A CONVENIENT SYNTHETIC METHOD FOR FLUORINE-CONTAINING NAPHTHO[1,2-d][1,3]THIAZINES FROM N,N-DIALKYL-2,4-BIS-(TRIFLUOROACETYL)-1-NAPHTHYLAMINES

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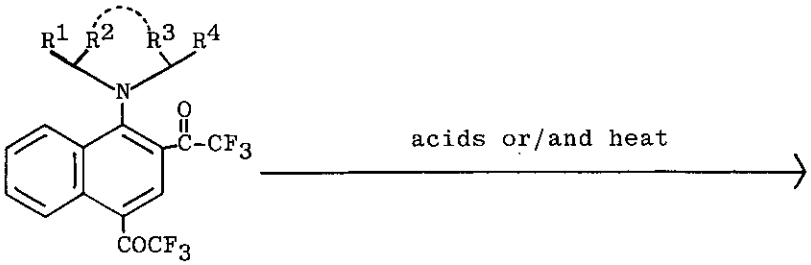
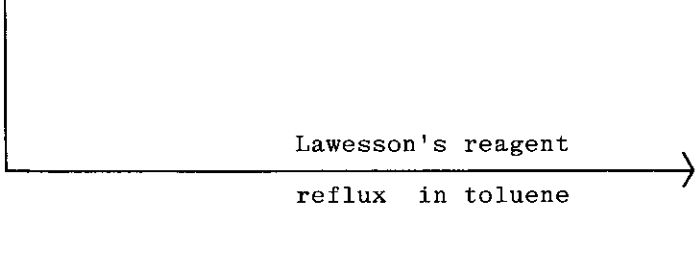
Abstract - The reaction of N,N-dialkyl-2,4-bis(trifluoroacetyl)-1-naphthylamines with Lawesson's reagent proceeded in refluxing toluene to give fluorine-containing naphtho[1,2-d][1,3]thiazines in satisfactory yields. The regioselectivity in this cyclization was also investigated.

We have recently reported that N,N-dialkyl-2,4-bis(trifluoroacetyl)-1-naphthylamines (**1**) undergo a novel cyclization to afford the corresponding fluorine-containing naphth[1,2-d][1,3]oxazines (**2**) in high yields.[1,2] As an extension of this work, we investigated the synthetic route to fluorine-containing naphtho[1,2-d][1,3]thiazines (**3**), the thia-analogs of **2**, by the reaction of N,N-dialkyl-2,4-bis(trifluoroacetyl)-1-naphthylamines (**1**) with 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (Lawesson's reagent). These naphthothiazines (**3**) bearing CF_3 group are expected to show interesting biological activities and are hardly accessible by other methods.[3-5]

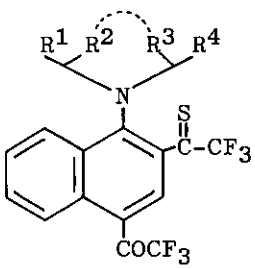
First we examined the reaction of **1** with Lawesson's reagent in refluxing toluene in order to convert carbonyl to thiocarbonyl at the 2-position.



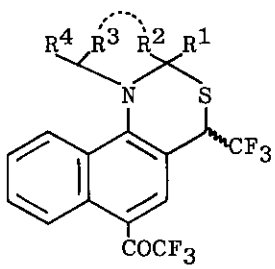
1a-g **2a-g**



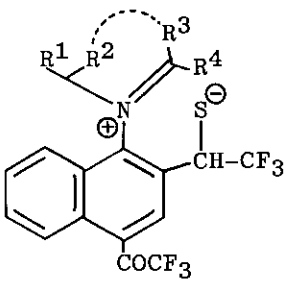
3a-g



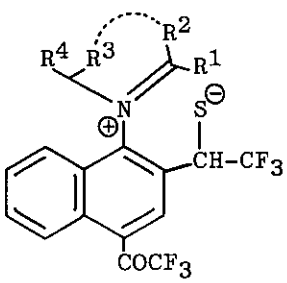
4a-g



5a-g



6a-g



7a-g

1-6	R^1	R^2	R^3	R^4	1-6	R^1	R^2	R^3	R^4
a:	H	H	H	H	e:	H	H	Me	Me
b:	H	$-(CH_2)_2-$		H	f:	Me	H	Me	Me
c:	H	$-(CH_2)_3-$		H	g:	H	$-(CH_2)_2-$		Me
d:	H	H	Me	H					

Table 1. Reaction of N,N-Dialkyl-2,4-bis(trifluoroacetyl)-1-naphthylamines (**1**) with Lawesson's Reagent[a)]

Entry	Substrate	Time (h)	Product[b)]	Yield[c)] (%)	Ratio of stereoisomers[d)]
1	**1a**	48	**3a**	61	-
2	**1b**	6	**3b**	53	75 : 25
3	**1c**	6	**3c**	62	100 : 0
4	**1d**	24	**3d**	81	85 : 15
5	**1e**	3	**3e/2e**	49/15	-
6	**1e**	12	**3e**	39	-
7[e)]	**1f**	24	**3f**	30	-
8	**1g**	6	**3g**	67	30 : 70

a) All reactions were performed with a similar procedure as described in the text, unless otherwise noted. b) Satisfactory ^{1}H-nmr and ir spectra and microanalyses (C±0.24, H±0.16, N±0.17, F±0.30) were obtained. c) Yields refer to pure isolated products. d) Stereochemistry is not determined yet. However, approximate ratios of the two stereoisomers could be estimated by ^{1}H-nmr analyses of the resulted mixtures. One stereoisomer shows a quartet with H-F coupling of 9 Hz for the benzylic proton ($C\underline{H}CF_3$) and the other one shows that of 8 Hz. The former and latter ratios are indicated on the right and left sides, respectively. e) The reaction of **1f** with Lawesson's reagent (2 equiv.) was carried out in refluxing tetrahydrofuran.

However, careful ^{1}H-nmr analysis of the crude products showed that the final products (**3**) were already formed without any detectable amounts of the expected thiocarbonyl intermediates (**4**). In Table 1, the reprerentative results of the present reaction are shown. Dimethylamino derivative (**1a**) reacted with 0.5 times molar amounts of Lawesson's reagent in refluxing toluene for 48 h to give naphthothiazine (**3a**) in 61% yield (Entry 1). In shorter reaction time (24 h), **3a** was obtained in low yields and was accompanied by the recovery of the unreacted substrate (**1a**). In

contrast to this, cyclic amino compounds such as pyrrolidinyl (**1b**) and piperidyl (**1c**) derivatives exhibited much higher reactivities than **1a** and the reactions completed within 6 h to afford the corresponding naphthothiazines (**3b** and **3c**) in 53% and 62% yields, respectively (Entries 2 and 3). We then tried to determine regioselectivity of the present naphthothiazine ring formation and examined this reaction with the use of unsymmetrically N,N-dialkyl-substituted compounds (**1d-g**) in place of symmetrically N,N-dialkyl-substituted ones (**1a-c**). In the case of N-methyl-N-ethyl derivative (**1d**), cyclization took place exclusively at the methylene of the N-ethyl group to give naphthothiazine (**3d**) as a single product in 81% yield (Entry 4). Formation of the other possible regioisomer (**5d**), where the ring closure occurred at the N-methyl, was not observed. The reaction of N-methyl-N-isopropyl derivative (**1e**) with Lawesson's reagent for 3 h in refluxing toluene proceeded regioselectively to afford the desired naphthothiazine (**3e**) in 49% yield together with 15% yield of naphthoxazine (**2e**) as a by-product (Entry 5). Elongation of the reaction time (12 h) led to no formation of **2e** but to a decreased yield (39%) of **3e** (Entry 6). In the cases of N-ethyl-N-isopropyl (**1f**) and 2-methylpyrrolidinyl (**1g**) derivatives, the cyclizations occurred in both cases at the tertiary carbon and not at the secondary one to give the corresponding naphthothiazines (**3f** and **3g**) in 30% and 67% yields, respectively (Entries 7 and 8).[6] Consequently, it was found that the reactivity in this cyclization increases in the order of methyl (Me) < methylene (Et) < methine (i-Pr). The present regioselectivity nearly resembles that in the synthesis of naphthoxazines (**2**).[2] On the whole, the present cyclization proceeded with exclusive or predominant stereoselectivities (Entries 2-4 and 8). In addition, naphthothiazine (**3a**) was found to be synthesized in 66% yield from the corresponding naphthoxazine (**2a**) on treatment with Lawesson's reagent in refluxing toluene for 48 h. A possible reaction course is as follows. The C=O → C=S transformation

using Lawesson's reagent takes place to generate in situ the intermediate (**4**), which undergoes thermal 1,5-H shift to produce the zwitterion (**6**). Subsequently, intramolecular nucleophilic attack of the negatively charged sulfur atom onto the iminium carbon results in the formation of **3**. Furthermore, it is assumed that the equilibrium between **2a** and **1a** exists under the present reaction conditions. Therefore, naphthothiazine (**3a**) is speculated to be formed from naphthoxazine (**2a**) by the following reaction path, **2a** → **1a** → **4a** → **6a** → **3a**.[7] On the other hand, the high regioselectivity observed in the formation of **3d-g** can be rationally explained by comparison of the difference in stability between the two possible iminium intermediates (**6** and **7**). The intermediate (**6**) having more highly substituted iminium double bond is more stable than **7** having less subsituted one, hence C-S bond formation occurs selectively at the more highly branched carbon atom, that is, at the carbon atom bearing R^3 and R^4.

Typical procedure is as follows. To a solution of **1a** (727 mg, 2 mmol) in toluene (8 ml) was added Lawesson's reagent (404 mg, 1 mmol) and the whole mixture was refluxed for 48 h. Evaporation and subsequent chromatography on silica gel using hexane/benzene (1:1) as an eluent gave **3a** (465 mg, 61%): mp 119-120 °C (hexane); ^{1}H-nmr (δ, $CDCl_3$): 8.93-8.77 (m, 1H, H-7), 8.30-7.96 (m, 2H, H-5 and -10), 7.86-7.39 (m, 2H, H-8 and -9), 4.48 (q_{AB}, 2H, J=17 Hz, $\Delta\delta_{AB}$=0.526 ppm, H-2), 4.41 (q, 1H, J=9 Hz, H-4), 3.04 (s, 3H, NCH_3); ir (KBr): $\nu_{C=O}$ 1691 cm^{-1}. Anal. Calcd for $C_{16}H_{11}NOF_6S$: C, 50.66, H, 2.92, N, 3.69, F, 30.05. Found: C, 50.81, H, 2.88, N, 3.74, F, 29.94.

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6. When the reaction of **1f** was run in toluene as a solvent, only a complex mixture of the decomposition products was obtained in much larger quantities.
7. In the absent of acid catalyst, no cyclization of **1a** into **2a** proceeded in refluxing toluene within 48 h.

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