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Aromatic ring transfer—a new synthesis of 2,4-diaryl-4*H*-3,1-benzothiazines

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Abstract—A new synthetic approach to 2,4-diaryl-4*H*-3,1-benzothiazines is described based on the rearrangement of 2-isothiocyano triarylmethanes in the presence of $AlCl_3$. An aryl ring is found to migrate to the carbon atom of an isothiocyano group followed by intramolecular cyclization as a result of electrophilic attack of the benzhydryl carbocation on the sulfur atom.

4*H*-3,1-Benzothiazine derivatives with aromatic substituents in positions 2 and (or) 4 exhibit many kinds of biological activity[1] and are of interest for the production of recording materials and photographic and laser techniques.[2] Moreover, they are valuable building blocks and can be used, in particular, for the synthesis of indole derivatives.[3]

Several synthetic approaches to 4*H*-3,1-benzothiazines have been elaborated. For example, 4-aryl and 4,4-diaryl derivatives of 4*H*-3,1-benzothiazine were synthesized through the cycloaddition reaction between ketenimines and the corresponding thiones.[4] 2-Amino-4-aryl-4*H*-3,1-benzothiazine derivatives are easy to obtain in high yield by the reaction of 2-aminobenzhydrol derivatives with thiourea in boiling ethanol in the presence of HBr.[5] Interaction of 2-aminobenzyl chloride with benzothioamides leads to 2-aryl-4*H*-3,1-benzothiazines in high yields.[3b] Sulfurization of aryl-substituted 4*H*-3,1-benzoxazines with P_2S_5 furnishes the corresponding benzothiazines in yields varying from good to high.[6] Various 2-acetylaminobenzylic alcohol derivatives give 2-aryl, 4-aryl and 2,4-diaryl substituted 4*H*-3,1-benzothiazines under treatment with Lawesson's reagent,[7] but this reaction is not always selective and can be accompanied by considerable formation of by-products. A rather original method for the synthesis of 2-aryl(heteroaryl)-4*H*-3,1-benzothiazine-4-ones is based on the acid-catalyzed aroylation of aromatic (heteroaromatic) substrates with 2-isothiocyano benzoates followed by intramolecular cyclization of the intermediate thioamides.[8]

We have discovered a new approach to the synthesis of 2,4-diaryl-4*H*-3,1-benzothiazines based on a rearrangement of 2-isothiocyano triarylmethanes in the presence of $AlCl_3$. 2-Aminotriarylmethanes **4** were used as starting materials for the synthesis of 2-isothiocyano triarylmethanes. Compounds **4a** and **4b** were prepared according to known methods.[9,10] 2-Nitrotriarylmethanes **3c–f** were synthesized by condensation of 2-nitrobenzaldehydes **1** and substituted benzenes **2** in the presence of $AlCl_3$,[11] and subsequent reduction with hydrazine hydrate in the presence of Raney Ni led to the corresponding amines **4c–f**[12] (Scheme 1).

Isothiocyanates **5** were obtained by treatment of amines **4** with thiophosgene in the presence of $NaHCO_3$.[13] Compound **5** underwent an easy rearrangement to 2,4-diaryl-4*H*-3,1-benzothiazines **6**[14] in the presence of $AlCl_3$ in *sym*-tetrachloroethane at rt. Formation of minor products was observed in all cases (TLC). Only in three cases, compounds **7a**,**d**,**f** were isolated in low yields and characterized (Scheme 2).

The assumed mechanism of the transformation is depicted in Scheme 3. The reaction probably begins with

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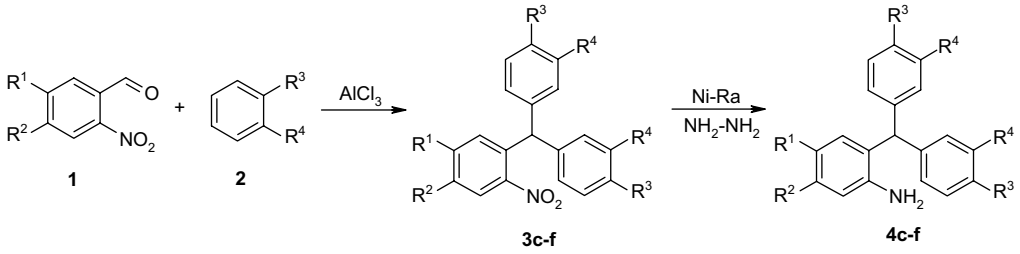
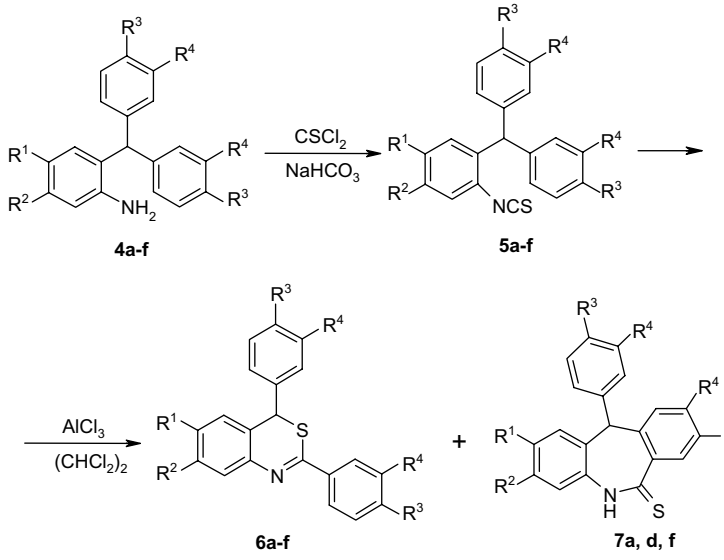


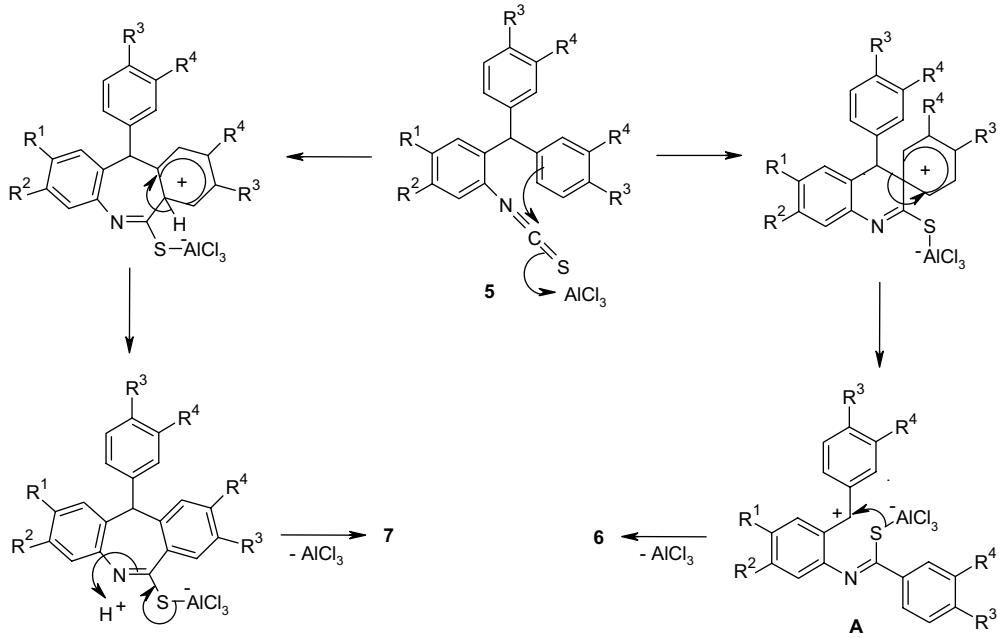
3, 4	R^1	R^2	R^3	R^4	Yield, %	
					3	**4**
c	H	H	OCH_2CH_2O		76	76
d	H	H	OMe	OMe	28	84
e	OMe	OMe	OMe	OMe	27	91
f	OMe	OMe	OEt	OEt	50	78

Scheme 1.



4 - 7	R^1	R^2	R^3	R^4	Yield, %		
					5	**6**	**7**
a	H	H	OH	H	57	49	3
b	H	H	Me	H	87	60	–
c	H	H	OCH_2CH_2O		59	61	–
d	H	H	OMe	OMe	77	37	7
e	OMe	OMe	OMe	OMe	78	30	–
f	OMe	OMe	OEt	OEt	65	26	5

Scheme 2.



Scheme 3.

activation of the isothiocyano group of **5** with $AlCl_3$ followed by intramolecular electrophilic attack on one of the aromatic rings. *ipso*-Substitution at the C_{sp3}–C_{Ar} bond is the main reaction pathway, which leads to formation of benzhydryl cation **A**. Next, the cation is attacked by the sulfur atom of a newly formed thioamide group to accomplish the formation of the benzothiazine ring. Intramolecular electrophilic attack on the *ortho*-position of an aromatic ring is responsible for the concurrent formation of minor dibenzoazepinethiones **7**.

In conclusion, we have reported a general rearrangement reaction of 2-isothiocyano triarylmethanes, which can be used for the synthesis of 2,4-diaryl-4*H*-3,1-benzothiazines. The mechanistic aspects involving *ipso*-attack of the isothiocyano group activated with $AlCl_3$ is worthy of further investigation.

Acknowledgement

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11. A typical procedure is as follows: To a cooled (5 °C) solution of 2-nitroveratraldehyde (2 g, 9.5 mmol) and 1,2-diethoxybenzene (3.3 g, 19.9 mmol) in CH_2Cl_2 (80 mL), $AlCl_3$ (1.9 g, 14.2 mmol) was added in small portions with stirring. The reaction mixture was stirred for 2.5 h, the cooling bath was removed, and stirring was continued at rt until full conversion was achieved (TLC). The mixture was poured into water (300 mL) and extracted with CH_2Cl_2. The organic layer was separated, dried with Na_2SO_4 and the solvent was removed in vacuo. Recrystallization of the

solid residue from methanol furnished 2.49 g (50%) of **3f** as yellow crystals. Mp 103–104 °C. Anal. Found: C, 66.16; H, 6.80%. $C_{29}H_{35}NO_8$; requires: C, 66.27; H, 6.71%; ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.25 (6H, t, $J = 7.0$ Hz, OCH_2CH_3), 1.31 (6H, t, $J = 7.0$ Hz, OCH_2CH_3), 3.61 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.91 (4H, q, $J = 7.0$ Hz, OCH_2CH_3), 3.99 (4H, q, $J = 7.0$ Hz, OCH_2CH_3), 6.09 (1H, s, CH), 6.49 (2H, dd, $J = 1.7$, 8.2 Hz, H_{Ar}), 6.53 (1H, s, H_{Ar}), 6.67 (2H, d, $J = 1.7$ Hz, H_{Ar}), 6.87 (2H, d, $J = 8.2$ Hz, H_{Ar}), 7.60 (1H, s, H_{Ar}).

12. A typical procedure is as follows: A mixture of the compound **3f** (2.4 g, 4.6 mmol), hydrazine hydrate (2 mL) and Raney Ni (1.5 g) in ethanol (40 mL) was stirred under reflux (TLC). The catalyst was filtered off, and the solution was treated with active charcoal followed by filtration and evaporation. Compound **4f** was obtained as a yellow oil (1.78 g, 78% yield), which was used for the next step without further purification.
13. A typical procedure is as follows: To a stirred solution of the compound **4f** (1.6 g, 3.2 mmol) in CH_2Cl_2 (10 mL) solutions of $CSCl_2$ (0.3 mL, 3.9 mmol) in CH_2Cl_2 (4 mL) and $NaHCO_3$ (0.84 g, 10 mmol) in water (30 mL) were added simultaneously at rt. At the end of the reaction (TLC) the mixture was poured into water (150 mL) and stirred for 6 h. The organic layer was extracted with CH_2Cl_2, separated and dried over Na_2SO_4. The solvent was evaporated and the oily residue was dissolved in hot hexane and filtered through a pad of silica gel. The solution was concentrated and crystallization from hexane furnished compound **5f** (1.12 g, 65% yield) as a colourless solid. Mp 117 °C. Anal. Found: C, 66.89; H, 6.68%. $C_{30}H_{35}NO_6S$ requires: C, 67.02; H, 6.56%; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.39 (6H, t, $J = 7.0$ Hz, OCH_2CH_3), 1.44 (6H, t, $J = 7.0$ Hz, OCH_2CH_3), 3.65 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.99 (4H, q, $J = 7.0$ Hz, OCH_2CH_3), 4.07 (4H, q, $J = 7.0$ Hz, OCH_2CH_3), 5.57 (1H, s, CH), 6.40 (1H, s, H_{Ar}), 6.53 (2H, dd, $J = 1.8$, 8.2 Hz, H_{Ar}), 6.66 (2H, d, $J = 1.8$ Hz, H_{Ar}), 6.73 (1H, s, H_{Ar}), 6.79 (2H, d, $J = 8.2$ Hz, H_{Ar}).
14. A typical procedure is as follows: To a solution of compound **5f** (0.89 g, 1.66 mmol) in *sym*-tetrachloroethane (5 mL), $AlCl_3$ (0.3 g, 2.25 mmol) was added. The reaction mixture was stirred for 24 h at rt (TLC), then poured into water (100 mL) and extracted with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4 and the solvent was removed in vacuo. The oily residue was purified by chromatography on silica gel (benzene–ethyl acetate–hexane, 2:3:6) to yield compound **6f** (0.23 g, 26% yield) as colorless crystals. Mp 124–125 °C (ethyl acetate–hexane). Anal. Found: C, 67.21; H, 6.72%. $C_{30}H_{35}NO_6S$ requires: C, 67.02; H, 6.56%; ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.23–1.28 (6H, m, OCH_2CH_3), 1.33–1.38 (6H, m, OCH_2CH_3), 3.75 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.88–3.96 (4H, m, OCH_2CH_3), 4.06–4.13 (4H, m, OCH_2CH_3), 5.53 (1H, s, CH), 6.49 (1H, dd, $J = 2.0$, 8.3 Hz, H_{Ar}), 6.77 (1H, d, $J = 8.3$ Hz, H_{Ar}), 6.82 (1H, s, H_{Ar}), 6.86 (1H, d, $J = 2.0$ Hz, H_{Ar}), 7.02 (1H, d, $J = 8.6$ Hz, H_{Ar}), 7.08 (1H, s, H_{Ar}), 7.52 (1H, dd, $J = 1.9$, 8.6 Hz, H_{Ar}), 7.64 (1H, d, $J = 1.9$ Hz, H_{Ar}). ^{13}C NMR (50 MHz, DMSO-d_6): δ 14.65 (4C); 43.31; 55.58; 55.72; 63.71; 63.81 (2C); 63.99; 110.34; 110.71; 111.15; 112.26; 112.64; 113.09; 114.62; 119.28; 121.36; 130.25; 135.06; 137.36; 147.61; 147.85; 148.06; 148.12; 148.50; 151.26; 154.35. MS (*m*/*z*, % relative intensity): 537 (M^+, 100), 507 (45), 506 (98), 328 (14), 327 (21), 43 (20). Yield of **7f** 0.04 g (5% yield), yellow crystals. Mp 186–187 °C (ethyl acetate–hexane). Anal. Found: C, 67.17; H, 6.41%. $C_{30}H_{35}NO_6S$ requires: C, 67.02; H, 6.56%; ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.21 (3H, t, $J = 7.0$ Hz, OCH_2CH_3), 1.24 (3H, t, $J = 7.0$ Hz, OCH_2CH_3), 1.31 (3H, t, $J = 7.0$ Hz, OCH_2CH_3), 1.37 (3H, t, $J = 7.0$ Hz, OCH_2CH_3), 3.71 (3H, s, OCH_3), 3.78 (2H, q, $J = 7.0$ Hz, OCH_2CH_3), 3.83 (3H, s, OCH_3), 3.92 (2H, q, $J = 7.0$ Hz, OCH_2CH_3), 4.03 (2H, q, $J = 7.0$ Hz, OCH_2CH_3), 4.15 (2H, q, $J = 7.0$ Hz, OCH_2CH_3), 5.18 (1H, s, CH), 6.30 (1H, d, $J = 8.1$ Hz, H_{Ar}), 6.32 (1H, s, H_{Ar}), 6.75 (1H, d, $J = 8.1$ Hz, H_{Ar}), 6.86 (1H, s, H_{Ar}), 7.01 (1H, s, H_{Ar}), 7.11 (1H, s, H_{Ar}), 7.71 (1H, s, H_{Ar}), 11.81 (1H, s, NH).