followed by pyrolysis of the resulting pyrazoline (Scheme 1). The isomers were separated by v.p.c. The amides **1***d* and **2***d* were prepared from the corresponding nitriles, **1***c* and **2***c*, by treatment with basic hydrogen peroxide (3).

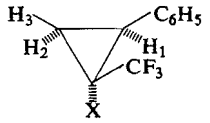
The analyses of the 100 MHz n.m.r. spectra were accomplished with the LAOCN 3 computer program (4). In order to resolve the coupling between the fluorine nuclei and the benzylic protons in **1***a–d* it was found necessary to decouple the aromatic protons. The analysis of **2***c* was verified by obtaining a satisfactory agreement between the derived parameters from both the 60 and 100 MHz spectra. The relative sign of the geminal coupling constant was confirmed in **1***b* and **2***b* by means of a spin tickling experiment (5). The refined spectral parameters are presented in Tables 1 and 2.

The assignment of the relative stereochemistry in **1***a* and **2***a* is based on the well verified assumption (6) that in cyclopropanes the *cis* vicinal coupling is larger than the *trans* vicinal coupling. The comparison of the derived coupling constants between the hydrogen α to the trifluoromethyl group (X = H) and H-2 and -3 in **1***a* and **2***a* places H-2 *cis* to the α-proton in **1***a* and H-3 *cis* to the α-proton in **2***a*. Since H-2 is *cis* to the benzylic proton in both **1***a* and **2***a*, this allows the assignment of **1***a* as *cis*-trifluoromethylphenyl cyclopropane[1] and **2***a* as *trans*-trifluoromethylphenylcyclopropane. This assignment is confirmed by a comparison of the derived coupling constants between the α-proton and H-1 in **1***a* (8.97 Hz) and **2***a* (4.63 Hz).

The stereochemical assignments of the nitriles **1***c* and **2***c* come from a competition experiment in which the nitriles were converted to amides by the action of basic hydrogen peroxide. It was expected that the rate of reaction of the compound with the nitrile *cis* to the phenyl would be slower than the unhindered isomer with the nitrile *trans* to the phenyl based on experiments with the model compounds *cis*- and *trans*-1-methyl-2-phenylcyclopropyl carbonitrile. A rate difference of approximately 10 was found between the two isomers and therefore allows the assignment of nitriles (**1***c* as *cis*- and **2***c* as *trans*-1-trifluoromethyl-2-phenylcyclopropyl carbonitrile) as well as the corresponding amides **1***d* and **2***d*. This assignment is also corroborated by the relative v.p.c. retention times of the nitriles (**1***c* = 31 min, **2***c* = 25 min) and the t.l.c. R_f's of the amides (ether eluant, **1***d* = 0.5, **2***d* = 0.7).

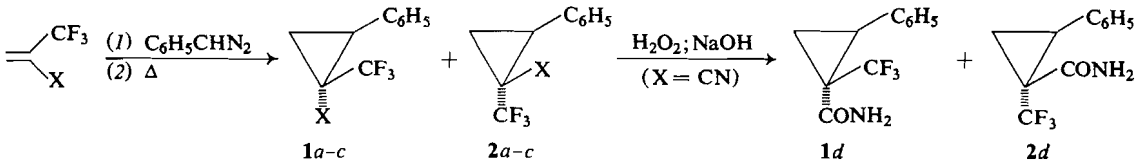
[1]All compounds are named as derivatives of cyclopropane for convenience in following the stereochemical assignments; *cis* and *trans* refer to the relative orientation of the trifluoromethyl and phenyl substituents.

TABLE 1. Refined spectral parameters*



Parameter	**1***a* (X = H)	**1***b* (X = Br)	**1***c* (X = CN)	**1***d* (X = $CONH_2$)
ω(F)	17.26	12.96	15.74	19.23
ω(1)	2.386	3.016	3.176	3.102
ω(2)	1.169	1.707	1.948	1.976
ω(3)	1.369	1.964	2.049	1.832
ω(X)	1.774	—	—	—
J(F1)	0.99	0.93	1.33	1.24
J(F2)	1.36	1.62	1.68	1.94
J(F3)	0.27	−0.03	−0.15	−0.06
J(FX)	7.49	—	—	—
J(12)	9.21	10.49	9.89	9.63
J(13)	7.24	8.57	8.83	8.25
J(1X)	8.97	—	—	—
J(23)	−5.84	−7.36	−6.94	−5.25
J(2X)	8.92	—	—	—
J(3X)	5.92	—	—	—

*Proton chemical shifts are reported in p.p.m. downfield from internal TMS; fluorine chemical shifts are reported in p.p.m. downfield from external trifluoroacetic acid. The maximum probable error for any parameter obtained from the LAOCN3 program is 0.022 Hz. We believe that an error limit of ±0.09 Hz should be placed on any reported parameter.



a X = H
b X = Br
c X = CN

SCHEME 1

With this series of six compounds in hand it was now possible to assign the bromides **1***b* and **2***b* on the basis of the four–bond fluorine proton coupling constants (J_{F2} and J_{F3}). It is observed that this four bond coupling is larger when the CF_3 and proton are *trans* to each other. Indeed, in the nitriles the spectra could only be fitted with a negative value of the *cis* coupling constant. Thus it was possible to assign **1***b* as *cis*- and **2***b* as *trans*-1-trifluoromethyl-2-phenylcyclopropyl bromide. This assignment is also consistent with the empirical observation that the fluorines on a CF_3 *cis* to a phenyl are deshielded by approximately 6 p.p.m. relative to those on a CF_3 *trans* to the phenyl.

Experimental

The n.m.r. spectra were taken of $CDCl_3$ solutions (≈20%) on a Varian HA-100 spectrometer. Peak positions were obtained to 0.1 Hz by means of charts calibrated by a Hewlett Packard 5512A frequency counter. The v.p.c.'s were run on an F&M model 700 with a 20 ft by 1/4 in. column of 20% carbowax 20 M on Chromosorb W with a gas flow of 100 ml/min at 145°.

1-Trifluoromethyl-2-phenylcyclopropane

A mixture of phenyldiazomethane (7) and excess trifluoropropene[2] at reflux was irradiated with two 300 W unfrosted incandescent lamps until all the phenyldiazomethane had reacted. The resulting crude pyrazoline was pyrolyzed directly in the v.p.c. injection port (200°) to give *cis*- and *trans*-1-trifluoromethyl-2-phenylcyclopropane. The v.p.c. retention times: *cis* 20 min, *trans* 13 min.

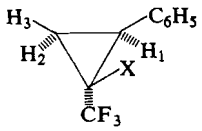
Anal. Calcd. for $C_{10}H_9F_3$: C, 64.52; H, 4.84; F, 30.64. Found: (*trans*): C, 64.66; H, 4.88; F, 30.32; (*cis*): C, 64.74; H, 4.91; F, 30.85.

1-Trifluoromethyl-2-phenylcyclopropyl Bromide

A solution of phenyldiazomethane in petroleum ether

[2]We thank E. I. du Pont de Nemours and Co. for a generous gift of this compound.

TABLE 2. Refined spectral parameters*



Parameter	2*a* (X = H)	2*b* (X = Br)	2*c* (X = CN)†	2*d* (X = $CONH_2$)
ω(F)	11.33	7.24	9.64	12.56
ω(1)	2.277	2.696	2.796	2.75
ω(2)	1.293	1.912	1.686	1.568
ω(3)	1.069	1.645	1.727	2.100
ω(X)	1.718	—	—	—
J(F1)	0.51	—‡	0.50	—‡
J(F2)	0.43	−0.03	−0.34	−0.01
J(F3)	1.09	1.35	1.39	1.90
J(FX)	6.59	—	—	—
J(12)	9.50	10.50	9.61	9.97
J(13)	6.31	8.31	8.15	7.85
J(1X)	4.63	—	—	—
J(23)	−5.65	−7.21	−6.50	−5.93
J(2X)	5.53	—	—	—
J(3X)	8.99	—	—	—

*Proton chemical shifts are reported in p.p.m. downfield from internal TMS; fluorine chemical shifts are reported in p.p.m. downfield from external trifluoroacetic acid. The maximum probable error for any parameter obtained from the LAOCN3 program was 0.027 Hz. We believe that an error limit of ±0.11 Hz should be placed on any reported parameter.

†In order to better resolve the second order spectrum approximately 5% C_6D_6 was added to the $CDCl_3$ solution.

‡The benzylic proton could not be effectively decoupled from the aromatic protons and thus sufficient resolution was not obtained to calculate this coupling constant.

was added to a refluxing solution of 2-bromo-3,3,3-trifluoropropene (8) in petroleum ether. The solvent was removed under reduced pressure when a pink color persisted and the crude pyrazoline was pyrolyzed directly in the v.p.c. injection port (injector temperature, 200°) to give *cis*- and *trans*-1-trifluoromethyl-2-phenylcyclopropyl bromide. The v.p.c. retention times: *cis* 36 min, *trans* 32 min.

Anal. Calcd. for $C_{10}H_8BrF_3$: C, 45.28; H, 3.01; Br, 30.14; F, 21.51. Found (*trans*): C, 45.38; H, 3.07; Br, 30.24; F, 21.23; (*cis*): C, 45.49; H, 3.12; Br, 30.27; F, 21.49.

1-Trifluoromethyl-2-phenylcyclopropanecarbonitrile

A crude mixture of *cis*- and *trans*-1-trifluoromethyl-2-phenylcyclopropanecarbonitrile, prepared by the addition of a solution of phenyldiazomethane in petroleum ether to a solution of α-trifluoromethylacrylonitrile[3] in petroleum ether at 0° followed by evaporation of the solvent under reduced pressure, was separated by preparative v.p.c. (retention times: *trans* 25 min, *cis* 31 min).

Anal. Calcd. for $C_{11}H_8F_3N$: C, 62.56; H, 3.82; N, 6.63. Found (*trans*): C, 62.67, H, 3.85; N, 6.55; (*cis*): C, 62.58; H, 3.89; N, 6.58.

1-Trifluoromethyl-2-phenylcyclopropanecarboxamide

cis-1-Trifluoromethyl-2-phenylcyclopropanecarboxamide was prepared from the reaction of *cis*-1-trifluoromethyl-2-phenylcyclopropanecarbonitrile (30 mg) in NaOH (0.3 ml) and 30% H_2O_2 (0.3 ml) in acetone (1 ml) at room temperature for 16 h followed by partitioning of the crude product between methylene chloride and water, preparative t.l.c. (silica gel HF; ether as eluant), and sublimation (80° at 10^{-3} mm Hg).

The *trans*-isomer was analogously prepared except for a longer reaction time (40 h). A mixture of the two amides could be separated by preparative t.l.c. (ether as eluant) with the *trans*-isomer having the highest R_f (0.5, 0.7).

Anal. Calcd. for $C_{11}H_{10}F_3NO$: C, 57.64; H, 4.40; N, 6.11. Found (*cis*): C, 57.44; H, 4.44; N, 6.04; (*trans*): C, 57.60; H, 4.44; N, 6.00.

Competition Experiment

To a stirred mixture of *cis*- (20.5 mg) and *trans*-1-trifluoromethyl-2-phenylcyclopropanecarbonitrile (20.5 mg) acetone (0.4 ml), 1.0 *N* NaOH (0.1 ml), and *o*-dichlorobenzene (15.9 mg) at 20° was added in one portion 30% H_2O_2 (0.80 ml). Aliquots were withdrawn and analyzed directly by v.p.c. by comparing the areas of the nitrile peaks and that of *o*-dichlorobenzene. After 1 h 4.8% of the *trans*-isomer had reacted whereas 53% of the *cis*-isomer had reacted.

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[3]Prepared from trifluoroacetone by the method of Buxton *et al.* (9).

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2-Arylimino-1,3-thiaazacycloalkanes

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The reaction of ω-bromoalkyl isothiocyanates with aromatic amines served as a general preparative method for homologous 2-arylimino-1,3-thiaazacycloalkanes. Rings containing seven to thirteen members were prepared in this way. The isothiocyanates and some of the thiaazacycloalkanes had anthelmintic activity.

La réaction d'isothiocyanates d'ω-bromoalkyles avec les amines aromatiques s'avère une méthode générale de préparation d'arylimino-2 thiaaza-1,3 cycloalcanes. Des cycles contenant de sept à treize atomes ont été préparés de cette manière. Les isothiocyanates et quelques-un des thiaazacycloalcanes possèdent une activité anthelmintique.

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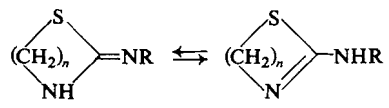
Five- and six-membered ring compounds having the general structures **A** and **B** have been extensively studied; the thiazine derivatives have



A **B**

shown potentially useful pharmacological properties (1) and the thiazolidines have anthelmintic action (2). Compounds in which $n > 3$ have not been previously reported; the preparation and some biological properties of compounds of general structure **A** where $n = 4$, 5, 6, 8, and 10 are described in this paper.

The methods commonly used for the preparation of 2-aryliminotetrahydro-1,3-thiazines were examined for possible applicability to the synthesis of larger rings. The most common procedure for preparing the six-membered rings is the acid-catalyzed cyclization of ω-hydroxyalkylthioureas (eq. 1). The reaction proceeded smoothly when $n = 3$ (or 2) but when $n = 4$, no cyclization occurred. Of the other methods which have been reported (1, 3, 4) for the synthesis of the six-membered rings, the reaction of 3-bromopropyl isothiocyanate with aromatic amines (1, 4) was the most readily adaptable to the synthesis of larger rings. The reaction of ω-bromopropylalkyl isothiocyanates with aromatic amines (eq. 2) was found to be a convenient general method.

[1] $$RNH\,C(=S)\,NH(CH_2)_nOH \xrightarrow[\text{HCl}]{\text{concentrated}} A$$

[2] $$Br(CH_2)nNCS + ArNH_2 \rightarrow A$$
(n = 4, 5, 6, 8, and 10)

The ω-bromoalkyl isothiocyanates (listed in Table 1) were obtained by the reaction of thiophosgene with ω-bromoalkylamine hydrobromides. In the case of the preparation of 4-bromopropyl isothiocyanate, it was observed that a variable amount (10–25%) of 4-chloropropyl isothiocyanate was also obtained, apparently by halogen exchange with thiophosgene. The ω-bromoalkylamines were obtained by standard methods from α,ω-dibromoalkanes via the monophthalimido derivatives.

Recent work by Toldy *et al.* (5), Cherbuliez