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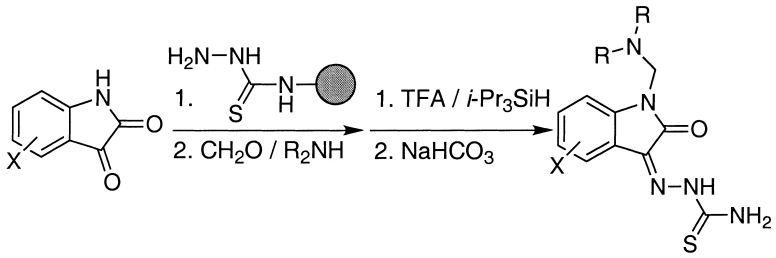

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Trityl Isothiocyanate Support for Solid-Phase Synthesis

Michael C. Pirrung* and Sunil V. Pansare‡

Department of Chemistry, Levine Science Research Center, Duke University, Durham, North Carolina 27708-0317

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Trityl isothiocyanate resin **1**, prepared from commercially available trityl chloride resin, is a useful precursor of the trityl thiosemicarbazide resin **2**. This resin can be employed in the solid-phase synthesis of a variety of supported isatin β-thiosemicarbazones **4** and their Mannich derivatives **6**. A variety of thioureas **7** can be easily prepared by the reaction of **1** with amines. The supported thioureas are directly and efficiently converted to 2-aminothiazole-5-carboxylates **8** by reaction with methyl 2-chloroacetoacetate.

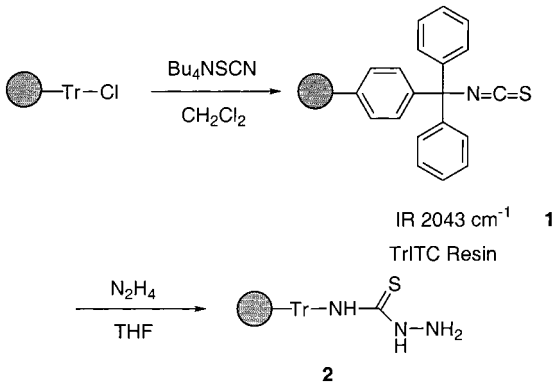
The development of new synthetic methods and reagents for organic synthesis using solid supports has been quite actively investigated, mainly due to the increased emphasis on combinatorial synthesis of libraries of small organic molecules.[1] Accordingly, novel functionalized resins are important both for attaching substrates to supports in solid-phase synthesis routes and in scavenging excess reagents in solution-phase synthesis routes.[2] Herein, we describe the preparation of a trityl isothiocyanate (TrITC) resin and its application in the solid-phase synthesis of a variety of isatin derivatives, thioureas, and thiazoles.

Synthesis of Isatin β-Thiosemicarbazone Mannich Bases

We required an efficient and general synthesis of isatin thiosemicarbazones such as methisazone, the thiosemicarbazone of *N*-methyl isatin,[3] as part of an ongoing investigation of antiviral agents. Related isatin thiosemicarbazones have antifungal and antibacterial activity.[4] Among the challenges in the preparation of libraries of isatin derivatives is their poor physical properties, particularly solubility in organic solvents, which we anticipated could be mitigated by performing the synthesis on solid phase. The simplest and most general means to link the target compounds to a resin was through the thiosemicarbazone. A supported thiosemicarbazide that would capture isatins from solution, permit manipulations to introduce *N*-alkyl or other groups, and then be easily removed from the solid support under mild acidic conditions[5] would enable the desired target molecules to be prepared. Preliminary solution-phase studies using *N*-4 trityl thiosemicarbazide[6] suggested that the envisioned synthetic plan was compatible with the trityl group and that a polymer-supported analogue would be an ideal reagent for this purpose. This resin, in turn, should be readily available from the reaction of a trityl isothiocyanate support with hydrazine.

Analogous to the literature preparation of trityl isothiocyanate,[7] treatment of a commercially available trityl chloride resin (Scheme 1) with tetrabutylammonium thiocyanate in dichloromethane at ambient temperature generates trityl isothiocyanate resin **1** in 96% yield. It displays a characteristic isothiocyanate infrared absorption at 2043 cm^{-1}. Reaction of this TrITC resin with hydrazine in THF at ambient temperature generates the trityl thiosemicarbazide resin **2** (97%).

Scheme 1



Resin loading experiments were conducted with **2** and 5-methyl isatin as a model substrate. Treatment of **2** with an excess of **3a** in ethanol solution did not result in thiosemicarbazone formation (nearly quantitative recovery of the isatin), but loading could be consistently achieved with 4−5 equiv of 5-methyl isatin in DMF as the solvent. Untreated isatin can be readily recovered from the DMF solution (Scheme 2) by evaporation.

The next step involves conversion of the supported isatin thiosemicarbazones **4** to the *N*-dialkylaminomethyl isatin derivatives **5**. Treatment of **4a** with excess piperidine and aqueous formaldehyde in DMF (method A, Scheme 2) following a modification of the literature procedure[8] gives the supported isatin derivative **5a**. This procedure could also be employed for the preparation of **5b**, **5c**, and **5e** (prepared from dimethylamine and formaldehyde), but not for **5d**. Solution-phase experiments suggest that the electron-rich isatin **3d** and its thiosemicarbazone derivatives form, among other products, the *N*-hydroxymethyl derivatives from direct reaction with formaldehyde rather than the required aminals,

‡ On leave from the Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411008, India.

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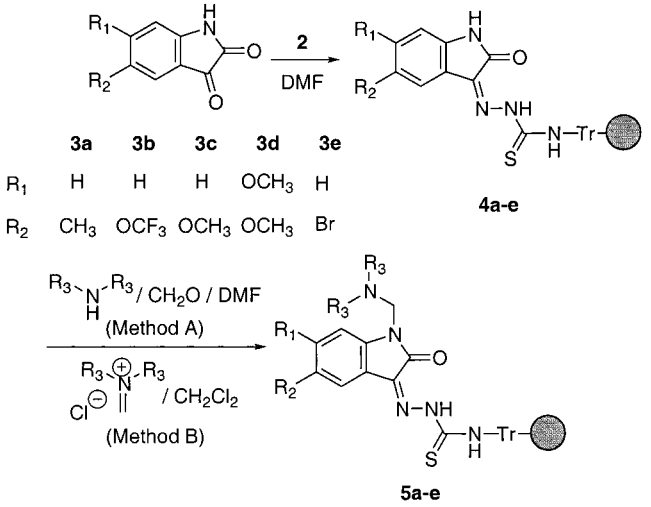
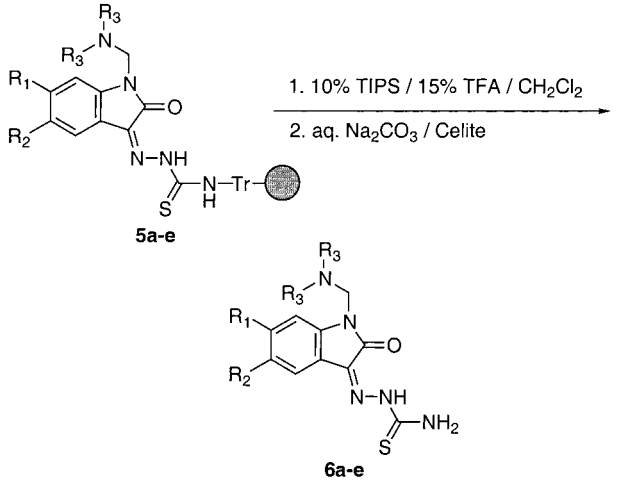
Scheme 2



Scheme 3



presumably due to the enhanced nucleophilicity of the isatin. The use of iminium salts[9] as the dialkylaminomethylenating agents avoids this problem. The aminal **5d** was prepared from **4d** by treatment with excess *N*-methylenepiperidinium chloride (generated in situ from 1,1′-methylenebispiperidine and acetyl chloride,[9] method B, Scheme 2) in dichloromethane. Thus, proper choice of the dialkylaminoalkylating agent provides easy access to a variety of *N*-dialkylaminomethyl isatin thiosemicarbazones. The iminium salt procedure (method B) is also applicable to electronically neutral isatin thiosemicarbazones such as **4a**, **4b**, **4c**, and **4e** and tolerates a range of diversity in the amine component, making it the procedure of choice for the preparation of combinatorial libraries of isatin derivatives related to **6**.[10] A small drawback of the iminium salt procedure for combinatorial library generation is the off-line preparation of the precursor methyleneamines, but this can be readily accomplished merely by stirring the secondary amine with formalin.

We next investigated a cleavage protocol to remove the *N*-dialkylaminomethyl isatin β-thiosemicarbazones from the support.[5] Somewhat unexpectedly, subjection of resin **5** to mild acidic conditions (1−5% TFA in dichloromethane) did not result in any cleavage. It is plausible that, at low acid concentration, competitive protonation of other Lewis basic sites in the isatin derivatives prevents protonation of the thiosemicarbazone moiety such that no cleavage is observed. Accordingly, the use of higher acid concentration (15% TFA in dichloromethane) results in rapid release from the resin (2 min, ambient temperature). The addition of silane reducing agents during the cleavage is beneficial to product purity. The optimal cleavage conditions involve presoaking the resin in a 10% solution of triisopropylsilane in dichloromethane, followed by addition of an equal volume of 30% solution of TFA in dichloromethane to achieve a final concentration of 15% TFA. Alternative cleavage protocols employing formic acid, trichloroacetic acid, or chlorotrimethylsilane in a variety of solvents are less efficient. It is noteworthy that the aminal functionality, which is generally expected to be acid-labile, is not affected by the acidic resin cleavage step. This may be due to the conjugation of the isatin nitrogen, which renders it poorly basic. Thus, it can neither be protonated as prelude to C−N cleavage assisted by the simple amine nitrogen nor facilitate departure of the simple amine when it is protonated.

The isatin derivatives **6** are initially obtained as trifluoroacetate salts; conversion to the free base is effected by a solid-supported neutralization protocol.[11] Celite is treated with a saturated aqueous solution of sodium carbonate, and a small column of this adsorbent is prepared in a plastic disposable syringe. Percolation of a dichloromethane solution of the trifluoroacetate salt through this column provides the *N*-dialkylaminomethyl isatin β-thiosemicarbazones **6** in 84−90% yield after evaporation (Scheme 3).

This reaction scheme is successful with electron-rich and electronically neutral isatins, but not with C7 substituted, sterically hindered isatins nor with electron-deficient isatins such as 5-nitroisatin. Neither dialkylaminomethylenation procedure is applicable to the latter substrates. Nonetheless, this solid-supported synthesis offers several attractive features. Handling (not to mention purification) of difficult intermediate isatins is avoided, and the final products are of sufficient purity for screening experiments (>85%). In addition, attempted solution-phase syntheses of some of the targets by reaction of preformed isatin Mannich bases[8] with thiosemicarbazide or by Mannich reaction of the isatin thiosemicarbazones[4] or *N*-trityl thiosemicarbazones is either inefficient or unsuccessful. The solid-phase synthesis of isatin derivatives such as **6** is therefore the procedure of choice for the preparation of both individual compounds and compound libraries. A sampling of the isatin derivatives that have been prepared by the above protocol is shown in Figure 1.

Synthesis of Thioureas and Thiazoles

The TrITC resin **1** is also an excellent starting material for the solid-supported synthesis of thioureas, important building blocks in the synthesis of heterocycles as well as critical components of several bioactive molecules.[12] Despite their utility, relatively few methods are available for the solid-supported synthesis of thioureas.[13]

Treatment of the TrITC resin with primary and secondary amines generates the corresponding resin-bound thioureas quantitatively. Removal from the support and isolation is achieved by cleavage with trifluoroacetic acid followed by

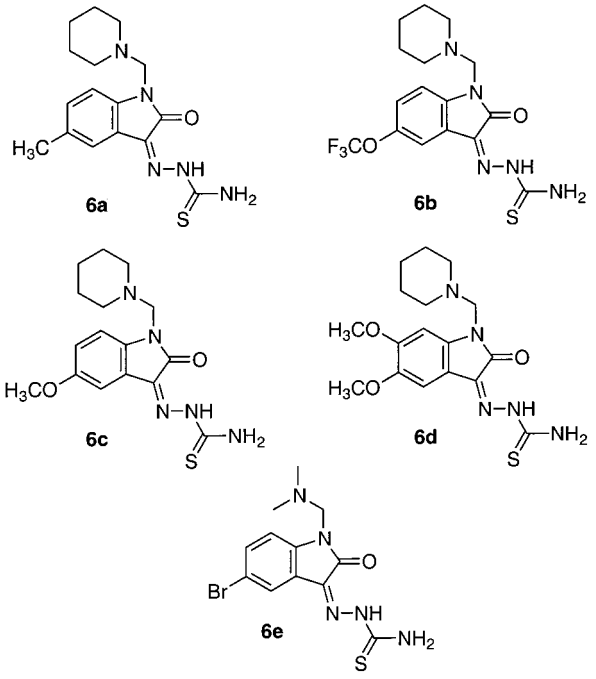


Figure 1. *N*-Dialkylaminomethyl isatin β-thiosemicarbazones prepared on solid phase.

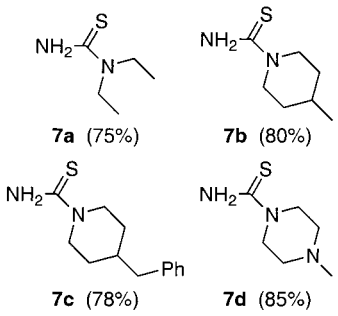
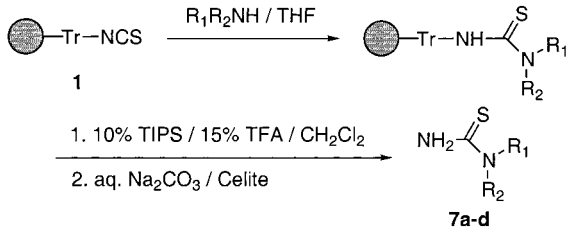


Figure 2. Thioureas prepared on solid phase from TrITC resin **1** and secondary amines.

Scheme 4



solid-supported neutralization with sodium carbonate according to the procedure described for the isatin derivatives (Scheme 4). Many thioureas are readily prepared by this procedure,[10] and a few representative secondary thioureas are shown in Figure 2. Primary thioureas are also readily prepared and serve as intermediates in the 2-aminothiazole syntheses following.

2-Aminothiazoles form a useful structural class in medicinal chemistry and have found applications in drugs targeted at ailments ranging from allergies to HIV infections.[14] The synthesis of substituted 2-aminothiazoles has therefore been the focus of many investigations. Solution-phase syntheses[15] of libraries of 2-aminothiazoles as well as

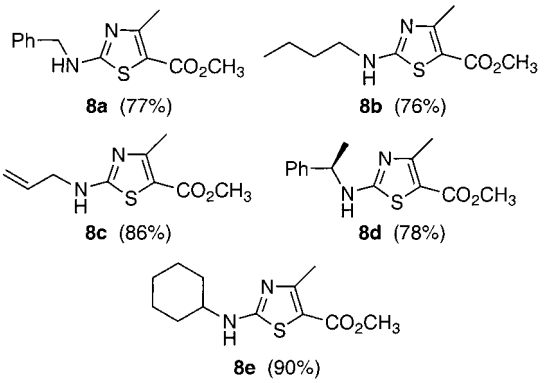
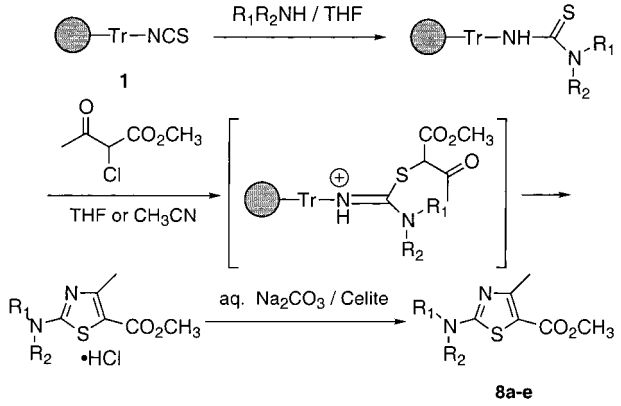


Figure 3. Substituted methyl 2-amino thiazole-5-carboxylates prepared on solid phase.

Scheme 5



solid-phase syntheses[16] of 2-aminothiazoles have been reported.

2-Aminothiazole-5-carboxylates are readily prepared by the condensation of a thiourea with a 2-haloacetoacetate.[17] A solid-phase version of this synthesis was examined with supported thioureas as prepared above from TrITC resin **1**. Our procedure involves treatment of the resin with an amine to form the thiourea (24 h, ambient) and subsequent reaction of the supported thiourea with methyl 2-chloroacetoacetate (4−5 equiv) in acetonitrile. The second stage of this process directly releases the thiazole into solution. Presumably, S-alkylation of the thiourea generates a cationic intermediate that undergoes heterolysis (Scheme 5), releasing the thiazole (or a precursor).

The 2-aminothiazole-5-carboxylic acid methyl esters are obtained as their hydrochloride salts and are converted to the free bases by solid-supported neutralization with sodium carbonate according to the procedure described for the isatins. Thiazoles derived from primary amines can be readily prepared by this method (Figure 3). Thiazoles might be similarly derived from secondary amines via the supported thioureas, but the product purity is low.

In conclusion, the TrITC resin **1** is a valuable precursor to a second novel and valuable resin, trityl thiosemicarbazide resin **2**, the only reported example of a solid-supported thiosemicarbazide. The latter is used in the four-step, solid-supported synthesis of a variety of isatin derivatives, and the former is used in solid-supported syntheses of thioureas and thiazoles. The ease of preparation of these resins and

the variety of applications of isothiocyanates in organic synthesis suggest other uses may be readily developed.

Experimental Section

Trityl chloride resin (0.95 mmol/g or 1.24 mmol/g) was obtained from Novabiochem. All commercial reagents were used without purification. 5-Methoxy isatin[18] and 5,6-dimethoxy isatin[19] were prepared according to the literature procedure. NMR analyses were performed using Varian 300 MHz or Varian 400 MHz instruments. GCMS was performed on a HP 5998A instrument using chemical ionization (NH_3), and FAB MS was performed on a JEOL SX102 instrument.

Trityl Isothiocyanate (TrITC) Resin (1). A suspension of polystyrene trityl chloride resin (Novabiochem, 2.0 g, 0.95 mmol/g, 1.9 mmol) in a solution of tetrabutylammonium thiocyanate (1.8 g, 6.0 mmol) in anhydrous dichloromethane (15 mL) was shaken at ambient temperature for 50 h. The resin was filtered, washed with dichloromethane (5 × 20 mL), and dried under reduced pressure to give 2.044 g of **1** (96% loading). IR (KBr pellet): 2043, 1655, 1602, 1492, 1446, 1415, 1315, 1277, 1178 cm^{-1}.

Trityl Thiosemicarbazide Resin (2). To a suspension of the TrITC resin **1** (2.0 g, 1.9 mmol) in anhydrous THF (8 mL) was added a solution of 1 M hydrazine in THF (6 mL, 6 mmol). The mixture was shaken at ambient temperature for 8 h. The resin was filtered, washed with THF (5 × 20 mL), and dried under reduced pressure to give **2** (2.0 g, 97% loading based on the weight of the resin).

Synthesis of Isatin Derivatives. General Procedures. The trityl thiosemicarbazide resin **2** was suspended in a solution of isatin **3** in DMF. The mixture was shaken at ambient temperature for 20−24 h and filtered. Untreated isatin was recovered from the filtrate. The functionalized resin was washed successively with DMF, THF, and dichloromethane (3 × 10 mL/g resin) and dried to constant weight. Conversion of the resin-bound isatin thiosemicarbazone **4** to the aminal derivative was achieved by one of the following procedures.

Method A. A mixture of **4**, 37% aqueous formaldehyde (5 mL/g resin), and a secondary amine (10 mmol/g resin) in DMF was shaken at room temperature for 24 h. The mixture was filtered, and the resin was washed with THF. The resin was shaken with DMSO for 15 min, filtered, washed with THF and dichloromethane (7 mL/g resin), and dried to constant weight.

Method B. A solution of the 1,1′-methylenebisamine (5 mmol/g resin) in dichloromethane (7 mL/g resin) was treated with acetyl chloride (5 mmol/g resin) (30 min, room temperature) to generate the iminium salt. This suspension was added to a suspension of **4** in dichloromethane. The mixture was shaken at ambient temperature for 3−5 h and filtered. The resin **5** was washed several times with dichloromethane and dried to constant weight.

Cleavage from Resin of Isatin Derivatives (6). The dried resin **5** was suspended in a solution of triisopropylsilane (TIPS) in dichloromethane (10%, 7.5 mL/g resin) for 10 min, and an equal volume of a solution of trifluoroacetic acid in dichloromethane (30%) was added dropwise. The mixture was shaken for 2−3 min, and all volatiles were removed under reduced pressure. The residue was suspended in dichloromethane, and the mixture was passed through a plug of Celite (3 g/g resin) soaked with saturated aqueous Na_2CO_3 (2.5 mL/g Celite). The dichloromethane solution obtained was dried ($NaSO_4$) and evaporated to give isatin derivatives **6** that were ∼85% pure by HPLC. Further purification could be achieved by recrystallization.

5-Methyl-1-piperidinomethyl-1*H*-indole-2,3-dione Thiosemicarbazone (6a). Reaction of trityl thiosemicarbazide resin **2** (200 mg, 0.95 mmol/g, 0.19 mmol) and 5-methyl isatin (162 mg, 1 mmol) in DMF (2 mL) for 24 h generated the supported thiosemicarbazone, which was treated with piperidine (0.2 mL, 2 mmol) and aqueous formaldehyde using the conditions of method A to give **5a**. Subsequent treatment with TIPS/TFA in dichloromethane followed by neutralization gave 57 mg (88%) of **6a** as a yellow solid. A portion was purified by recrystallization from ethyl acetate. mp: 205−206 °C (ethyl acetate, lit.[4] mp 206 °C (ethyl acetate)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (1H, bs, NH), 7.40 (1H, dd, J = 0.6, 1.2, C4*H*), 7.16 (1H, dd, J = 3,9, C6*H*), 6.95 (1H, d, J = 9, C7*H*), 4.46 (2H, s, NCH_2N), 2.53 (4H, m, NCH_2), 2.33 (3H, s, CH_3), 1.6−1.5 (4H, m, CH_2), 1.44−1.38 (2H, m, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$ + DMSO-d_6): δ 178.6 (*C*═S), 161.2 (N*C*═O), 141.0 (*C*═N), 131.8 (Ar*C*), 131.0 (Ar*C*), 130.7 (Ar*C*), 120.5 (Ar*C*), 118.6 (Ar*C*), 110.0 (Ar*C*), 61.9 (N*C*H_2N), 51.4 (N(*C*H_2)$_2$), 25.1 (2x*C*H_2), 23.3 (*C*H_2), 20.5 (*C*H_3). IR (film): 3418, 3246, 3157, 2937, 1692, 1600, 1491, 1436, 1341, 1303, 1152, 1120, 1082, 1039, 989, 808 cm^{-1}. MS (DIP CI): *m*/*z* 98 (45), 114 (25), 148 (70), 161 (100), 235 (40), 332 (MH^+, 7).

5-Trifluoromethoxy-1-piperidinomethyl-1*H*-indole-2,3-dione Thiosemicarbazone (6b). Reaction of trityl thiosemicarbazide resin **2** (200 mg, 0.95 mmol/g, 0.19 mmol) and 5-trifluoromethoxyisatin (231 mg, 1.00 mmol) in DMF (2.5 mL) for 24 h generated the supported thiosemicarbazone that was treated with piperidine (0.15 mL, 1.5 mmol) and aqueous formaldehyde using the conditions of method A to give **5b**. Subsequent treatment with TIPS/TFA in dichloromethane followed by neutralization gave 66 mg (84%) of **6b** as a yellow solid. A portion was purified by recrystallization from 1:1 ethanol/water. mp: 176−178 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.8 (1H, br s, N*H*), 7.52 (1H, br s, N*H*), 7.46−7.44 (1H, m, C4*H*), 7.26−7.24 (m, 1H, C6H), 7.10 (1H, d, J = 6, C7*H*), 6.60 (1H, br s, N*H*), 4.40 (2H, s, NCH_2N), 2.60−2.55 (4H, m, NCH_2), 1.60−1.55 (4H, m, CH_2), 1.55−1.40 (2H, m, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 179.8 (*C*═S), 161.6 (N*C*═O), 145 (*C*═N), 142.3 (Ar*C*O), 130.7 (Ar*C*), 128.2 (Ar*C*), 124.2 (Ar*C*), 120.3 (O*C*F_3), 113.9 (Ar*C*), 111.9 (Ar*C*), 63.0 (N*C*H_2N), 52.1 (N(*C*H_2)$_2$), 25.8 (*C*H_2), 24.0 (*C*H_2). IR (film): 3267, 3125, 1698, 1620, 1488, 1340, 1261, 1223, 1148, 1111, 1079, 1033 cm^{-1}. MS (FAB, NBA): 402 (MH^+).

5-Methoxy-1-piperidinomethyl-1*H*-indole-2,3-dione Thiosemicarbazone (6c). Reaction of trityl thiosemicarbazide resin **2** (200 mg, 0.95 mmol/g, 0.19 mmol) and 5-methoxy isatin (177 mg, 1.00 mmol) in DMF (2.5 mL) for 24 h generated the supported thiosemicarbazone which was treated with piperidine *N*-methyleneiminium chloride (1 mmol) using the conditions of method B to give **5c**. Subsequent treatment

with TIPS/TFA in dichloromethane followed by neutralization gave 61 mg (90%) of **6c** as a red solid. A portion was purified by recrystallization from ethanol. mp: 179−181 °C (ethanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.8 (1H, bs, N*H*), 7.50 (1H, br s, N*H*), 7.04 (1H, d, J = 2.4, C4*H*), 7.00 (1H, d, J = 5, C6*H*), 6.85 (1H, dd, J = 5,1, C7*H*), 6.70 (1H, br s, N*H*), 4.36 (2H, s, NCH_2N), 3.76 (3H, s, OCH_3), 2.50 (4H, m, NCH_2), 1.50 (4H, m, CH_2), 1.30 (2H, m, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9 (*C*═S), 162.0 (N*C*═O), 156.0 (*C*═N), 138.1 (Ar*C*O), 132.4 (Ar*C*), 117.7 (Ar*C*), 105.9 (Ar*C*), 62.8 (N*C*H_2N), 55.9 (O*C*H_3), 52.1 (N(*C*H_2)$_2$), 25.7 (2 × *C*H_2), 23.9 (*C*H_2). IR (film): 3263, 2939, 1692, 1601, 1488, 1437, 1283, 1231, 1172, 1146, 1111 cm^{-1}. MS (FAB, NBA): 348 (MH^+).

5,6-Dimethoxy-1-piperidinomethyl-1*H*-indole-2,3-dione Thiosemicarbazone (6d). Reaction of trityl thiosemicarbazide resin **2** (200 mg, 0.95 mmol/g, 0.19 mmol) and 5-methoxy isatin (207 mg, 1.00 mmol) in DMF (2.5 mL) for 24 h generated the supported thiosemicarbazone which was treated with piperidine *N*-methyleneiminium chloride (1 mmol) using the conditions of method B to give **5d**. Subsequent treatment with TIPS/TFA in dichloromethane followed by neutralization gave 63 mg (85%) of **6d** as a red solid. A portion was purified by recrystallization from CH_2Cl_2/hexane. mp: 230−232 °C (CH_2Cl_2/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.8 (1H, br s, N*H*), 7.50 (1H, br s, N*H*), 7.05 (1H, s, C7*H*), 6.70 (1H, s, C4*H*), 4.40 (2H, s, NCH_2N), 3.95 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 2.60 (4H, m, N(CH_2)$_2$), 1.60 (4H, m, 2 CH_2), 1.50 (2H, m, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 179.4 (*C*═S), 162.1 (N*C*═O), 152.7 (*C*═N), 145.7 (Ar*C*), 139.5 (Ar*C*), 110.0 (Ar*C*), 104.1 (Ar*C*), 96.2 (Ar*C*), 62.7 (N*C*H_2N), 56.6 (O*C*H_3), 56.4 (O*C*H_3), 52.0 (N(*C*H_2)$_2$), 25.9 (2 × *C*H_2), 24.0 (*C*H_2). IR (film): 3266, 2936, 1693, 1621, 1483, 1342, 1207, 1150, 1113, 1079 cm^{-1}. MS (FAB, NBA): 378 (MH^+).

5-Bromo-1-dimethylaminomethyl-1*H*-indole-2,3-dione Thiosemicarbazone (6e). Reaction of **2** (200 mg, 0.19 mmol) and 5-bromoisatin (226 mg, 1.00 mmol) in DMF (2 mL) gave **4e**, which was treated with aqueous dimethylamine (1 mL of 40% solution) and aqueous formaldehyde using the conditions of method A to give **5e**. Subsequent treatment with TIPS/TFA and neutralization gave 60 mg (86%) of **6e** as a yellow solid. A portion was purified by precipitation from ethyl acetate by addition of hexane (heating causes decomposition). mp: 86−88 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.8 (1H, br s, NH), 7.70 (1H, d, J = 2, C4*H*), 7.50 (1H, dd, J = 2, 8 C6*H*), 7.5 (1H, br s, N*H*), 6.95 (1H, d, J = 8, C7*H*), 4.4 (2H, s, NCH_2N), 2.2 (6H, s, N(CH_3)$_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$ + DMSO-d_6): δ 179.3 (*C*═S), 160.8 (N*C*═O), 141.9 (*C*═N), 133.2 (Ar*C*Br), 123.2 (Ar*C*), 120.8 (Ar*C*), 112.0 (Ar*C*), 62.6 (N*C*H_2N), 42.7 (N(*C*H_3)$_2$). IR (film): 3156, 2961, 1693, 1608, 1468, 1204, 1147, 1049 cm^{-1}. MS (FAB, NBA): 356, 358 (MH^+).

Synthesis of Thioureas. General Procedure. The amine was added to a suspension of TrITC resin **1** in anhydrous THF, and the mixture was shaken at ambient temperature for 24 h. The resin was filtered, washed with dichloromethane, and dried under reduced pressure. Cleavage of the thiourea from the resin was done as described for the isatin derivatives. All thioureas were pure by ^{1}H NMR.

1,1-Diethyl Thiourea (7a).[20] Prepared from TrITC resin **1** (1.24 mmol/g, 400 mg, 0.49 mmol) and diethylamine (0.16 mL, 1.5 mmoL) in THF (2 mL). Yield: 98 mg (75%). mp: 100−101 °C (ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.02 (2H, br s, NH_2), 3.8−3.4 (4H, br, NCH_2), 1.20 (6H, t, J = 6, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 179.7 (*C*═S), 48−42 (br, N*C*H_2), 12.5 (*C*H_3). IR (film): 3377, 3296, 3189, 2974, 1626, 1524, 1361, 1080 cm^{-1}. MS (GC/CI (NH_3)): *m*/*z* 133 (MH^+).

4-Methyl-piperidine-1-carbothioic Acid Amide (7b).[21] Prepared from TrITC resin **1** (1.24 mmol/g, 400 mg, 0.49 mmol) and 4-methylpiperidine (0.18 mL, 1.5 mmol) in THF (2 mL). Yield: 63 mg (80%). mp: 100−101 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.02 (2H, br s, NH_2), 4.60−4.40 (2H, br, NCH_2), 3.00 (2H, dt, J = 3, 12, NCH_2), 1.8−1.6 (3H, m, CH_2C*H*), 1.4−1.2 (2H, m, CH_2), 0.95 (3H, d, J = 6, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 179.9 (*C*═S), 48.7 (br, 2 × NCH_2), 33.5 (2 × *C*H_2), 30.4 (*C*H), 21.4 (*C*H_3). IR (film): 3285, 3179, 2954, 1626, 1508, 1456, 1363, 1311, 1262, 1084, 1018, 968, 839, 799 cm^{-1}. MS (GC/CI (NH_3)): *m*/*z* 159 (MH^+).

4-Benzyl-piperidine-1-carbothioic Acid Amide (7c). Prepared from TrITC resin **1** (1.24 mmol/g, 400 mg, 0.49 mmol) and 4-benzylpiperidine (0.26 mL, 1.5 mmol) in THF (2 mL). Yield: 90 mg (78%). mp: 118−119 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): 7.3−7.1 (5H, m, Ar*H*), 6.06 (2H, br s, NH_2), 4.5 (2H, br, NCH_2), 2.96 (2H, dt, J = 3,12, NCH_2), 2.55 (2H, d, J = 6.6, CH_2Ph), 1.8−1.7 (4H, m, (CH_2)$_2$CH), 1.4−1.2 (2H, m, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 180.0 (C═S), 139.4 (ArC_{ipso}), 128.9 (Ar*C*), 128.2 (Ar*C*), 126.0 (Ar*C*), 48.7 (br, N*C*H_2), 42.6 (*C*H_2Ph), 37.6 (*C*H), 31.6 (2 × *C*H_2). IR (film): 3292, 3182, 2911, 2845, 1615, 1509, 1454, 1347, 1262, 1089, 965 cm^{-1}. MS (GC/CI (NH_3)): *m*/*z* 235 (MH^+).

4-Methyl-piperazine-1-carbothioic Acid Amide (7d).[22] Prepared from TrITC resin **1** (1.24 mmol/g, 400 mg, 0.49 mmol) and 4-methylpiperazine (0.17 mL, 1.5 mmol) in THF (2 mL). Yield: 126 mg (94% as trifluoroacetate) before solid-phase neutralization, 66 mg (85%) after. mp: 170−172 °C (THF). ^{1}H NMR (300 MHz, CD_3OD): δ 3.83 (4H, bt, J = 6, NCH_2), 2.45 (4H, t, J = 6, NCH_2), 2.30 (3H, s, CH_3). ^{13}C NMR (75.5 MHz, CD_3OD): δ 182.0 (*C*═S), 56.0, 46.0. IR (film): 2924, 2854, 1645, 1445, 1374, 1347, 1261, 1212, 1152, 1095, 1022 cm^{-1}. MS (GC/CI (NH_3)): *m*/*z* 160 (MH^+).

Synthesis of Thiazoles. General Procedure. TrITC resin **1** and a primary amine in THF were shaken at ambient temperature for 8−10 h. The mixture was filtered, and the resin was washed thoroughly with THF and dichloromethane and dried. A mixture of this resin and methyl 2-chloroacetoacetate in anhydrous THF or acetonitrile was shaken at ambient temperature for 16−24 h. The mixture was filtered, the resin was washed several times with dichloromethane, and the combined filtrate and washings were concentrated. The residue was dissolved in dichloromethane and subjected to the Na_2CO_3/Celite treatment as described for the isatin derivatives. Concentration of the dichloromethane solution gave the requisite thiazoles that were pure by ^{1}H NMR.

Further purification could be effected by flash column chromatography on silica gel or by recrystallization.

2-Benzylamino-4-methyl-thiazole-5-carboxylic Acid Methyl Ester (8a). Prepared from TrITC resin **1** (100 mg, 1.24 mmol/g, 0.120 mmol) and benzylamine (0.11 mL, 1.0 mmol) in THF followed by reaction with methyl 2-chloroacetoacetate (60 μL, 0.50 mmol) in THF. The crude product was purified by flash column chromatography on silica gel (hexane:ethyl acetate 1:1) to give 25 mg (77%) of **8a**. mp: 123−124 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$): 7.14 (1H, br s, N*H*), 4.38 (2H, s, CH_2Ph), 3.69 (3H, s, CO_2CH_3), 2.38 (3H, s, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.2 (*C*═O), 162.8 (Ar*C*), 159.6 (Ar*C*), 136.3 (ArC_{ipso}), 128.8 (Ar*C*), 127.9 (Ar*C*), 127.4 (Ar*C*), 109.0 (Ar*C*), 51.5 (NCH_2), 49.8 (OCH_3), 17.3 (CH_3). IR (film): 3194, 2189, 1696, 1597, 1532, 1427, 1374, 1266, 1204, 1150, 1106, 1087 cm^{-1}. MS (GC/CI (NH_3)): *m*/*z* 263 (MH^+).

2-Butylamino-4-methyl-thiazole-5-carboxylic Acid Methyl Ester (8b). Prepared from TrITC resin **1** (200 mg, 1.24 mmol/g, 0.24 mmol) and butylamine (0.10 mL, 1.0 mmol) in THF followed by reaction with methyl 2-chloroacetoacetate (122 μL, 1.00 mmol) in CH_3CN. The crude product was purified by recrystallization from hexane to give 41 mg (76%) of **8b**. mp: 79−81 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.20 (1H, br s, NH), 3.70 (3H, s, OCH_3), 3.16 (2H, t, J = 6, NCH_2), 2.46 (3H, s, ArCH_3), 1.62−1.52 (2H, m, CH_2), 1.38−1.28 (2H, m, CH_2), 0.88 (3H, t, J = 6.6, CH_2CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.3 (*C*═O), 162.9 (Ar*C*), 159.9 (Ar*C*), 108.6 (Ar*C*), 51.5 (NCH_2), 45.9 (OCH_3), 31.1 (CH_2), 20.1 (CH_2), 17.5 (CH_3), 13.8 (CH_3). IR (film): 3200, 2924, 1702, 1596, 1531, 1428, 1370, 1334, 1266, 1190, 1148, 1097 cm^{-1}. MS (GC/CI (NH_3)): *m*/*z* 229 (MH^+).

2-Allylamino-4-methyl-thiazole-5-carboxylic Acid Methyl Ester (8c). Prepared from TrITC resin **1** (100 mg, 1.24 mmol/g, 0.12 mmol) and allylamine (0.08 mL, 1.0 mmol) in THF followed by reaction with methyl 2-chloroacetoacetate (60 μL, 0.50 mmol) in CH_3CN. The crude product was purified by recrystallization from hexane to give 22 mg (86%) of **8c**. mp: 92−93 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.00 (1H, br, N*H*), 5.8−5.7 (1H, m, C*H*), 5.27 (1H, br d, J = 18, C═CH_2), 5.17 (1H, br d, J = 12, C═CH_2), 3.8 (2H, br d, J = 6, CH_2N), 3.72 (3H, s, CO_2CH_3), 2.45 (3H, s, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.3 (*C*═O), 162.8 (Ar*C*), 159.4 (Ar*C*), 132.2 (Ar*C*, *C*H), 117.8 (CH═*C*H_2), 51.5 (NCH_2), 48.3 (OCH_3), 17.4 (CH_3). IR (film): 3202, 3086, 2923 (br), 1696, 1597, 1537, 1422, 1337, 1272, 1188, 1095 cm^{-1}. MS (GC/CI (NH_3)): *m*/*z* 213 (MH^+).

(*R*)-4-Methyl-2-(1-phenyl-ethylamino)-thiazole-5-carboxylic Acid Methyl Ester (8d). Prepared from TrITC resin **1** (200 mg, 1.24 mmol/g, 0.24 mmol) and (*R*)-(+)-α-methyl benzylamine (0.32 mL, 2.5 mmol) in THF followed by reaction with methyl 2-chloroacetoacetate (122 μL, 1.00 mmol) in CH_3CN. The crude product was purified by flash chromatography (hexane:ethyl acetate 4:1) to give 54 mg (78%) of **8d** as a gum. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.3−7.2 (5H, m, Ar*H*), 6.40 (1H, br, N*H*), 4.43 (1H, q, J = 6, C*H*), 3.67 (3H, s, OCH_3), 2.43 (3H, s, CH_3), 1.50 (3H, d, J = 6, CHCH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.1 (*C*═O), 162.8 (Ar*C*), 159.4 (Ar*C*), 141.7 (ArC_{ipso}), 128.7 (Ar*C*), 127.7 (Ar*C*), 125.9 (Ar*C*), 55.9 (N*C*H), 51.4 (OCH_3), 23.7 (CH_3), 17.4 (CHCH_3). IR (film): 3198, 2950, 1704, 1528, 1432, 1373, 1327, 1275, 1208, 1190, 1153, 1093 cm^{-1}. MS (GC/CI (NH_3)): *m*/*z* 277 (MH^+).

2-Cyclohexylamino-4-methyl-thiazole-5-carboxylic Acid Methyl Ester (8e). Prepared from TrITC resin **1** (110 mg, 1.24 mmol/g, 0.14 mmol) and cyclohexylamine (0.06 mL, 0.5 mmol) in THF followed by reaction with methyl 2-chloroacetoacetate (0.06 mL, 0.50 mmol) in CH_3CN. The crude product was purified by recrystallization from dichloromethane/hexane to give 31 mg (90%) of **8e**. mp: 142−143 °C (CH_2Cl_2/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.93 (1H, br s, N*H*), 3.78 (3H, s, OCH_3), 3.23 (1H, m, N*CH*), 2.52 (3H, s, CH_3), 2.1−2.0 (2H, m, CH_2), 1.8−1.7 (2H, m, CH_2), 1.68−1.58 (1H, m, CH_2), 1.44−1.14 (5H, m, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.9 (*C*═O), 162.9 (Ar*C*), 159.5 (Ar*C*), 108.4 (Ar*C*), 55.4 (N*C*H), 51.5 (OCH_3), 32.6 (CH_2), 25.4 (CH_2), 24.6 (CH_2), 17.4 (CH_3). IR (film): 3205, 3090, 2993, 2937, 2854, 1697, 1573, 1539, 1434, 1273, 1188, 1148, 1108, 1087 cm^{-1}. MS (GC/CI (NH_3)): *m*/*z* 255 (MH^+).

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