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THERMAL CONDENSATION OF SUBSTITUTED IMIDAZOLES WITH TRIFLUOROACETALDEHYDE

SHOZO FUJII, YASUO MAKI, HIROSHI KIMOTO *

Government industrial Research Institute, Nagoya;
Hirate-cho, Kita-ku, Nagoya 462 (Japan)

and LOUIS A. COHEN

Laboratory of Chemistry, National Institute of Arthritis,
Diabetes, Digestive and Kidney Diseases, National Institutes
of Health; Bethesda, Maryland 20205 (U.S.A.)

SUMMARY

The title condensation provides the corresponding (1'-hydroxy-2',2',2'-trifluoroethyl)imidazoles in yields dependent on the electronic nature of the substituent: ortho-para directors promote the reaction while meta directors retard it strongly. 1-Alkylimidazoles gave only 2-adducts. 2-Substituted imidazoles yielded 4(5)-adducts together with small amounts of 4,5-bis-adducts. 4(5)-Substituted imidazoles provided 5(4)-adducts as the main products together with 2-adducts and 2,5(4)-bis-adducts.

INTRODUCTION

We have recently described[1] the facile thermal condensation of imidazole with trifluoroacetaldehyde. In continuation of the study, the reaction has been extended to substituted imidazoles in order to expand the synthetic scope and to evaluate directing and activating/deactivating effects of the substituents.

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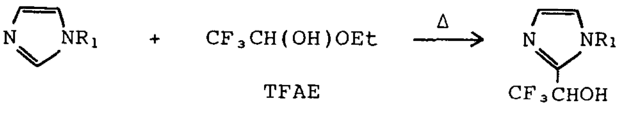
RESULTS AND DISCUSSION

The condensation was performed by simple reflux (Method A) with equimolar amounts of imidazoles and trifluoroacetaldehyde ethyl hemiacetal (TFAE, bp 103-105°C). The reaction time was estimated according to the expected reactivity of the imidazole. With the less reactive imidazoles, sealed tubes were used for heating at the higher temperature (Method B, oil bath at 150-155°C). The optimum conditions for this condensation have not been examined; however, extended heating at the higher temperature did not always increase the yield of adducts because TFAE was found to decompose under the conditions adopted for Method B. The reaction methods and isolated product yields are given in Table 1. Product mixtures were resolved by silica gel chromatography; almost all the adducts could be purified by recrystallization and were characterized by elemental analysis, IR, mass and NMR spectra (Table 2). Although no mass spectral data are listed, large molecular ion peaks were found for all adducts; another major peak corresponds to the ion generated by loss of the trifluoromethyl group from the molecule.

Thermal condensation of 1-substituted imidazoles

Reactivity of 1-alkylimidazoles was less than that of imidazole[1] and of other alkylimidazoles. Thus, only 5% of the adduct (Ia) was found together with 95% unreacted TFAE (by ^{19}F NMR direct analysis) after reflux with 1-methylimidazole for 8 hours. The yield was increased to 12.5% at higher reaction temperature and to 24% with 1-benzylimidazole. The condensation occurs exclusively at C-2 of the imidazole ring. The



Ia,b,c

R_1 : a) CH_3, b) CH_2CH_3, c) $CH_2C_6H_5$

TABLE 1

Thermal condensation of substituted imidazoles with trifluoroacetaldehyde ethyl hemiacetal

Imidazoles					Reaction		Yields		
R_1 (N-1)	R_2 (C-2)	R_3 (C-4)	R_4 (C-5)	(mmol)	Method[a]	time (hour)	2-adduct (%)	4-adduct (%)	bis-adduct (%)[b]
Me	H	H	H	20	B	24	12.5	0	0
Et	H	H	H	20	B	24	16.5	0	0
Bz	H	H	H	20	B	24	23.8	0	0
H	Me	H	H	20	A	6	—	62.2	9.7
H	Et	H	H	20	A	6	—	76.5	7.2
H	Ph	H	H	20	A	6	—	71.2	4.4
H	CF_3	H	H	10	A	24	—	8.5[c]	0
H	H	Me	H	20	A	3	11.1	73.3	15.5
H	H	Ph	H	17.3	A	8	5.2	61.1	13.3
H	H	Cl	H	10	A	10	4.0	24.9	11.2
H	H	CH_2OH	H	20	A	10	6.1	20.1	13.9
H	H	CF_3	H	10	A	10	0	0	0
H	H	NO_2	H	10	A	10	0	0	0
Me	Me	H	H	20	B	24	—	36.3(5) 1.3(4)	0
H	Me	Me	H	20	A	8	—	91.7	—
H	Et	Me	H	20	A	2	—	76.0	—
H	Ph	Me	H	20	A	0.5	—	72.4	—
H	H	Me	Me	10	A	8	2.6	—	—
H	H	Ph	Ph	20	A	15	6.4	—	—
H	H	Cl	Cl	20	A	6	66.2	—	—
Benzimidazole				20	A	8	0	—	—

[a] Method A : Heated at reflux with equimolar amount of TFAE.
Method B : Heated in a sealed tube (oil bath 150-155 °C) with equimolar amount of TFAE.

[b] Calculated on the basis of TFAE.

[c] Estimated on the basis of ^{19}F NMR of a mixture with 2-trifluoromethylimidazole.

TABLE 2

NMR data of the products

	Products[a]				Chemical shifts (ppm)[b]							
	R_1 (N-1)	R_2 (C-2)	R_3 (C-4)	R_4 (C-5)	H-2[c]	H-4[c]	H-5[c]	CH-2[d]	CH-4(5)[d]	CF_3-2[e]	CF_3-4(5)[e]	etc.
Ia	Me	X	H	H		6.84[f]	7.08[f]	5.37		0.92		3.81s
Ib	Et	X	H	H		6.86[f]	7.18[f]	5.38		0.90		1.38t, 4.24q
Ic	Bz	X	H	H		6.86[f]	6.94[f]	5.55		1.51		5.31,5.52AB, 7.22s
IIa	H	Me	X	H			7.02		5.04		- 0.69	2.30s
IIb	H	Et	X	H			7.03		5.04		- 0.57	1.22t, 2.68q
IId	H	Ph	X	H			7.29		5.18		- 0.75	7.3 ~ 7.5m, 7.8 ~ 8.0m
IIe	H	CF_3	X	H			7.45		5.19		- 0.89	14.50s
IIIa	H	Me	X	X					5.39		- 0.49	2.31s
IIIb	H	Et	X	X					5.37		- 0.18	1.21t, 2.69q
IIId	H	Ph	X	X					5.50		- 0.03	7.3 ~ 7.5m, 7.8 ~ 8.1m
IVa	H	H	Me	X	7.56				5.18		- 0.42	2.26s
IVd	H	H	Ph	X	7.72				5.45		1.24	7.2 ~ 7.7m
IVf	H	H	Cl	X	7.68				5.34		- 0.88	
IVg	H	H	CH_2OH	X	7.62				5.28		- 0.53	4.71s
Va	H	X	Me	H			6.73	5.16		- 0.59		2.16s
Vd	H	X	Ph	H			7.54	5.33		- 0.46		7.2 ~ 8.1m
Vf	H	X	Cl	H			7.16	5.35		- 0.43		
Vg	H	X	CH_2OH	H			7.00	5.28		- 0.27		4.54s
VIa	H	X	Me	X				5.12	5.22	- 0.55	- 0.45	2.28s

VIa'	H	X	Me	X			5.09	5.21	- 0.57	- 0.68	2.28s
VId	H	X	Ph	X			5.33	5.44	0.06	1.10	7.3 ~ 7.7m
VId'	H	X	Ph	X			5.30	5.37	- 0.13	0.94	7.3 ~ 7.7m
VIf	H	X	Cl	X			5.31	5.28	- 0.22	- 0.74	
VIf'	H	X	Cl	X			5.34	5.32	- 0.11	- 0.65	
VIg	H	X	CH_2OH	X			5.24	5.27	- 0.59	- 0.35	4.72s
VII	Me	Me	H	X	6.81			5.26		0.49	2.28s, 3.62s
VIII	Me	Me	X	H		6.99		4.93		- 0.45	2.26s, 3.60s
IXa	H	Me	Me	X				5.01		- 0.69	2.17s, 2.23s
IXb	H	Et	Me	X				5.04		- 0.57	1.19t, 2.61q, 2.18s
IXd	H	Ph	Me	X				5.15		- 0.50	2.30s, 7.2 ~ 8.0m
Xa	H	X	Me	Me			5.15		- 0.55		2.09s
Xd	H	X	Ph	Ph			5.38		- 0.09		7.1 ~ 7.6m
Xf	H	X	Cl	Cl			5.23		- 0.56		

[a] X = CF_3CHOH

[b] 0.5 ~ 2% acetone-d_6 solution, with TMS as internal reference for ^1H, and positive δ values show downfield from the external reference, trifluoroacetic acid, for ^{19}F.

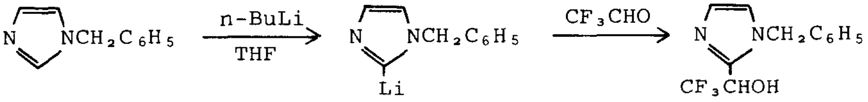
[c] singlet

[d] quartet J = 7Hz

[e] doublet J = 7Hz

[f] Assignments according to reference 2.

structures of the adducts (Ia-c) were elucidated on the basis of their ^1H NMR spectra. The two signals for the imidazole ring protons of the adducts appear at 6.8-7.2 ppm, in the region expected for H-4 and H-5 [2]. Structural assignments were confirmed by an alternative preparation of Ic. Thus, deprotonation of 1-benzylimidazole with n-butyllithium was followed by reaction of the carbanion with trifluoroacetaldehyde to give Ic in 12.5% yield[3]. It is well established that lithiation of 1-substituted imidazoles occurs exclusively at C-2 [4].

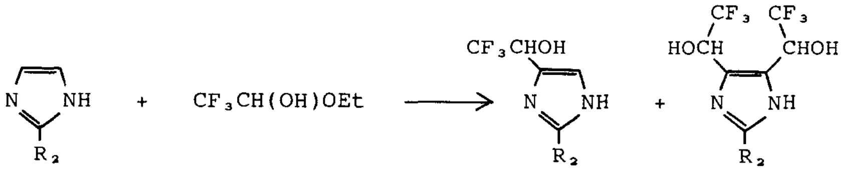


Ic

Thermal condensation of 1-substituted imidazoles with formaldehyde[5] or with other aldehydes[4b] has been reported to give 2-adducts. Trifluoroacetaldehyde also condenses at C-2 with complete regiospecificity but with poor yield. Imidazole itself affords the 2-adduct only as a minor product (8.8% yield)[1]. We had anticipated, therefore, that the formation and debenzylation[6] of Ic would provide a better route to the 2-adduct of imidazole; however, the yield and the need for high reaction temperature proved unsatisfactory. The alternative route, via the lithium derivative, was not better and we are now trying to increase the yields through both routes.

Thermal condensation of 2-substituted imidazoles

The thermal condensation of 2-alkyl- and 2-phenylimidazole[7] provided 4(5)-adducts (IIa,b,d) in good yield; small



IIa,b,d,e IIIa,b,d

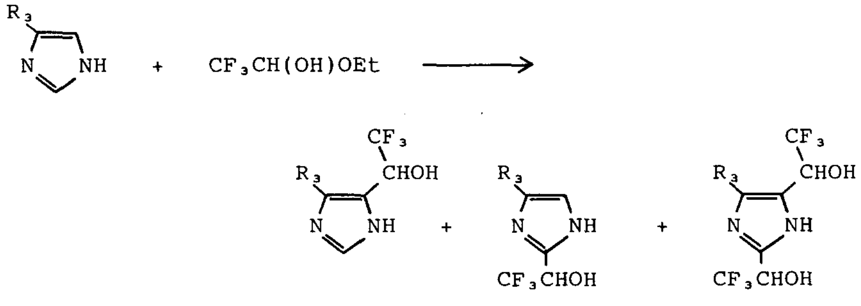
R_2 : a) CH_3, b) CH_2CH_3, d) C_6H_5, e) CF_3

amounts of the 4,5-bis-adducts (IIIa,b,d) were also obtained. Strong electronegative groups (e.g., trifluoromethyl) decrease reactivity, and the yield of IIe was 8.5%; no corresponding bis-adduct was detected by direct analysis with GC-MS and ^{19}F NMR. Chromatographic separation of IIe from unreacted 2-trifluoromethylimidazole proved difficult and the yield shown in Table 1 was estimated on the basis of ^{19}F NMR of a crystalline mixture of the two compounds. The phenyl group has both an electron-releasing resonance effect and an electron-withdrawing inductive effect and, in contrast to the trifluoromethyl group, does not reduce reactivity. Most likely, any C-2 substituent whose value of σ_p^+ is less positive than that of σ_p (usually ortho-para directors) will promote the condensation reaction.

The bis-adducts (IIIa,b,d) each has two asymmetric carbons and may occur as mixtures of diastereoisomers; however, NMR signals failed to resolve nor could the isomers be separated by chromatography. The CH and CF_3 signals of the tautomerically equivalent side chains of IIIa,b,d appear as one quartet and one doublet, respectively.

Thermal condensation of 4(5)-substituted imidazoles

4(5)-Substituted imidazoles afforded mainly 5(4)-adducts (IVa,d,f,g), together with lesser amounts of 2-adducts (Va,d,f,g) and 2,5(4)-bis-adducts (VIa,d,f,g). Imidazoles with strong electronegative substituents (e.g., nitro and tri-



IVa,d,f,g Va,d,f,g VIa,d,f,g

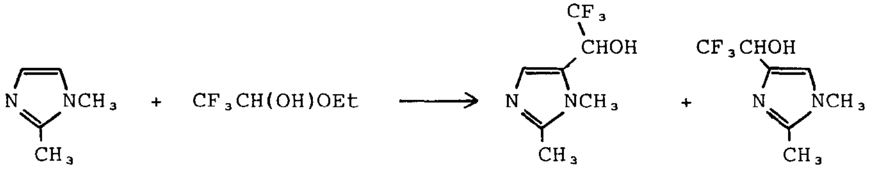
R_3 : a) CH_3, d) C_6H_5, f) Cl, g) CH_2OH

fluoromethyl) gave no adducts and unchanged starting materials were recovered quantitatively. As with 2-R-imidazoles, the condensation seems to be favored by ortho-para directing groups. The products (IVg, Vg and VIg) obtained from 4-hydroxymethylimidazole could be separated by silica gel chromatography; except for one of the diastereoisomers of the bis-adduct (VIg), however, the compounds failed to crystallize. Direct analysis by ^{19}F NMR showed that the 2,5(4)-bis-adducts (VIa,d,f,g) were obtained as mixtures of equal amounts of diastereoisomers, which could be separated by cautious silica gel chromatography. The two position isomers (IV and V) of the mono-adducts are readily differentiated on the basis of their ^{1}H NMR spectra. The imidazole-ring proton at C-2 usually appears at lower field than that at C-4(5) (Table 2) [8].

The condensations of 4(5)-methylimidazole with formaldehyde[9] and with trichloroacetaldehyde[10] have been reported to yield 5(4)-adducts; however, by-products were not reported in these early studies. The hydroxymethylation of 4(5)-bromoimidazole afforded a poor yield of the 5(4)-adduct while 4(5)-nitroimidazole gave no adduct[5c]; the hydroxymethylations of 4(5)-phenyl- and 4(5)-chloroimidazole have not been reported. Except for its greater reactivity, the condensation of trifluoroacetaldehyde with 4(5)-substituted imidazoles seems to parallel the results with formaldehyde and with trichloroacetaldehyde.

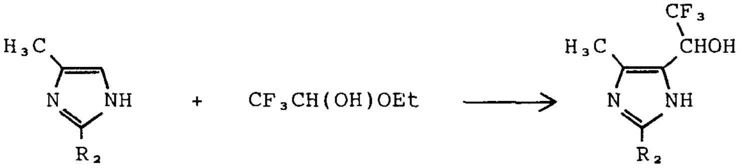
Thermal condensation of bis-substituted imidazoles

When heated in a sealed tube for 24 hours with TFAE, 1,2-dimethylimidazole provided the 5-adduct (VII) in 36.3% yield together with 1.3% of the 4-adduct. Structures were assigned on the basis of literature NMR data for H-4 and H-5 [2]. The selective substitution at C-5 is consistent with earlier evidence that C-2 and C-5 may be considered equivalent to para positions on a benzene ring while C-2 and C-4 show a meta relationship[11]. The hydroxymethylation of 1,2-dimethylimidazole has been reported to give the 5-adduct initially[12]; although several 1,2-bis-substituted imidazoles were found to give 4,5-bis-hydroxymethylated products eventually[12], no bis adduct was observed in the condensation with TFAE.



VII VIII

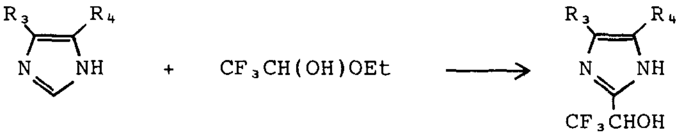
The thermal condensation of 2,4(5)-bis-substituted imidazoles with TFAE afforded 5(4)-adducts (IXa,b,d) in good yield, whereas the hydroxymethylation of 4(5)-methyl-2-phenylimidazole has been reported to be unsuccessful[13].



IXa,b,d

R_2 : a) CH_3, b) CH_2CH_3, d) C_6H_5

4,5-Bis-substituted imidazoles gave the expected 2-adducts (Xa,d,f), but in puzzling yields. 4,5-Dimethylimidazole should have been the most reactive but gave the poorest yield (2.6%), while 4,5-dichloroimidazole gave Xf in 66% yield. The low yield



Xa,d,f

R_3, R_4 : a) CH_3, d) C_6H_5, f) Cl

with 4,5-diphenylimidazole may be due, primarily, to its poor solubility in TFAE. Benzimidazole provided no adduct and was recovered quantitatively.

The literature data, together with our past[1] and present results, provide fairly strong evidence that aldehyde condensation at the three ring positions of imidazole may involve distinct and competitive mechanisms. Thus far, we have resisted written speculation about these mechanisms but are pursuing further studies which may bring order to a reaction with a history of mystery[14].

EXPERIMENTAL

Materials

TFAE was obtained from Central Glass Co., Ltd., and was distilled prior to use. The hemiacetal (bp 103-105°C) contained less than 5% ethanol as an azeotropic mixture. 2-Trifluoromethylimidazole (mp 146-147°C) and 4-trifluoromethylimidazole (mp 150-151°C) were prepared by photochemical trifluoromethylation of imidazole[15]. 4-Chloroimidazole (mp 119-120°C) and 4,5-dichloroimidazole (mp 181-182°C) were prepared by chlorination of imidazole[3]. 1-Benzylimidazole (mp 67-69°C) was prepared according to a published method[4b]. Other imidazoles were obtained from various commercial sources.

Analytical methods and instrumentation

Analytical methods and instrumentation have been described previously[1]. ^{1}H NMR spectra were recorded with TMS as internal reference; ^{19}F NMR spectra are reported with positive δ values downfield from the external reference, trifluoroacetic acid. The homogeneity and identity of each product were verified by NMR, IR, MS, GLC and TLC. Melting points are uncorrected. **All the products synthesized in this study are new compounds** and are listed in Table 3 together with their melting points and elemental analysis.

Thermal condensation of 1-substituted imidazoles with TFAE

A 10ml glass tube, containing 1-methylimidazole (1.64g, 20 mmol) and TFAE (2.88g, 20 mmol), was sealed under argon and was heated in an oil bath (150-155°C) for 24 hours. The reaction mixture was analyzed directly by GC-MS and ^{19}F NMR (ethanol solution): only one doublet was found at 0.51 ppm together with unreacted TFAE at -6.35 ppm in the ratio 17:83. After evaporation of ethanol and TFAE, the residual material was applied to a column of 100ml of silica gel and the column was eluted with (a) dichloromethane-ether, 1:1, (b) ether, and (c) ethyl acetate. There was obtained (after recrystallization) 0.45g (12.5% yield) of Ia as colorless needles, mp 139-140°C, from acetone-ether. The order of elution from the column was Ia (eluted with a) and 1-methylimidazole (with c).

This procedure is representative of all the thermal condensations of 1-substituted imidazoles.

Thermal condensation of 2-substituted imidazoles with TFAE

A mixture of 2-methylimidazole (1.64g, 20 mmol) and TFAE (2.88g, 20 mmol), in a 20ml flask, was heated at reflux under argon for 6 hours. With a rise in temperature, the mixture became homogeneous and the liberated ethanol refluxed. After storage overnight at ambient temperature, the reaction mixture deposited 1.53g of crystalline IIa which was collected by filtration and washed twice with 10% ethanol in ether. The filtrate and washings were combined and evaporated under reduced pressure. The residual material was applied to a column of silica gel (100 ml); the column was eluted with (a) ether-ethyl acetate, 1:1, (b) ether-ethyl acetate, 1:4, (c) ethyl acetate , and (d) ethyl acetate-methanol, 9:1. Combination with the first fraction gave a total yield of 2.24g (62.2%) of IIa as colorless plates, mp 168-169°C, from acetone. A second product consisted of 0.27g (9.7%) of IIIa as colorless plates, mp 212-218°C (decomp.), from acetone; this material may be an unresolved mixture of diastereoisomers. The order of elution from the column was bis-adduct (eluted with a and b), mono-adduct (with c), and 2-methylimidazole (with d).

This procedure is representative of the thermal condensations of 2-substituted imidazoles, except for 2-trifluoromethylimidazole (see footnote c in Table 1).

TABLE 3

The products obtained from the thermal condensation of substituted imidazoles with TFAE

Products[a]					mp	Crystal form	Formula	Calcd. (%)			Found (%)		
	R_1 (N-1)	R_2 (C-2)	R_3 (C-4)	R_4 (C-5)	(°C)	(solvent)[b]		C	H	N	C	H	N
Ia	Me	X	H	H	139 ~ 40	needles (A-E)	$C_6H_7F_3N_2O$	40.01	3.92	15.55	40.07	3.88	15.57
Ib	Et	X	H	H	88 ~ 90	needles (C)	$C_7H_9F_3N_2O$	43.30	4.67	14.43	43.03	4.67	14.51
Ic	Bz	X	H	H	114 ~ 15	grains (E)	$C_{12}H_{11}F_3N_2O$	56.25	4.33	10.93	56.37	4.40	10.98
IIa	H	Me	X	H	168 ~ 69	plates (A)	$C_6H_7F_3N_2O$	40.01	3.92	15.55	40.36	3.86	15.41
IIb	H	Et	X	H	174 ~ 75	plates (A)	$C_7H_9F_3N_2O$	43.30	4.67	14.43	43.17	4.61	14.22
IId	H	Ph	X	H	217 ~ 18	plates (A)	$C_{11}H_9F_3N_2O$	54.55	3.75	11.57	54.32	3.78	11.64
IIIa	H	Me	X	X	212 ~ 14[c]	plates (A)	$C_8H_8F_6N_2O_2$	34.54	2.90	10.07	34.85	3.17	10.39
IIIb	H	Et	X	X	174 ~ 75	needles (A)	$C_9H_{10}F_6N_2O_2$	37.00	3.45	9.59	37.12	3.53	9.66
IIId	H	Ph	X	X	218 ~ 19	plates (C)	$C_{13}H_{10}F_6N_2O_2$	45.89	2.96	8.23	45.93	3.17	8.28
IVa	H	H	Me	X	121 ~ 23	grains (E)	$C_6H_7F_3N_2O$	40.01	3.92	15.55	39.86	3.78	15.39
IVd	H	H	Ph	X	179 ~ 80	grains (B)	$C_{11}H_9F_3N_2O$	54.55	3.75	11.57	54.55	3.89	11.50
IVf	H	H	Cl	X	183 ~ 85	columns (C)	$C_5H_4ClF_3N_2O$	29.95	2.01	13.97	29.88	1.99	14.11
Va	H	X	Me	H	197 ~ 98[c]	plates (A)	$C_6H_7F_3N_2O$	40.01	3.92	15.55	40.26	3.93	15.50
Vd	H	X	Ph	H	189 ~ 90	plates (C-F)	$C_{11}H_9F_3N_2O$	54.55	3.75	11.57	54.26	3.93	11.42
Vf	H	X	Cl	H	196 ~ 98[c]	plates (C-E)	$C_5H_4ClF_3N_2O$	29.95	2.01	13.97	30.04	2.11	13.78
VIa	H	X	Me	X	184 ~ 85	plates (C)	$C_8H_8F_6N_2O_2$	34.54	2.90	10.07	34.63	3.01	10.10
VIa'	H	X	Me	X	192 ~ 93	grains (C)	$C_8H_8F_6N_2O_2$	34.54	2.90	10.07	34.38	2.94	10.02

VId	H	X	Ph	X	189 ~ 90	needles (C)	$C_{13}H_{10}F_6N_2O_2$	45.89	2.96	8.23	45.78	3.04	8.24
VIf	H	X	Cl	X	192 ~ 96$^{c)}$	plates (C)	$C_7H_5ClF_6N_2O_2$	28.16	1.69	9.38	28.25	1.71	9.63
VIf'	H	X	Cl	X	214 ~ 15	plates (C-E)	$C_7H_5ClF_3N_2O_2$	28.16	1.69	9.38	28.37	1.75	9.34
VIg	H	X	CH_2OH	X	176 ~ 79	grains (E)	$C_8H_8F_6N_2O_3$	32.67	2.74	9.52	32.38	2.84	9.45
VII	Me	Me	H	X	183 ~ 84	needles (A)	$C_7H_9F_3N_2O$	43.30	4.67	14.43	43.36	4.84	14.45
VIII	Me	Me	X	H	131 ~ 33	powder (A)	$C_7H_9F_3N_2O$	43.30	4.67	14.43	43.27	4.85	14.32
IXa	H	Me	Me	X	157 ~ 58	needles (A)	$C_7H_9F_3N_2O$	43.30	4.67	14.43	43.58	4.39	14.48
IXb	H	Et	Me	X	173 ~ 74	prisms (A)	$C_8H_{11}F_3N_2O$	46.16	5.33	13.46	46.38	5.51	13.54
IXd	H	Ph	Me	X	235 ~ 36	plates (G)	$C_{12}H_{11}F_3N_2O$	56.25	4.33	10.93	56.21	4.60	10.88
Xa	H	X	Me	Me	131 ~ 33	plates (C)	$C_7H_9F_3N_2O$	43.30	4.67	14.43	43.31	4.83	14.32
Xd	H	X	Ph	Ph	228 ~ 29$^{c)}$	needles (A-E)	$C_{17}H_{13}F_3N_2O$	64.15	4.12	8.80	63.98	4.23	8.55
Xf	H	X	Cl	Cl	212 ~ 14$^{b)}$	plates (A)	$C_5H_3Cl_2F_3N_2O$	25.56	1.29	11.92	25.71	1.22	12.11

[a] X = CF_3CHOH

[b] Solvents for recrystallization A : acetone, B : benzene, C : chloroform, E : ether, F : ethyl acetate, G : ethanol.

[c] decomposed.

Thermal condensation of 4(5)-substituted imidazoles with TFAE

A mixture of 4(5)-methylimidazole (1.64g, 20 mmol) and TFAE (2.88g, 20 mmol) was heated at reflux for 3 hours. The reaction mixture was analyzed directly by GC-MS and ^{19}F NMR (ethanol solution): two mono-adducts and equal amounts of the diastereoisomers of bis-adducts were found. The reaction mixture was evaporated under reduced pressure and the residual material was applied to a column of silica gel (180ml); the column was eluted with (a) dichloromethane-ether, 1:1, (b) ether, (c) ether-ethyl acetate, 1:1, (d) ethyl acetate, and (e) ethyl acetate-methanol, 9:1. The impure fractions were rechromatographed on small silica gel columns (100ml each). There was obtained 2.64g (73.3%) of IVa as colorless grains, mp 121-123°C from acetone; 0.40g (11.1%) of Va as colorless plates, mp 197-198°C (decomp.) from acetone; and a total 0.43g (15.5%) of the diastereoisomers of VIa as colorless plates, mp 184-185°C from chloroform and VIa' as colorless grains, mp 192-193°C from chloroform. The order of elution from the silica gel column was bis-adducts (eluted with a), 2-mono-adduct (with b and c), 4-mono-adduct (with d), and 4(5)-methylimidazole (with e).

This procedure is typical of the thermal condensations of 4(5)-substituted imidazoles, other reaction conditions and product yields being listed in Table 1.

Thermal condensation of bis-substituted imidazoles with TFAE

A mixture of 2,4-dimethylimidazoles with TFAE (2.88g, 20 mmol) was heated at reflux for 8 hours. The mixture was stored overnight at ambient temperature; the crystalline deposit was collected by filtration and washed twice with acetone to give 1.58g of IXa. The filtrate and washings were combined and evaporated. Chromatography on 100ml of silica gel and elution with (a) ether-ethyl acetate, 1:1 and (b) ethyl acetate gave an additional 2.07g of product. Recrystallization of the combined fractions from acetone gave 3.56g (91.7%) of IXa as colorless needles, mp 157-158°C.

This procedure is representative of the thermal condensations of bis-substituted imidazoles with TFAE except for 1,2-dimethylimidazole (see Table 1).

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