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ACID CATALYZED CYCLIZATION OF N,N-DIALKYL-2,4-BISTRIFLUOROACETYL-1-NAPHTHYLAMINES TO NAPHTHO[1,2-d][1,3]OXAZINES

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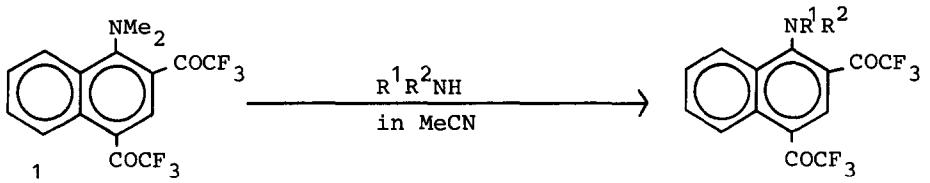
Summary: N,N-Dialkyl-2,4-bistrifluoroacetyl-1-naphthylamines(1 and 2) underwent cyclization in the presence of acids such as trifluoroacetic acid, p-toluenesulfonic acid or silica gel to give naphtho[1,2-d][1,3]oxazines(3 and 4) in high yields.

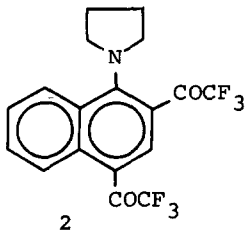
In our preceding communication[1] it was reported that N,N-dimethyl-2,4-bistrifluoroacetyl-1-naphthylamine(1), which can be readily prepared from commercially available N,N-dimethyl-1-naphthylamine and trifluoroacetic anhydride, reacts with various amines quite easily under mild conditions to give the corresponding nitrogen-nitrogen exchanged products in excellent yields as shown by equation (1). For example, pyrrolidyl derivative(2) can be obtained quanti-



1 (1)

tatively merely by refluxing dimethylamino compound(1) with pyrrolidine in acetonitrile. As an extension of this work the nitrogen-oxygen exchange reaction[2] of 1 with water to yield 2,4-bistrifluoroacetyl-1-naphthol was attempted. During this study it was found that when a small quantity of trifluoroacetic acid was added into this reaction system to remove dimethylamine produced, a small amount of unexpected product(3) was formed together with many unidentified materials. Surprisingly, none of the expected 2,4-bistrifluoroacetyl-1-naphthol was detected. This result prompted us to investigate this peculiar acid catalyzed cyclization of 1 and 2 to naphthoxazines(3 and 4) in some detail, and we now wish to communicate the results(Table 1).

In a typical experiment, a solution of dimethylamino compound(1) (1 g, 2.75 mmol) in trifluoroacetic acid (6.3 ml, 82.88 mmol) was refluxed with stirring for 65 h. After usual work-up there was obtained 0.978 g (98% yield) of 1,4-dihydro-1-methyl-4-trifluoromethyl-6-trifluoroacetyl-2H-naphtho[1,2-d][1,3]-oxazine(3) as yellow crystals (from chloroform), mp.103.5-4.0 °C. Attempted



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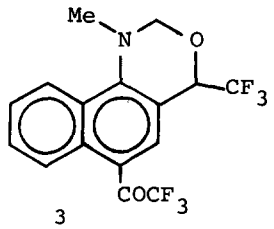

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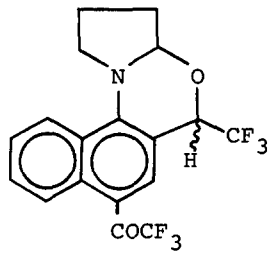


two stereoisomers 4a,b

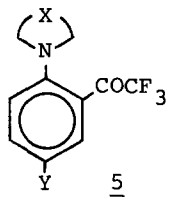
Table 1. Acid Catalyzed Cyclization of 2,4-Diacyl-1-naphthylamines(1 and 2)

Entry	Substrate	Acid	Solvent	Temp(°C)	Time(h)	Yield(%)	Product	4a/4b[a]
1	1	CF_3CO_2H[b]	CF_3CO_2H	refl	65	98	3	-
2	2	CF_3CO_2H[b]	CF_3CO_2H	rT	44	97	4a,b	65:35
3	2	CF_3CO_2H[b]	CF_3CO_2H	refl	0.5	97	4a,b	65:35
4	1	TsOH[c]	toluene	refl	24	80	3	-
5	2	TsOH[c]	toluene	refl	23	99	4a,b	70:30
6	1	SiO_2[d]	none	80	24	93	3	-
7	2	SiO_2[d]	none	30	48	100	4a,b	15:85

a) Ratio of stereoisomers. b) Trifluoroacetic acid was used as solvent.
c) Molar ratio; [TsOH]/[Substrate]=0.3/1. d) Commercially available silica gel for column chromatography (Wakogel C-300) was directly used. Weight ratio; $[SiO_2]$/[Substrate]= 10/1.

cyclization of 1 in CF_3CO_2D under the same conditions as above afforded 3 without any incorporation of the deuterium. Structural assignment of 3 was performed by ^{1}H-NMR, IR and elemental analyses as follows: ^{1}H-NMR(δ, $CDCl_3$): 8.87-8.70(m, 1H, 7-H), 8.23-7.97(m, 2H, 5-H and 10-H), 7.73-7.41(m, 2H, 8-H and 9-H), 5.27(q, 1H, J_{H-F}=7.2 Hz, $CHCF_3$), 4.75(q_{AB}, 2H, J=10.8 Hz, $\Delta\delta_{AB}$=0.16 ppm, NCH_2O), 3.17 (s, 3H, NCH_3); IR(KBr): $\nu_{C=O}$=1700cm^{-1}; Anal(%): Calcd. for $C_{16}H_{11}NF_6O_2$: C, 52.90; H, 3.05; N, 3.86; F, 31.38: Found: C, 53.20; H, 2.98; N, 3.88; F, 31.38. Rate of this cyclization was examined by sampling aliquots at appropriate time intervals; [time(h)]/[conversion(%)]: 17/66, 26/81, 50/98, 65/100. At room temperature this reaction did not proceed to any appreciable extent even for 9 days. In contrast, reaction of pyrrolidyl derivative(2) in trifluoroacetic acid did proceed even at room temperature, and after 44 h it afforded 1,2,3,3a-tetrahydro-5-trifluoromethyl-5H-naphtho[1,2-d]pyrrolo[2,1-b][1,3]oxazine(4) in 97% yield. In its ^{1}H-NMR spectrum, there appeared two sets of diagnostic signals for 5-H($CHCF_3$) and 3a-H(NCHO), which exhibited presence of two stereoisomers(4a and 4b) in a ratio of about 65:35. The major stereoisomer(4a) showed absorption for 5-H at 5.07(q, J_{H-F}=8.4 Hz) and that for 3a-H at 5.17(broad s). The minor one(4b) showed a signal for 5-H at 5.32(q, J_{H-F}=6.0 Hz) and that for 3a-H at 4.87(broad s). At the reflux temperature this cyclization was completed within 0.5 h to give 97% yield of 4a-4b in a ratio of 65:35. The reactions of 1 and 2

with the use of 0.3 times molar amounts of p-toluenesulfonic acid in refluxing toluene for 23-4 h also gave 3 and 4a-4b mixture (ratio; 70/30) in 80% and 99% yields, respectively. Without acid catalyst, refluxing of dimethylamino derivative(1) in toluene for 168 h resulted in almost quantitative recovery of the substrate. However in the case of pyrrolidyl derivative(2) refluxing in toluene for 116 h without acids gave 4 in 10% conversion. Interestingly, silica gel was also found to serve as an effective and mild acid catalyst for the present cyclization. Compound(1) was adsorbed on silica gel and allowed to stand at 80 °C for 24 h without any solvent to afford cleanly 3 in 93% yield after simple desorption with dichloromethane. In the case of 2, silica gel catalyzed cyclization at 30 °C for 48 h gave a 15:85 mixture of 4a-4b quantitatively. It seems of interest to note here that silica gel catalyzed cyclization of 2 proceeds fairly stereoselectively with predominant formation of 4b in striking contrast to the cases catalyzed by trifluoroacetic acid or p-toluenesulfonic acid, where the other isomer(4a) is produced in a slight excess.



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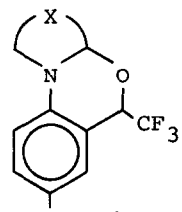

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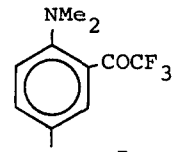

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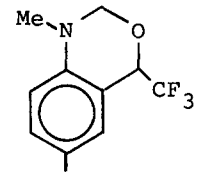

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X = $-(CH_2)_2-$, $-(CH_2)_3-$; Y = Me, MeO

Verboom and his co-workers reported previously apparently analogous cyclization reaction in their communication[3] that N-2-trifluoroacetylphenyl substituted cyclic amines(5) react in n-butanol at 118 °C for 20-90 h to give benzoxazines(6). However, no description is given as to the acid catalysis of this cyclization and also as to the case of acyclic amines such as 7. According to our experiments both 5[X=$-(CH_2)_2-$, Y=Me and MeO] and 7[4] did not cyclize in refluxing trifluoroacetic acid (24-96 h) and acyclic 7 did not react in boiling n-butanol for 89-93 h to yield 8. Furthermore, it was found that the cyclization of 5[X=$-(CH_2)_2-$, Y=MeO] did proceed even in much less polar toluene (reflux, 116 h) to give 6 in 85% yield. It seems noteworthy that there are notable differences in reactivity between the present naphthalene-system(1 and 2) and the benzene-system(5 and 7), which are summarized in Table 2. First, benzene-system(5) undergoes this cyclization thermally but not under acid catalyzed condition, while in naphthalene-system(1 and 2) both thermal and acid catalyzed cyclizations occur though the former proceeds slowly in none-polar solvents.[2] Second, although this cyclization is limited to cyclic amino compounds(5) in benzene-system, both cyclic(2) and acyclic(1) amino compounds can undergo the cyclization in naphthalene-system. Third, the cyclization in

benzene-system is reported[3,5] to be accelerated by electron release from the para substituent Y of 5, the cyclization of the naphthalene-system(1 and 2) occurs quite easily even in the presence of strongly electron withdrawing para $COCF_3$ group.

Table 2. Comparison of the Cyclization Between Naphthalene- and Benzene-System

system	Naphthalene system	benzene system
cyclization condition	acid catalyzed	thermal
amino substituent(NR^1R^2)	both acyclic and cyclic	only cyclic
p-substituent (Y)	$COCF_3$	Me, MeO (not with $COCF_3$)

Further works are now undertaken in our laboratory, together with some experiments from mechanistic standpoint of view.

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References and Notes

1. Hojo, M. ; Masuda, R. ; Okada, E., Tetrahedron Lett., 1987, 28, 6199.
2. Refluxing of 1 in n-butanol provided cleanly a quantitative yield of 1-n-butoxy-2,4-bistrifluoroacetylnaphthalene. This nucleophilic nitrogen -oxygen exchange reaction at aromatic carbon atom will be reported in our forthcoming paper. In contrast to this, 2 cyclized under the same condition to give 4 in almost quantitative yield.
3. Verboom, W. ; van Dijk, B. G. ; Reinhoudt, D. N., Tetrahedron Lett., 1983, 24, 3923.
4. Compounds(7) were synthesized according to the method described in Hojo, M.; Masuda, R. ; Okada, E., Tetrahedron Lett., 1986, 27, 353, and references cited therein.
5. It was reported[3] that the effect of substituent Y in 5 on the rate of the cyclization ($K_{OMe} > K_{Me}$) can be explained in terms of a more effective stabilization of the positive charge at the nitrogen atom of the intermediary zwitterion by the methoxy group.

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