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A Straightforward Synthesis of Benzothiazines

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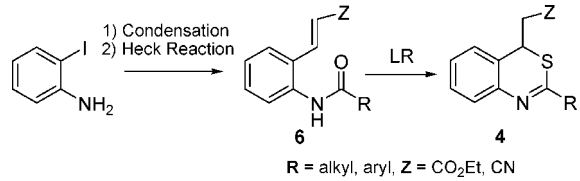
ABSTRACT



A series of 4*H*-3,1-benzothiazines have been successfully synthesized through a three-step sequence starting from commercially available 2-iodoaniline. The key step consists of the cyclization of compounds 6 via an intramolecular *S*-conjugate addition. The synthesis is straightforward, gives good yields and offers a broad range of possibilities since R can be many alkyl or aryl groups and Z a suitable electron-withdrawing functionalization.

Heterocycles having the 4*H*-3,1-benzothiazine nucleus are systems of great interest because of their biological activity,[1] as well as their applications in recording and photographic materials.[2] Several synthetic routes have been described in the literature to obtain 4*H*-3,1-benzothiazines. The most used route involves the condensation between 2-aminobenzyl chloride and thioamides, a reaction that also works with other substrates such as thioureas or benzopyran-2-thiones as sulfur sources.[3] A related process uses 2-aminobenzyl or 2-(*N*-acylamino)benzyl alcohols as starting materials.[1a,c,4] Another strategy is to use the cycloaddition of thiones to conveniently functionalized ketenimines.[5] A minor amount of benzothiazine has also been isolated as a byproduct of the Willgerodt−Kindler reaction, which involves a similar cycloaddition reaction.[6] Moreover, various isothiocyanates have been used as starting materials to obtain this heterocycle through other cyclization processes.[1f,7] Direct thionation of quinazolines or benzoxazines derivatives has also been described.[8] Finally, other approaches to 4*H*-3,1-benzothiazines are limited to a restricted range of products.[9]

Our recent studies demonstrated that under phosphine organocatalysis[10] thioamides can effectively react with

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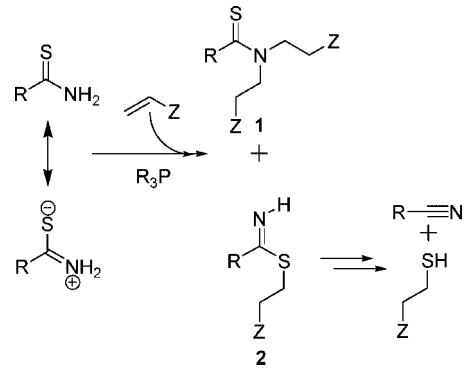
electron-poor olefins generating not only the expected *N*-adduct **1** but also the *S*-adduct derivative **2** (Scheme 1).[10a]

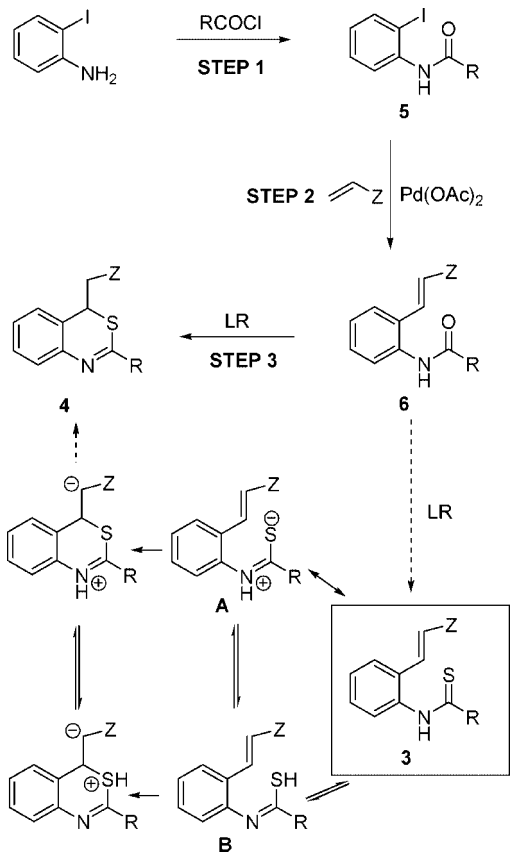
Scheme 1



This result can be explained by the ability of the sulfur atom of thioamides to stabilize the negative charge induced by the conjugation of the neighboring nitrogen atom.

These results prompted us to investigate a new family of substrates that would favor the *S*-addition over the *N*-addition reaction. For this reason we focused on thioamides **3** in Scheme 2, which would be expected to undergo intramolecular cyclization. The formation of the six-membered ring in **4** would definitely favor the desired *S*-adduct, allowing us to obtain a new family of 4*H*-3,1-benzothiazines.

Scheme 2



Our synthetic proposal conveniently starts with 2-iodoaniline (Scheme 2). After condensation, Mizoroki−Heck reaction, and thionation of the amide group by Lawesson's reagent (LR), the cyclization would take place. The stabilization of the zwitterionic resonance structure A or tautomer B of thioamide **3** would favor the cyclization without requiring a catalyst (Scheme 2). This synthesis is very simple, gives good yields, and makes it possible to obtain a broad diversity of 4*H*-3,1-benzothiazines by varying the R and the Z substituents.

The results obtained for the synthesis of precursors **6** are depicted in Table 1. *o*-Iodoaniline reacted successfully with different acyl chlorides in the presence of triethylamine in diethyl ether at room temperature, affording amides **5** in good yields (73−85%). Only the 4-nitroaniline derivative required changing conditions ($CHCl_3$, reflux)[11] to obtain a moderate yield of the product (43%).

Table 1. Synthesis of Amides **5** (Step 1, Scheme 2)[a] and Precursors **6** (Step 2, Scheme 2)[b]

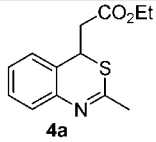
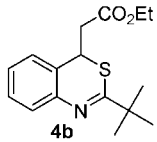
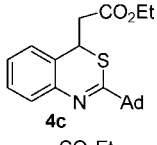
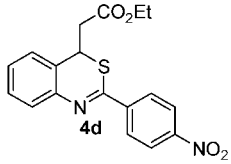
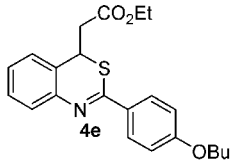
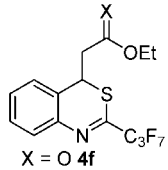
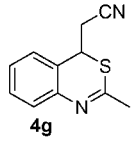
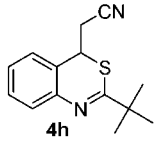
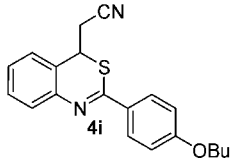
			yield (%)[c]	
entry	R	Z	compounds **5**	compounds **6**
1	CH_3	CO_2Et	**5a** (85)	**6a** (95)
2	^{t}Bu	CO_2Et	**5b** (79)	**6b** (91)
3	Ad	CO_2Et	**5c** (75)	**6c** (83)
4	$NO_2C_6H_4$	CO_2Et	**5d** (43)[d]	**6d** (96)
5	$BuOC_6H_4$	CO_2Et	**5e** (73)	**6e** (99)
6	C_3F_7	CO_2Et	**5f** (80)	**6f** (87)
7	CH_3	CN	**5a** (85)	**6g** (84)[e]
8	^{t}Bu	CN	**5b** (79)	**6h** (48)[f]
9	$BuOC_6H_4$	CN	**5e** (73)	**6i** (77)[f]

[a] Reactions performed in diethyl ether at room temperature, using 1.1 equiv of acyl chloride and 1.1 equiv of Et_3N. [b] Reactions performed in refluxing THF, using 2−10% mol of $Pd(OAc)_2$, 1 equiv of Bu_3N, and 2 equiv of olefin. [c] Isolated yields. [d] Reaction performed in refuxing $CHCl_3$. [e] DMF at 80 °C was used. [f] CH_3CN at 80 °C was used.

Amides **5** were then treated with ethyl acrylate in the presence of $Pd(OAc)_2$ and tributylamine in refluxing THF, giving **6** with excellent yields (83−99%, Table 1). Mizoroki−Heck reactions using acrylonitrile (Table 1, entries 7−9) were performed in CH_3CN or DMF at 80 °C because conversions were <100% when THF was used. As commonly occurs using the nitrile derivative, the products were obtained as a mixture of *Z*/*E* isomers.[12]

Finally, compounds of type **6** were cyclized by reaction with Lawesson's reagent in refluxing toluene, using different molar ratios depending on the substrate (Table 2). For instance, benzothiazines **4a** and **4g** were obtained in good yields using only 0.5 equiv of LR. However, more hindered compounds such as *tert*-butyl or adamantyl derivatives required 1 and 3 equiv, respectively, as well as longer reaction times (entries 2, 3, 8). The fact that the Lawesson's reagent has a specific order of reactivity toward different functional groups,[13] i.e., R-OH > P═O > R-CO-NHR′ > R-CO-R′ > R-CO-OR′, allowed us to perform chemoselective processes in the presence of esters (entries 1−6, Table 2).

Table 2. Synthesis of 4*H*-3,1-Benzothiazines **4** (Step 3, Scheme 2)[a]

Entry	Compounds **4**	Equiv. LR	Time (h)	Yield (%)[b]
1	 **4a**	0.5	1	77
2	 **4b**	1	3	95
3	 **4c**	3	3	76
4	 **4d**	3	2.5	63
5	 **4e**	1	2.5	72
6	 X = O **4f** X = S **7f**	6	3 days	(c)
7	 **4g**	0.5	3	51
8	 **4h**	1	3	61
9	 **4i**	1	4	41

[a] Reactions performed in refluxing toluene. [b] Isolated yields. [c] Reaction performed in a closed reactor at 160 °C. Low reaction conversion and formation of the byproduct **7f**. Product not isolated.

Compounds containing aromatic substituents were synthesized successfully using the same reaction conditions (entries 4, 5, 9). Substrates with an electron-rich group such as **6e** and **6i** were more reactive than the equivalent with an electron-poor derivative, **6d**, the former requiring 1 equiv and the latter 3 equiv of LR. The reactivity of perfluoroalkyl derivative **6f** was much lower than the one observed for the alkyl or aryl compounds.

Benzothiazine **4f** was detected in reactions using a large amount of LR (up to 6 equiv) and high temperatures (up to 150 °C). However isolation was difficult as a result of the presence of starting material (low reaction conversions) and dithionated compound **7f** (Table 2, entry 6).

Some attempts were carried out to cyclize compounds of type **6** with Z = $COCH_3$, but complex mixtures of the desired product and byproducts were obtained. This result can be explained by the higher reactivity of ketones compared to that of esters, which would favor the formation of dithionated products equivalent to **7f** (entry 6, Table 2).[13]

4*H*-3,1-Benzothiazines **4a**−**4i** are easily identified by their characteristic α- and *β*-carbonyl(cyano) signals in the ^{1}H NMR spectra (ca. 2.6 and ca. 4.5 ppm, respectively). Noteworthy is the observed diastereotopic relationship between the -CH_2- protons of the ester group in compounds **4a**−**f**, indicative of a restricted movement of this side chain (see Supporting Information).

In conclusion, we have designed a new, rapid, and high-yielding synthetic approach to 4*H*-3,1-benzothiazines that has as a key step a noncatalyzed intramolecular *S*-conjugate addition of a thioamide. Another advantage is the versatility due to the broad range of acyl chlorides and electronically poor olefins that can be used.

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Supporting Information Available: Experimental details, product characterization and full spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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