tetrahydrofuran solution after distillation of the solvent, weighed 0.320 g. Crystallization from pentane, in which the material is quite soluble, furnished a few crystals of **1**, mp 42–45°, no depression when mixed with the product, mp 44–46°, from the reaction of phenylmagnesium bromide with *trans*-2,3-dichloro-1,4-dioxane.[5b] The infrared spectra of the uncrystallized material and the latter[5b] were identical.

In an alternate preparation, 10.0 g (0.0324 mole) of **4b**, 41.0 g (0.334 mole) of 1-bromopropane, and 12.2 g (0.50 g-atom) of magnesium were processed in an analogous way. Crude **1**, weighing 7.6 g (97%), was subjected to a chromatographic procedure on alumina using pentane–ether as an eluent.[5b] The middle fractions (4.3 g total) crystallized after removal of the solvent. These all melted between 40 and 44° (no depression) and had infrared spectra identical with the 2,3-diphenyl-1,4-dioxane (mp 46°), prepared as described.[5b] While the three fractions immediately preceding and immediately following (1.2 g total) would not crystallize, their infrared spectra were indistinguishable from crystalline **1**.

Registry No.— **1**, 4336-11-2; *cis*-**1**, 4336-10-1; **4a**, 7593-64-8; **4b**, 7593-65-9; **6**, 7593-66-0; (+)-**6**, 7650-75-1; (−)-**6**, 7593-67-1.

Acknowledgment.—A part of this research was supported by National Science Foundation Grant GP-4656.

Iminodioxolanes from Fluoro Ketones and Alkyl Isocyanides

W. J. MIDDLETON, D. C. ENGLAND, AND C. G. KRESPAN

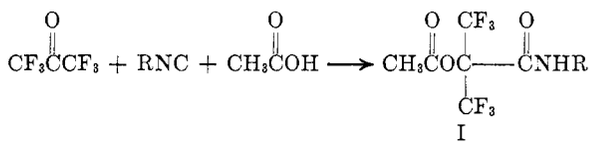
Contribution No. 1263 from the Central Research Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware

Received November 23, 1966

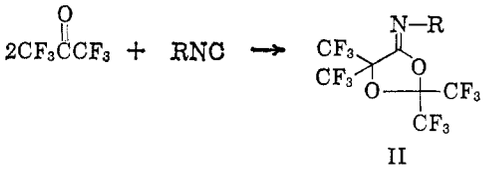
Iminodioxolanes are obtained from the reaction of fluoro ketones, such as hexafluoroacetone, with alkyl isocyanides.

Many diverse products can be prepared from the reaction of a carbonyl compound with an alkyl isocyanide in the presence of a third component (HX).[1] An example is the Passerini reaction, in which α-acyloxycarboxylic acid amides are formed from ketones, isocyanides, and carboxylic acids.[2] However, there appears to be no report of a stable reaction product formed from a ketone and an isocyanide alone.[2a]

We have found that fluoro ketones, such as hexafluoroacetone, undergo the Passerini reaction with extreme ease to give high yields of α-acyloxycarboxylic acid amides (I). If no carboxylic acid is present, however, an immediate and exothermic reaction still occurs, even at very low temperatures, and a 2:1 adduct of the ketone and isocyanide is formed. This adduct, which is a 4-iminodioxolane (II), is the only product formed regardless of the molar ratio of the reactants or the order of addition.



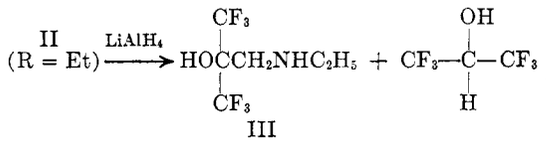
I



II

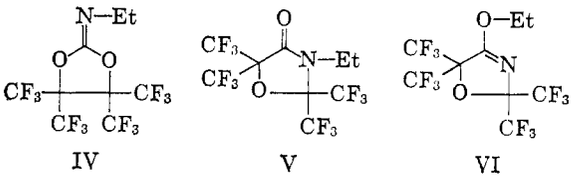
The iminodioxolane (II, R = Et) prepared from hexafluoroacetone and ethyl isocyanide is exceptionally resistant to both acidic and basic hydrolysis. It is unaffected by refluxing concentrated hydrochloric acid or aqueous 10% sodium hydroxide solution. In addition, it has high thermal stability, as it can be distilled at atmospheric pressure and heated at 300° in a sealed tube without decomposition. Products formed from hexafluoroacetone and other isocyanides, such as methyl, cyclohexyl, and *t*-butyl isocyanides, appear to have similar hydrolytic and thermal stability.

The structures of these adducts were established as iminodioxolanes (II) by elemental analysis and spectral data. The adducts show two kinds of fluorine in equivalent amounts in their F^{19} nmr spectra; the H^1 nmr spectra are consistent with an alkyl group attached to nitrogen; the infrared spectra show absorption between 5.64 and 5.68 mμ for the imino group. Because of their surprising hydrolytic stability, however, a more rigorous structure proof for these products was obtained by a reductive degradation of the hexafluoroacetone–ethyl isocyanide adduct. Reduction of II (R = Et) with lithium aluminum hydride gave the amine (III) and hexafluoroisopropyl alcohol. The



III

reduction product (III) shows that in II the carbon of the isocyanide unit is attached to the carbon of a ketone unit, and therefore rules out the iminocarbonate structure (IV) for the adduct. Other possible isomeric rearrangement structures (V and VI) were eliminated from consideration by an independent synthesis of these compounds.[3]



IV V VI

(1) I. Ngi, *Angew. Chem.*, **74**, 9 (1962).

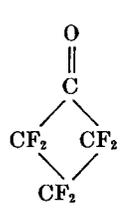
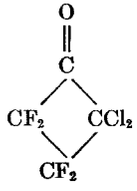
(2) M. Passerini, *Gazz. Chim. Ital.*, **61**, 964 (1931), and preceeding communications.

(2a) NOTE ADDED IN PROOF.—N. P. Gambaryan, E. M. Rokhlin, Yu. V. Zeifman, C. A. Simonyan, and I. L. Knunyants [*Dokl. Akad. Nauk. SSSR*, **166**, 864 (1966)] have recently described the reaction of hexafluoroacetone and nitropentafluoroacetone with cyclohexyl isocyanide to give dioxolanes.

(3) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **32**, 951 (1967).

Table I

Iminodioxolanes from Fluoro Ketones and Isocyanides

Reactants			Dioxolanes					Carbon, %		Hydrogen, %		Fluorine, %		Nitrogen, %	
Ketone	Isocyanide	Product	Formula	Yield, %	Bp, °C (mm)	$n^{25}D$	Infrared, μ (C=N)	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
CF_3COCF_3	Methyl	4-Methylimino-2,2,5,5-tetrakis(trifluoromethyl)-1,3-dioxolane	$C_8H_3F_{12}NO_2$	87	53 (90 mm)	1.3090	5.62, 5.67, doublet	25.76	26.19	0.81	1.05	61.12	60.73	3.76	3.81
	Ethyl	4-Ethylimino-2,2,5,5-tetrakis(trifluoromethyl)-1,3-dioxolane	$C_9H_5F_{12}NO_2$	80	120–121	1.3151	5.65	27.93	27.78	1.30	1.49	58.88	58.84	3.62	3.66
	Cyclohexyl	4-Cyclohexylimino-2,2,-5,5-tetrakis(trifluoromethyl)-1,3-dioxolane	$C_{13}F_{11}F_{12}NO_2$	90	33–34 (1.0)	1.3556	5.68	35.40	34.65	2.52	2.20	51.67	51.60	3.18	3.75
	t-Butyl	4-*t*-Butylamino-2,2,5,5-tetrakis(trifluoromethyl)-1,3-dioxolane	$C_{11}H_9F_{12}NO_2$	75	52–53(2.6)	1.3240	5.64	31.82	32.48	2.19	2.39	54.92	54.97		
CF_3COCF_2Cl	Ethyl	4-Ethylimino-2,5-bis(trifluoromethyl)-2,5-bis(chlorodifluoromethyl)-1,3-dioxolane[a,b]	$C_9H_5Cl_2F_{10}NO_2$	88	55.6–56 (10)	1.3634	5.70	25.74	25.94	1.20	1.33	45.24	45.04	3.33	3.40
$CF_2ClCOCF_2Cl$	Cyclohexyl	4-Cyclohexylimino-2,2,-5,5-tetrakis(chlorodifluoromethyl)-1,3-dioxolane[c]	$C_{13}H_{11}F_8Cl_4NO_2$	95	89 (1)	1.4308	5.65	30.8	31.1	2.2	2.4	30.0	30.1	2.8	3.0
$CF_2ClCOCFCl_2$	Ethyl	4-Ethylimino-2,5-bis(chlorodifluoromethyl)-2,5-bis(dichlorofluoromethyl)-1,3-dioxolane[d]	$C_9H_5Cl_6F_6NO_2$	85	83–86 (0.25)	1.4507 (supercooled) (mp 28–30)	5.72	22.23	22.51	1.04	1.26	23.46	23.23	2.65	2.56
	Methyl	11-Methylimino-5,10-dioxaperfluorodispiro-[3.1.3.2]undecane	$C_{10}H_3F_{12}NO_2$	89	69 (50)	1.3415	5.68	30.25	30.47	0.77	0.98	57.43	57.31	3.53	3.47
	Ethyl	11-Ethylimino-5,10-dioxaperfluorodispiro-[3.1.3.2]undecane	$C_{11}H_5F_{12}NO_2$	60	72 (50)	1.3411	5.65	32.1	32.4	1.2	1.2	55.5	55.6	3.4	3.8
	t-Butyl	11-*t*-Butylimino-5,10-dioxaperfluorodispiro-[3.1.3.2]undecane	$C_{13}H_9F_{12}NO_2$	93	85 (50)	1.3475	5.65	35.6	34.6	2.1	2.2	51.9	51.8	3.2	3.5
	*t*-Butyl	11-*t*-Butylimino-3,3,7,7-tetrachloro-5,10-dioxaperfluorodispiro-[3.1.3.2]undecane[e]	$C_{13}H_9F_8Cl_4NO_2$	84	68 (1)	1.4192	5.65	30.9	31.5	1.8	1.9	30.1	30.3	2.8	3.2

[a] Mixture of *cis* and *trans* isomers. [b] *Anal.* Calcd: Cl, 16.88. Found: 16.72. [c] *Anal.* Calcd: Cl, 28.0. Found: 27.8. [d] *Anal.* Calcd: Cl, 43.79. Found: 43.58. [e] *Anal.* Calcd: Cl, 28.1. Found: Cl, 27.9.

Other fluoro ketones, in addition to hexafluoroacetone, react spontaneously when mixed with alkyl isocyanides, and iminodioxolanes have been prepared from chloropentafluoroacetone, 1,3-dichlorotetrafluoroacetone, 1,3,3-trichlorotrifluoroacetone, hexafluorocyclobutanone, and 2,2-dichlorotetrafluorocyclobutanone by this method. The chlorofluoroacetones all react at slower rates than does hexafluoroacetone, in proportion to the amount of chlorine they contain. Hexafluoroacetone and hexafluorocyclobutanone react immediately with ethyl isocyanide, even at −78°, but 1,3,3-trichlorotrifluoroacetone requires several hours at room temperature. The iminodioxolanes prepared by this reaction are listed in Table I.

Experimental Section[4]

Reactions of Fluoro Ketones with Isocyanides.—The iminodioxolanes listed in Table I were prepared by mixing, with cooling, the fluoro ketones with the appropriate isocyanides and distilling the mixture. Either reagent can be added to the other with similar results. This reaction is specifically illustrated by the following.

Hexafluoroacetone was distilled into a flask, fitted with a Dry Ice cooled condenser that contained 27.5 g (0.2 mole) of ethyl isocyanide. The rate of addition and cooling was adjusted so that the temperature of the reaction mixture remained below 50°. The addition was stopped when no further evidence of an exothermic reaction was observed. The reaction mixture was distilled to give 4-ethylimino-2,2,5,5-tetrakis(trifluoromethyl)-1,3-dioxolane as a colorless liquid, bp 120–121°. The H^1 nmr spectrum showed a triplet (J = 8 cps) at τ 8.75 (3 H) and a quartet (J = 8 cps) at 6.39. The F^{19} nmr spectrum showed two septets (J = 5.25 cps) centered at 75.6 and 81.2 ppm.

Reduction of 4-Ethylimino-2,2,5,5-tetrakis(trifluoromethyl)-1,3-dioxolane.—A stirred solution of 5.0 g of lithium aluminum hydride and 39 g (0.1 mole) of the dioxolane in 150 ml of ether was heated at reflux for 20 hr and then cooled. The excess hydride was decomposed by successive additions of 5 ml of water, 5 ml of 15% aqueous sodium hydroxide solution, and 15 ml of water. The mixture was filtered, and the filtrate was distilled to give three principal fractions. The most volatile fraction (5.1 g, bp 77–82°) was shown to be a mixture of 2H-hexafluoroisopropyl alcohol[5] and ether by F^{19} and H^1 nmr, infrared, and gas chromatographic analysis. The second fraction (9.4 g, bp 118–121°) was unreduced starting material. The third fraction [8.2 g, bp 46–46.5° (10 mm), $n^{25}D$ 1.3400] was identified as N-ethyl-3,3,3-trifluoro-2-(trifluoromethyl)-2-hydroxypropylamine by elemental analysis and spectral data. The F^{19} nmr spectrum showed a singlet at 79.7 ppm. The H^1 nmr spectrum showed a singlet at τ 5.87 (CH + NH) that disappeared upon treatment with D_2O, a singlet at 6.94 (CH_2), a quartet (J = 7 cps) at 8.29 (CH_2), and a triplet (J = 7 cps) at 8.92 (CH_3).

Anal. Calcd for $C_6H_6F_6NO$: C, 32.01; H, 4.03; F, 50.64; N, 6.22. Found: C, 32.37; H, 4.25; F, 50.43; N, 6.85.

N-Ethyl-3,3,3-trifluoro-2-trifluoromethyl-2-acetoxypropionamide.—Ethyl isocyanide (0.55 g, 0.01 mole) was added rapidly to a solution of 1 ml (at −78°, *ca.* 0.01 mole) of hexafluoroacetone and 1 ml of acetic acid in 5 ml of ether cooled to −78°. The reaction mixture was stirred and warmed to 25°. A heavy, white precipitate formed. The mixture was cooled again, and the precipitate was collected on a filter, washed with pentane, and recrystallized from hexane to give 2.0 g (71% yield) of N-ethyl-3,3,3-trifluoro-2-trifluoromethyl-2-acetoxypropionamide as colorless needles, mp 87–87.5°. The mass spectrum showed major ions at m/e 281 (parent), 238 (parent with loss of CH_3CO), 72 ($EtNHCO^+$), and 43 (CH_3CO^+).

Anal. Calcd for $C_8H_9F_6NO_3$: C, 34.17; H, 3.23; F, 40.55; N, 4.98. Found: C, 34.37; H, 3.33; F, 40.45; N, 5.08.

N-Cyclohexyl-3,3,3-trifluoro-2-trifluoromethyl-2-acetoxypropionamide.—Hexafluoroacetone (11 ml at −78°, 0.1 mole) was slowly distilled into a flask fitted with a Dry Ice cooled reflux condenser containing 9 g (0.15 mole) of acetic acid. Cyclohexyl isocyanide (10.9 g, 0.1 mole), was added dropwise to the stirred reaction mixture. At the end of the addition the reaction mixture solidified. The solid was broken up and recrystallized from benzene to give 25.3 g of N-cyclohexyl-3,3,3-trifluoro-2-trifluoromethyl-2-acetoxypropionamide as colorless needles, mp 135–136°.

Anal. Calcd for $C_{12}H_{15}F_6HO_3$: C, 43.00; H, 4.52; F, 34.01; N, 4.17. Found: C, 43.17; H, 4.71; F, 34.07; N, 4.27.

Registry No.—4-Ethylimino-2,2,5,5-tetrakis(trifluoromethyl)-1,3-dioxolane, 7775-61-3; N-ethyl-3,3,3-trifluoro-2-(trifluoromethyl)-2-hydroxypropylamine, 7730-48-5; N-ethyl-3,3,3-trifluoro-2-(trifluoromethyl)-2-acetoxypropionamide, 7730-49-6; N-cyclohexyl-3,3,3-trifluoro-2-trifluoromethyl-2-acetoxypropionamide, 7730-50-9; 4-methylimino-2,2,5,5-tetrakis(trifluoromethyl)-1,3-dioxolane, 7730-51-0; 4-cyclohexylimino-2,2,5,5-tetrakis(trifluoromethyl)-1,3-dioxolane, 5771-96-0; 4-*t*-butylimino-2,2,5,5-tetrakis(trifluoromethyl)-1,3-dioxolane, 7730-53-2; 4-ethyl-2,5-bis(trifluoromethyl)-2,5-bis(chlorodifluoromethyl-1,3-dioxolane, 7730-54-3; *trans* isomer of **8**, 7730-55-4; 4-cyclohexylimino-2,2,5,5-tetrakis(chlorodifluoromethyl)-1,3-dioxolane, 7730-56-5; 4-ethylimino-2,5-bis(chlorodifluoromethyl)-2,5-bis(dichlorofluoromethyl)-1,3-dioxolane, 7730-57-6; 11-methylimino-5,10-dioxaperfluorodispiro[3.1.3.2]-undecane, 7730-58-7; 11-ethylimino-5,10-dioxaperfluorodispiro[3.13.2]undecane, 7730-59-8; 11-*t*-butylimino-5,10-dioxaperfluorodispiro[3.1.3.2]undecane, 7730-60-1; 11-*t*-butylimino-3,3,7,7-tetrachloro-5,10-dioxaperfluorodispiro[3.1.3.2]undecane, 7770-96-9.

(4) Fluorine nmr spectra were obtained with a Varian Associates high-resolution spectrometer operating at 56.4 Mc. Spectra were calibrated in terms of higher field displacement in parts per million (ppm) from the F^{19} resonance of trichlorofluoromethane. Proton spectra were obtained on a Varian A-60 spectrometer.

(5) W. J. Middleton and R. V. Lindsey, Jr., *J. Am. Chem. Soc.* **86**, 4948 (1964).