

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

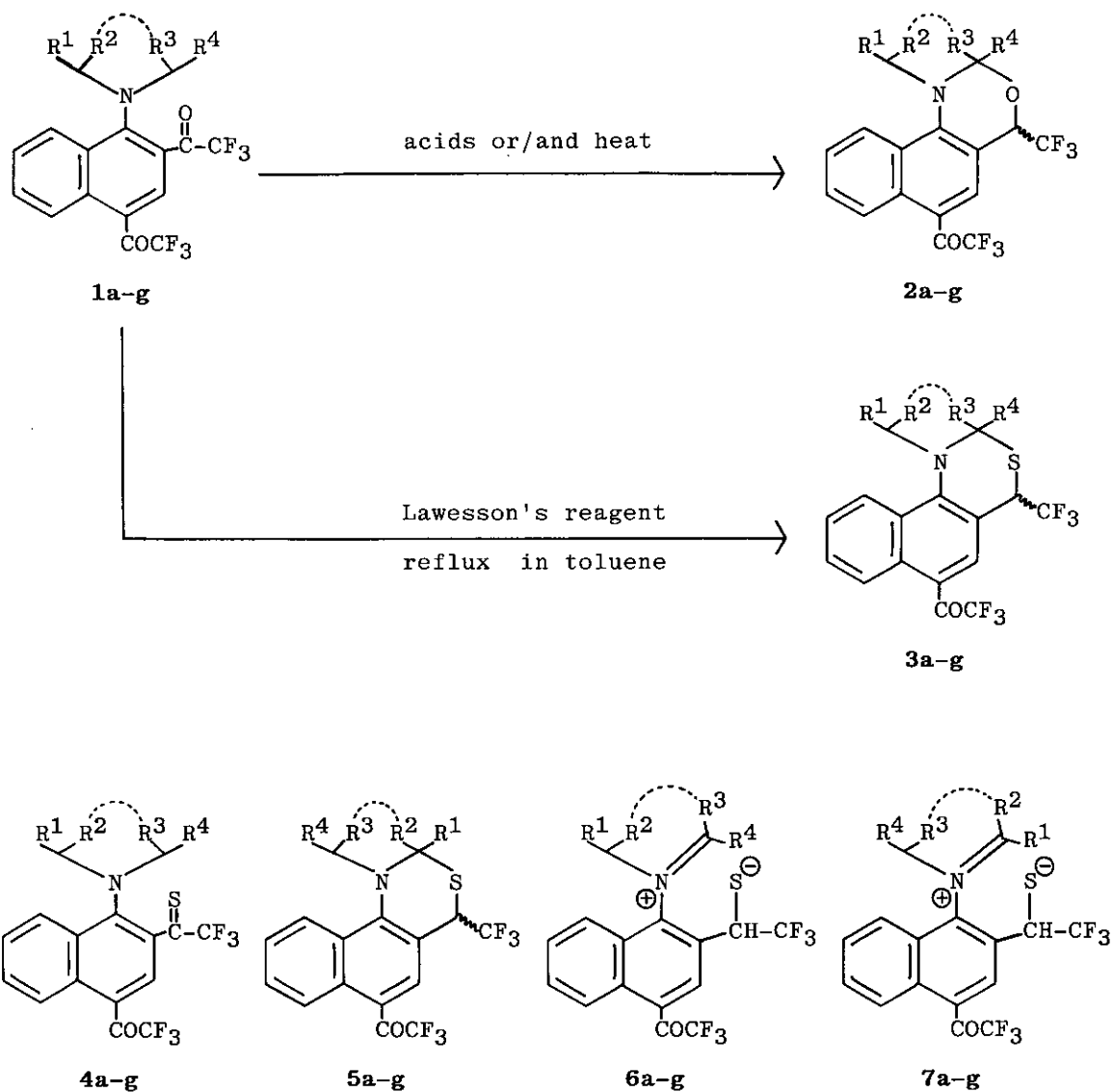
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Abstract - The reaction of N,N-dialkyl-2,4-bis(tri-
fluoroacetyl)-1-naphthylamines with Lawesson's reagent
proceeded in refluxing toluene to give fluorine-con-
taining naphtho[1,2-d][1,3]thiazines in satisfactory
yields. The regioselectivity in this 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 CF₃ 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.



1-6	R ¹	R ²	R ³	R ⁴
a:	H	H	H	H
b:	H	-(CH ₂) ₂ -	H	
c:	H	-(CH ₂) ₃ -	H	
d:	H	H	Me	H

1-6	R ¹	R ²	R ³	R ⁴
e:	H	H	Me	Me
f:	Me	H	Me	Me
g:	H	-(CH ₂) ₂ -		Me

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 ¹H-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 ¹H-nmr analyses of the resulted mixtures. One stereoisomer shows a quartet with H-F coupling of 9 Hz for the benzylic proton (CHCF_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 ¹H-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 representative 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, $2a \rightarrow 1a \rightarrow 4a \rightarrow 6a \rightarrow 3a$.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 substituted one, hence C-S bond formation occurs selectively at the more highly branched carbon atom, that is, at the carbon atom bearing R³ and R⁴. 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); ¹H-nmr (δ, CDCl₃): 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, Δδ_{AB}=0.526 ppm, H-2), 4.41 (q, 1H, J=9 Hz, H-4), 3.04 (s, 3H, NCH₃); ir (KBr): ν_{C=O} 1691 cm⁻¹. Anal. Calcd for C₁₆H₁₁NOF₆S: 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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