ORGANIC LETTERS

2000
Vol. 2, No. 23
3667−3670

Rapid and Efficient Synthesis of 2-Amino-4*H*-benzothiazines

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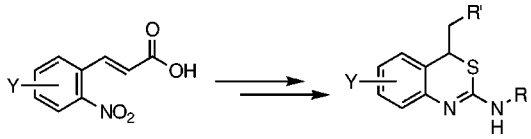
Received September 12, 2000

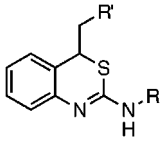
ABSTRACT



The benzothiazine nucleus is a relatively unexplored class of compounds, from the standpoint of both synthetic chemistry and biological activity. We have developed a rapid, high-yielding synthesis of benzothiazines in which a precursor aryl thiourea is prepared on solid phase. Addition of trifluoroacetic acid catalyzes a conjugate addition reaction to form the desired heterocycle and releases it from the resin.

The synthesis of heterocyclic systems is of continuing interest in the field of organic chemistry, at least in part as a result of the large number of biologically active molecules that contain heterocyclic rings.[1] A heterocyclic ring system that has been relatively unexplored, with respect to both its synthesis and its biological activity, is the 4-alkyl-4*H*-benzothiazine nucleus (**1**).[2] As part of a continuing program in the development of novel synthetic methodology for the preparation of biologically active substances, we recently disclosed a highly selective method for the catalytic reduction of nitroarenes.[3] It occurred to us during the course of that work that we could potentially employ this reduction as the first step toward the synthesis of a variety of benzo-fused heterocycles. In this communication, we report the synthesis of a series of 2-anilino-4-alkyl-4*H*-benzothiazines, which employs the acid-catalyzed intramolecular conjugate addition of a thiourea to an α,β-unsaturated carbonyl compound as a key step.

As shown in Scheme 1, our plan was to first immobilize a 2-nitrocinnamic acid on Wang[4] or Rink amide[5] resin. As



1

demonstrated in our previous work, treatment of this resin-immobilized nitroarene (**2** or **3**) with catalytic $CrCl_2$ in the presence of excess Mn metal and TMSCl in DMF would provide a hexamethyldisilazane (**4** or **5**), which could subsequently be converted to the aniline (**6** or **7**) by stirring in aqueous DMF. Addition of an isothiocyanate would then provide a thiourea (**8** or **9**). Treatment of **8** or **9** with trifluoroacetic acid (TFA) in methylene chloride would trigger nucleophilic attack of the thiourea on the α,β-unsaturated carbonyl system, as well as releasing the final cyclized product **10** or **11** from the resin.

Our results are summarized in Tables 1 and 2. The solid-supported aminocinnamic acids were condensed with phenylisothiocyanate (**12**), *p*-tolylisothiocyanate (**13**), *p*-methoxy phenylisothiocyanate (**14**), *m*-trifluoromethyl phenylisothiocyanate (**15**), or cyclohexylisothiocyanate (**16**). For both Wang (Table 1) and Rink amide (Table 2) resins, products were obtained in moderate to excellent yield, particularly when one considers that this sequence concatenates six transformations (resin loading, nitro group reduction, hexamethyldisilazane hydrolysis, isothiocyanate addition, cyclization, and cleavage) into four chromatography-free steps.

(1) For recent reviews of heterocycle synthesis, see: (a) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449−472. (b) Franzén, R. G. *J. Comb. Chem.* **2000**, *2*, 195−214.

(2) For syntheses of 4-aryl and unsubstituted 4*H*-3,1-benzothiazines, see: (a) Nishio, T. *J. Org. Chem.* **1997**, *62*, 1106−1111. (b) El-Desoky, S. I.; Kandeel, E. M.; Abd-el-Rahman, A. H.; Schmidt, R. R. *J. Herocycl.Chem.* **1999**, *36*, 153−160.

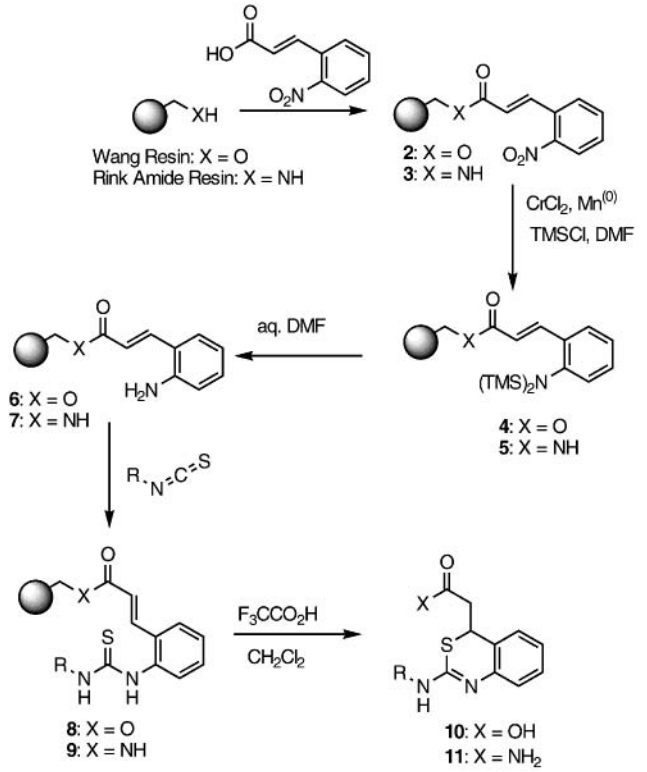
(3) (a) Hari, A.; Miller, B. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2777−2779. (b) Hari, A.; Miller, B. L. *Org. Lett.* **2000**, *2*, 691−693.

(4) Wang, S. *J. Am. Chem. Soc.* **1973**, *95*, 1328−1333.

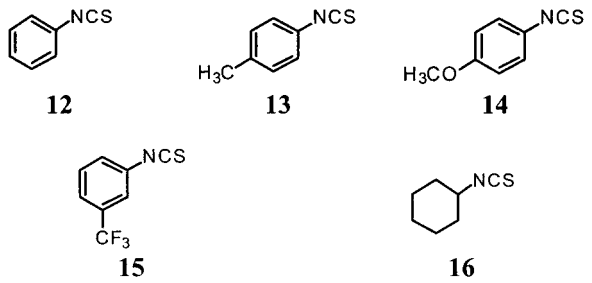
(5) Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787−3790.

10.1021/ol006580m CCC: $19.00
Published on Web 10/21/2000

Scheme 1

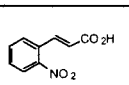
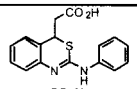
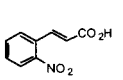
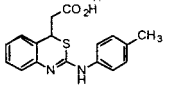
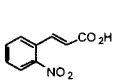
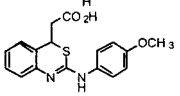
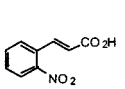
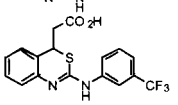
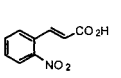
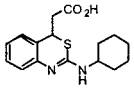
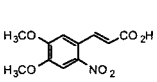
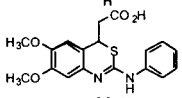
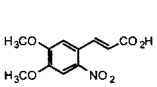
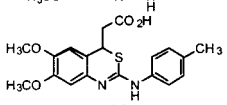
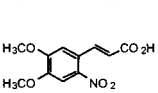
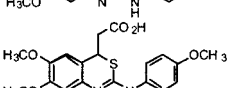
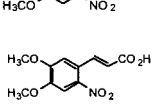
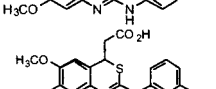
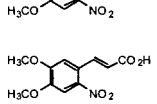
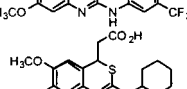
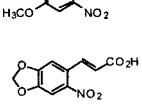
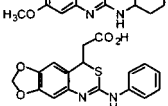
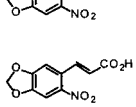
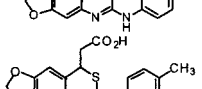
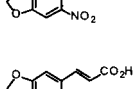
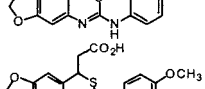
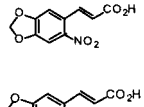
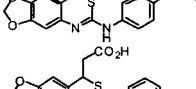


Best yields were obtained with alkoxy-substituted 2-nitrocinnamic acid and aryl isothiocyanates (Table 1, entries 6−9 and 11−14).[6]



Most products were obtained in reasonably high purity, as judged by HPLC and ^{1}H NMR analysis of the crude products (Figure 1). Assignment of product structures as 2-amino-4*H*-benzothiazines rather than the isomeric quinazoline-2-thione was based primarily on the chemical shift of the C-4 proton ($\delta = 4.5-4.7$ ppm), a value inconsistent with published values for quinazoline-2-thiones.[9] Reaction with cyclohexyl isothiocyanate was unsuccessful, providing complex mixtures of materials that could not be separated

Table 1. Preparation of Benzothiazines on Wang Resin

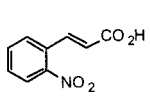
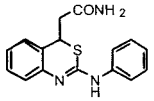
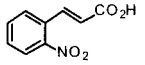
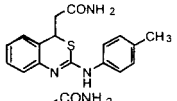
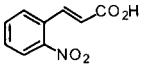
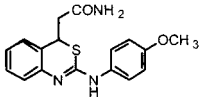
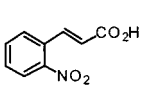
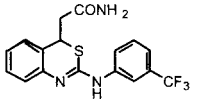
entry	cinnamic acid	isothiocyanate	product	yield (%)
1		**12**		62[c]
2		**13**		56[a]
3		**14**		67[a]
4		**15**		73[b]
5		**16**		15[a]
6		**12**		65[c]
7		**13**		67[b]
8		**14**		73[b]
9		**15**		78[b]
10		**16**		0
11		**12**		69[b]
12		**13**		60[b]
13		**14**		63[b]
14		**15**		71[b]

[a] Conversion based on ^{1}H NMR. [b] Crude yield (75−95% pure by HPLC). [c] Isolated yield.

(6) **Representative Experimental Procedure.** 4,5-Dimethoxy 2-nitrocinnamate was loaded onto 50 mg of Wang resin (Advanced Chemtech, 1.2 mmol/g) and reduced using catalytic $CrCl_2$ in the presence of Mn metal and TMSCl as reported previously. After separation of the resin from Mn and transfer to a second reaction vessel (Bio-Rad Bio-Spin 1.5 mL polyethylene chromatography column fitted with a porous polymer frit), it was treated with 1.0 mL of 50% aqueous DMF for 12 h at room temperature. The aqueous DMF solution was then removed, and the resin was washed with DMF and CH_2Cl_2. After drying the resin thoroughly on an aspirator, 29 μL (0.24 mmol, 4 equiv) of phenyl isothiocyanate (Aldrich) was then shaken with the resin in 1.0 mL of DMF for 12 h. The resin was then thoroughly washed with DMF, CH_3OH, and CH_2Cl_2. Cyclization and product release was accomplished by treatment of the resin with 1.0 mL of 50% trifluoroacetic acid in CH_2Cl_2 for 30 min. This solution was drained off, and the resin washed with 1 mL of CH_2Cl_2. The CH_2Cl_2 solutions were combined, and solvent was removed in vacuo. Purification of the crude sample by preparative reverse-phase HPLC (C18 column, 10−100% 0.1% TFA/CH_3CN in 0.1% TFA/H_2O) provided the desired benzothiazine essentially pure as a white solid (14 mg, 65%).

(7) Analytical HPLC was performed on a Hewlett-Packard series 1050 quaternary HPLC system, equipped with a Hamilton PRP-1 0.3 cm × 15 cm reverse-phase column. A linear gradient of 10−100% CH_3CN (0.1% CF_3CO_2H) in H_2O (0.1% CF_3CO_2H) was performed over 30 min at a flow rate of 300 μL/min.

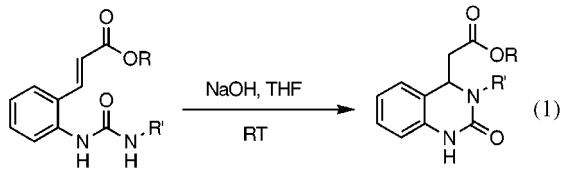
Table 2. Preparation of Benzothiazines on Rink Amide Resin

entry	cinnamic acid	isothiocyanate	product	yield
1		**12**		67[c]
2		**13**		28[a]
3		**14**		40[a]
4		**15**		71[b]

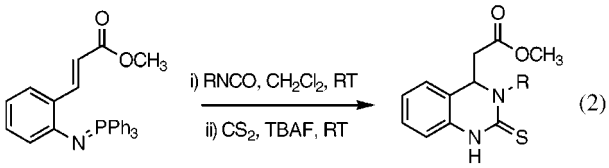
[a] Conversion based on ^{1}H NMR. [b] Crude yield (75−95% pure by HPLC). [c] Isolated yield.

chromatographically (Table 1, entries 5 and 10). We suspect the reaction fails in this case at the isothiocyanate addition stage. Although it is difficult to test this directly on the resin, we found that treatment of methyl 2-aminocinnamate with cyclohexyl isothiocyanate in DMF produced a complex mixture of products.

This methodology is complementary to solution-phase methods reported recently by Xin and co-workers for the synthesis of dihydroquinazolines (eq 1)[8] and the solution-phase dihydroquinazoline-2-thione and 4*H*-3,1-benzothiazine-2-thione preparation reported by Tárraga, Molina, and López (eq 2).[9] Both of these processes are essentially base-driven, providing significantly different products than are obtained with our acid-mediated process.



(1)



(2)

Curious as to the comparative reactivity of solid-supported urea derivatives under acidic conditions, we derivatized a

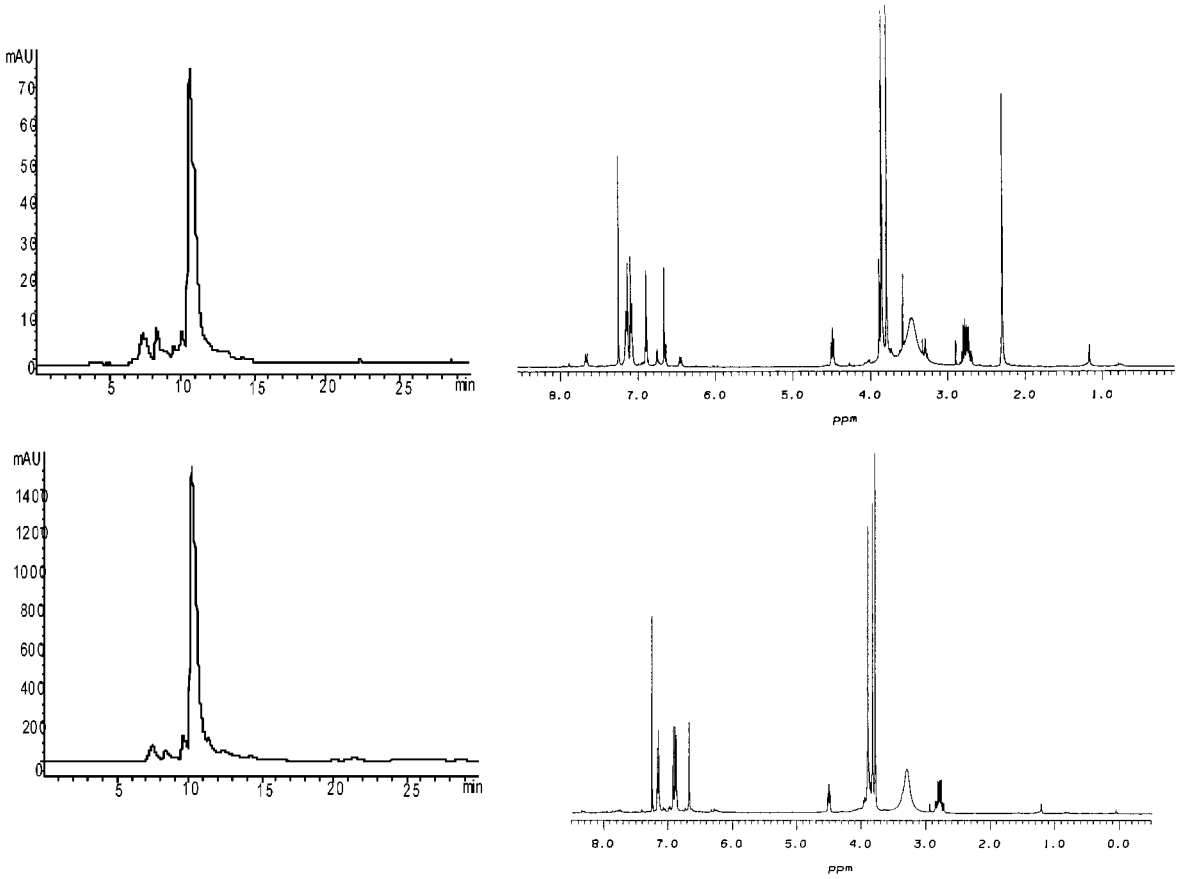
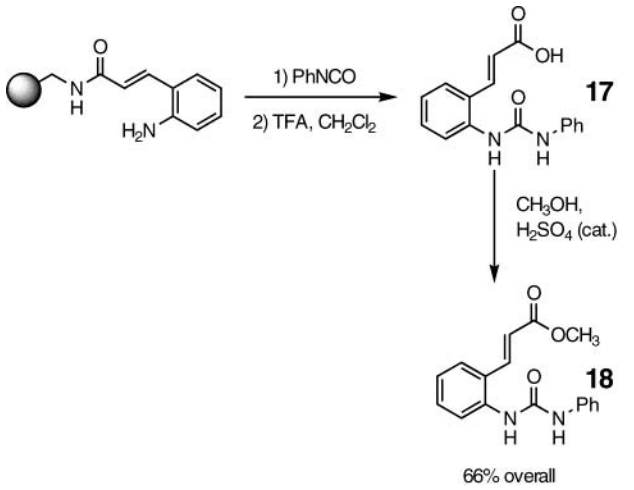


Figure 1. Representative analytical HPLC trace (λ = 254 nm)[7] and NMR spectrum (^{1}H, 400 MHz, $CDCl_3/CH_3OD$) of the crude product from Table 1, entry 7 (top) and Table 1, entry 8 (bottom).

resin-loaded *o*-amino cinnamate with phenyl isocyanate as shown in Scheme 2. Treatment of this resin with CF_3CO_2H

Scheme 2



in CH_2Cl_2 yielded a product that appeared to be **17** by ^1H NMR but could not be isolated chromatographically. Subsequent esterification of this crude product provided a compound that was verified to be **18**.[10] Presumably, cyclization does not occur in this case as a result of the lower nucleophilicity of the urea oxygen relative to the thiourea sulfur atom.

In summary, we have developed a method for the synthesis of 2-amino-4*H*-benzothiazines, which takes advantage of an acid-catalyzed intramolecular cyclization of thioureas prepared on solid support. Efforts to examine the bioactivity of combinatorial libraries of this relatively unexplored class of heterocycles are underway in our laboratory.

Acknowledgment. This research was supported by the Eastman Kodak Corporation.

Supporting Information Available: Full spectroscopic data is provided for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006580M

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