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Synthesis of Heterocyclic Thiosulfonates

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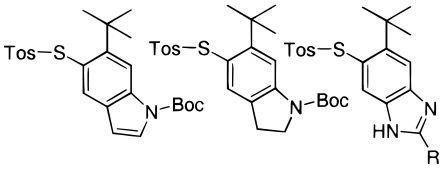
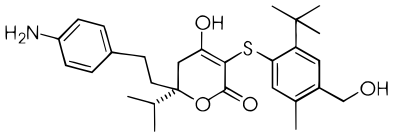
ABSTRACT



A simple synthesis of heterocyclic thiosulfonates containing indole, indoline, benzoimidazole, and quinoxaline rings is described. The synthesis of these thiosulfonates involves the preparation of the appropriately substituted thiols followed by sulfonylation to give thiosulfonates. The corresponding thiols were prepared in a simple and efficient manner by using a thiocyanation reaction either prior to heterocycle ring formation or after heterocycle ring formation. These thiosulfonates were coupled successfully to the 5,6-dihydropyran-2-one ring to give products that showed excellent HIV protease activity.

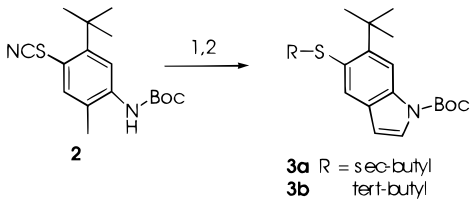
Thiosulfonates have been used extensively in organic synthesis.[1] These reagents are extremely valuable electrophiles and have been used for the sulfenylation of various anions.[2] We have been using sulfenylation of pyran-2-ones as well as 5,6-dihydropyran-2-ones with thiosulfonates for the synthesis of nonpeptidic human immunodeficiency virus-1 (HIV) protease inhibitors.[3] Recently, we described PD-178390 (1) as our preclinical candidate.[4] We wish to replace the 3-S-Ph(2-*tert*-butyl-4-hydroxymethyl-5-methyl) moiety with various heterocycles to study the resulting structure−activity relationships. Although the synthesis of these unsubstituted heterocycles is well-known in the chemical literature, the synthesis of corresponding thiols or thiosulfonates is lacking. Herein we report a simple synthesis of various heterocyclic thiosulfonates, which are useful for the introduction of thioheterocycles.



1 (PD 178390)

Synthesis of indole[5]-containing thiosulfonates began with Boc-protected 3-*tert*-butyl-6-methyl-4-thiocyanatoaniline[6] **2** (Scheme 1). Dilithiation of **2** with *sec*-butyllithium or *tert*-butyllithium at −78 °C, followed by treatment with DMF, afforded the 2-hydroxyindoline.[7] However, the alkyllithium also attacked the thiocyanate group to yield the S-alkylated product. The crude material was treated with a few drops of

Scheme 1[a]



[a] Reagents: (1) Addition of *sec*-butyllithium or *tert*-butyllithium at −78 °C, warmed to −30 to −45 °C, 15 min; followed by the addition of DMF at −35 °C; warmed to rt, 1 h; (2) concd HCl/THF, 10 min.

(1) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363.
(2) Zelfirov, N. S.; Zyk, N. V.; Beloglazkina, E. K.; Kuateladze, A. G. *Sulfur Rep.* **1993**, *14*, 223.
(3) Tait, B. D.; Hagen, S.; Domagala, J. M.; Ellsworth, E. L.; Gajda, C.; Hamilton, H. W.; Vara Prasadm J. V. N.; Ferguson, D.; Graham, N.; Hupe, D.; Nouhan, C.; Tummino, P. J.; Humblet, C.; Lunney, E. A.; Pavlovsky, A.; Rubin, J.; Gracheck, S. J.; Baldwin, E. T.; Bhat, T. N.; Erickson, J. W.; Gulnik, S. V.; Liu, B. *J. Med. Chem.* **1997**, *40*, 3781.
(4) Vara Prasad, J. V. N.; Boyer, F. E.; Domagala, J. M.; Ellsworth, E. L.; Gajda, C.; Hamilton, H. W.; Hagen, S. E.; Markoski, L. J.; Steinbaugh, B. A.; Tait, B. D.; Humblet, C.; Lunney, E. A.; Pavlovsky, A.; Rubin, J. R.; Ferguson, D.; Graham, N.; Holler, T.; Hupe, D.; Nouhan, C.; Tummino, P. J.; Urumov, A.; Zeikus, E.; Zeikus, G.; Gracheck, S. J.; Saunders: J. M.; VanderRoest, S.; Brodfuehrer, J.; Iyer, K.; Sinz, M.; Gulnik, S. V.; Erickson, J. W. *Bioorg. Med. Chem.* **1999**, *7*, 2775.

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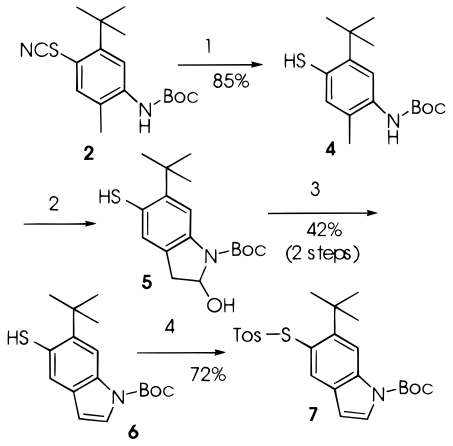
Scheme 2[a]



[a] Reagents: (1) DTT (4 equiv), EtOH reflux, 16 h; (2) Addition of *sec*-butyllithium or *tert*-butyllithium at −78 °C, warmed to −0 to −45 °C, 15 min; followed by the addition of DMF at −35 °C; warmed to rt, 1 h; (3) concd HCl/THF, 10 min; (4) tosyl bromide, pyridine, rt, 16 h.

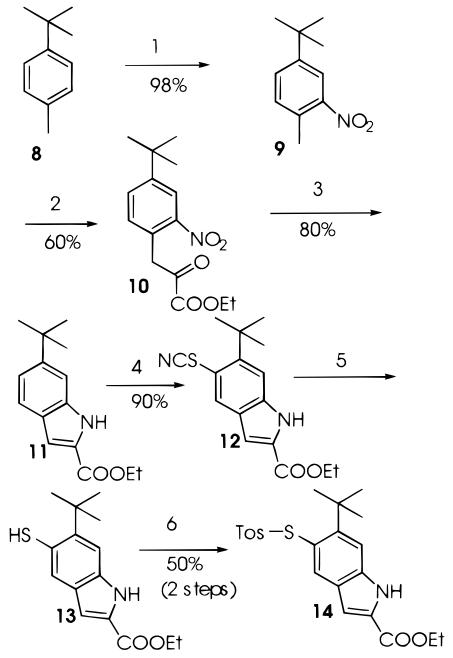
concentrated HCl in THF to afford the corresponding indole derivative **3**.

In an alternate approach (Scheme 2), **2** was reduced to thiol by treating it with dithiothreitol. The trilithiated anion of **4** (generated by treating **4** with *sec*-butyllithium or *tert*-butyllithium at −78 °C in THF) was condensed with DMF to afford the corresponding 2-hydroxyindoline **5** in good yields. Compound **5** was dehydrated with *p*-toluenesulfonic acid to yield indole derivative **6**. Isolation of **5** was unnecessary, since treatment of the crude reaction mixture with two drops of hydrochloric acid gave indole **6**. The crude indole thiol **6** on sulfonylation[8] with tosyl bromide in the presence of pyridine afforded indole-containing thiosulfonate **7** in excellent yield.

The 2-carbethoxy-substituted indole containing thiosulfonate was synthesized as shown in Scheme 3. 4-Methyl-*tert*-butylbenzene **8** was first nitrated to obtain 3-*tert*-butyl-6-methyl-nitrobenzene **9**.[9] The anion generated from **9**, on treatment with potassium in ethanol, was condensed with diethyl oxalate to obtain compound **10**.[10] The nitro group in compound **10** was reduced with Fe/AcOH, followed by cyclization to give 2-carbethoxy-6-*tert*-butylindole **11**. Compound **11** on thiocyanation afforded thiocyanate **12**.[11] Compound **12** was converted to the corresponding thiotosylate **14** via a two-step protocol: (a) conversion of thiocyanate to thiol **13** and (b) sulfonylation of thiol to thiosulfonate **14**.

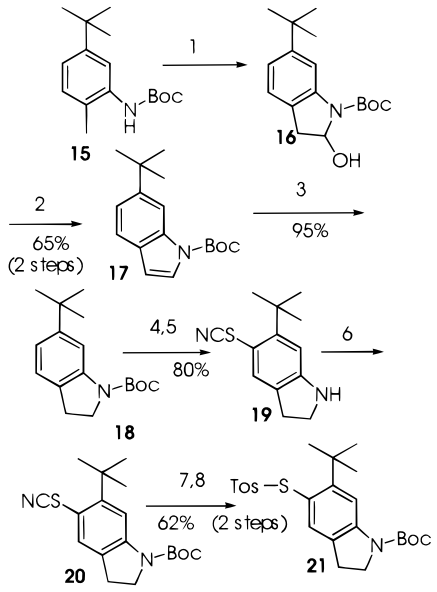
Indoline-containing thiosulfonate was synthesized as shown in Scheme 4. Boc-protected 3-*tert*-butyl-5-methylaniline **15**

Scheme 3[a]



[a] Reagents: (1) HNO_3, H_2SO_4; (2) K, ethanol, ether, 4 h, followed by diethyl oxalate, 30 min, addition of 9, rt, 4 h; (3) Fe/AcOH, reflux, 2 h; (4) NH_4SCN (6 equiv), Br_2 (1.2 equiv), 0 °C, 4 h, followed by warming to rt, 1 h; (5) NaSH (3 equiv), $NaBH_4$ (6 equiv), MeOH/H_2O in 2:1 ratio, addition at 0 °C, rt for 16 h; (6) tosyl bromide, pyridine, CCl_4, 0 °C, 16 h.

Scheme 4[a]



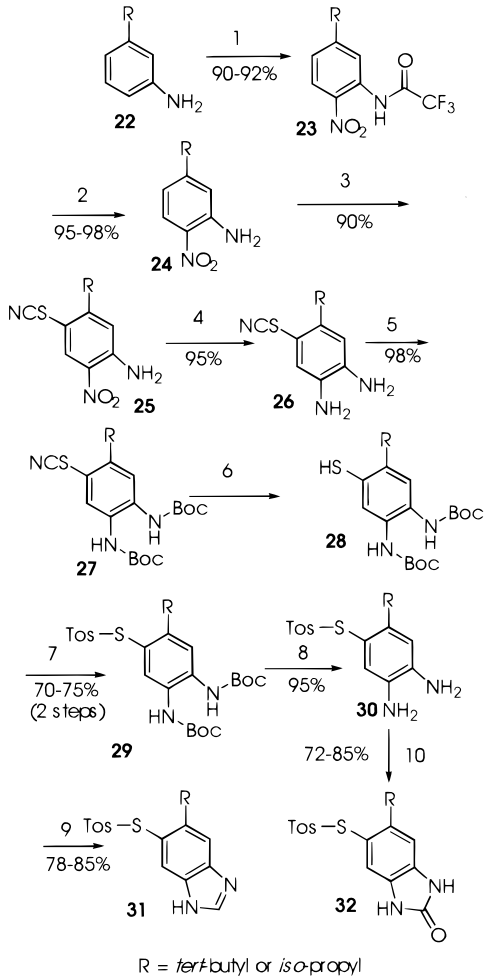
[a] Reagents: (1) Addition of *sec*-butyllithium or *tert*-butyllithium at −78 °C, warmed to −30 to −45 °C, 15 min; followed by the addition of DMF at −35 °C; warmed to rt, 1 h; (2) concd HCl/THF, 10 min; (3) H_2 (50 psi), 20% Pd/C, 16 h; (4) 4 N HCl in dioxane, 2 h; (5) NaSCN (6 equiv), NaBr (1.2 equiv) Br_2 (1.2 equiv), 0 °C, 4 h, followed by warming to rt, 1 h; (6) Boc anhydride, EtOAc/hexanes in 1:3 ratio, reflux, 16 h; (7) DTT (4 equiv), EtOH reflux, 16 h; (8) tosyl bromide, pyridine, CCl_4, 0 °C, 16 h.

on dilithiation (vide supra), followed by treatment with DMF, afforded the corresponding 2-hydroxyindoline **16**. Dehydration of the crude material **16** afforded 5-*tert*-butylindole **17** in excellent yields. Compound **17** was hydrogenated using

20% palladium over charcoal to give indoline derivative **18**. Deprotection of the Boc group in **18**, followed by thiocyanation[6,11,12] yielded the corresponding thiocyanate **19**. The indoline nitrogen in **19** was protected as a Boc derivative **20** and the thiocyanate was converted to thiotosylate **21** via thiol as described above (Scheme 4).

A synthesis of benzoimidazole containing thiosulfonates is shown in Scheme 5. Nitration of 3-*tert*-butylaniline or

Scheme 5[a]

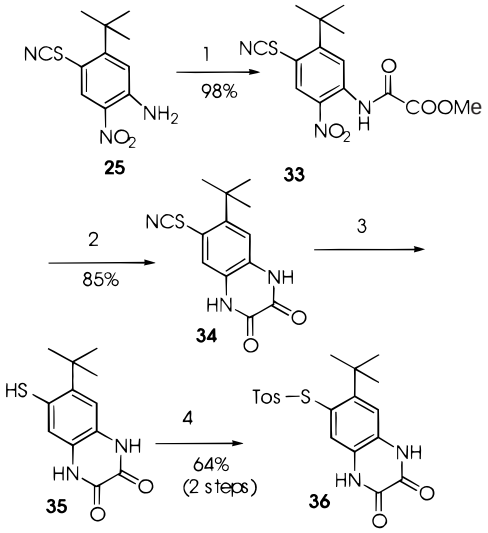


[a] Reagents: (1) Trifluoroacetic anhydride, KNO_3, 0 °C for 1 h; rt for 1 h; (2) 7% aqueous K_2CO_3, MeOH, rt, 16 h; (3) NaSCN(6 equiv), NaBr (1.2 equiv) Br_2 (1.2 equiv), 0 °C, 4 h, followed by warming to rt, 1 h; (4) H_2 (50 psi), Raney nickel, THF, 16 h; (5) Boc anhydride, EtOAc/hexanes in 1:3 ratio, reflux, 16 h; (6) NaSH (3 equiv), $NaBH_4$ (6 equiv), MeOH/H_2O in 2:1 ratio, addition at 0 °C, rt for 16 h; (7) tosyl bromide, pyridine; (8) 4 N HCl in dioxane, followed by neuatralizing with a buffer of pH 7.5; (9) 95% HCOOH reflux, 3 h; (10) triphosgene, Et_3N, THF, 90 °C, 1.5 h.

3-isopropylaniline **22** was performed using trifluoroacetic anhydride and potassium nitrate in excellent yields to obtain **23**.[13] The trifluoroacetyl group in compound **23** was removed on treatment with aqueous K_2CO_3 to give **24**.[12] Compound **24** on subjecting to thiocyanation conditions afforded the corresponding thiocyanate **25** as the only regioisomer. The compound **25** was hydrogenated using Raney nickel as catalyst to give diamine **26**. Boc protection of amino groups gave **27**, which was reduced with DTT to give thiol **28**. Compound **28** on sulfonylation was converted to thiosulfonate **29**, followed by cleavage of the Boc groups using 4 N HCl in dioxane gave the diamine **30**. Imidazole ring formation was accomplished by treating **30** with formic acid to give **31** in excellent yields.[14] Compound **30** on treatment with triphosgene afforded imidazol-2-one-containing thiosulfonates **32** in excellent yields.

The synthesis of quinoxalinedione-containing thiosulfonates began with thiocyanate **25** (Scheme 6). Compound

Scheme 6[a]



[a] Reagents: (1) ClCOCOOMe, pyridine, 0 °C, rt for 16 h; (2) H_2 (50 psi), Raney nickel, THF, 16 h; NaSH (3 equiv), $NaBH_4$ (6 equiv), MeOH/H_2O in 2:1 ratio, addition at 0 °C, rt for 16 h; (4) tosyl bromide, pyridine.

25 was acylated with methyl chlorooxoacetate in the presence of pyridine to furnish **33** in quantitative yield.[15] The nitro group in compound **33** was hydrogenated using Raney nickel

(5) Clark, R. D.; Muchowski, J. M.; Fisher, L. E.; Flippin, L. A.; Repke, D. B.; Souchet, M. *Synthesis* **1991**, 871.

(6) Vara Prasad, J. V. N.; Boyer, F. E.; Domagala, J. M.; Ellsworth, E. L.; Gajda, C.; Hagen, S. E.; Markoski, L. J.; Tait, B. D.; Lunney, E. A.; Tummino, P. J.; Ferguson, P. J.; Holler, T.; Hupe, D.; Nouhan, C.; Gracheck, S. J.; VanderRoest, S.; Saunders: J.; Iyer, K.; Sinz, M.; Brodfuehrer, J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1481.

(7) All the compounds were characterized by ^1H NMR and mass spectra.

(8) Ranasinghe, M. G.; Fuchs, P. L. *Synth. Commun.* **1988**, *18*, 227.

(9) Hagen, S.; Vara Prasad, J. V. N.; Boyer, F. E.; Domagala, J. M.; Ellsworth, E. L.; Gajda, C.; Hamilton, H. W.; Markoski, L. J.; Steinbaugh, B. A.; Tait, B. D.; Lunney, E. A.; Tummino, P. J.; Ferguson, D.; Hupe, D.; Nouhan, C.; Gracheck, S. J.; Saunders: J. M.; VanderRoest, S. *J. Med. Chem.* **1997**, *40*, 3707.

(10) Gagliardi, S.; Nadler, G.; Consolandi, E.; Parini, C.; Morvan, M.; Legave, M.-N.; Belfiore, P.; Zocchetti, A.; Clarke, G. D.; James, I.; Nambi, P.; Gowen, M.; Farina, C. *J. Med. Chem.* **1998**, *41*, 1568.

(11) Wardell, J. L. In *The Chemistry of Thiol Group*; Patai, S., Ed.; John Wiley & Sons: New York, 1974; 230p.

(12) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999.

as the catalyst to yield the corresponding amine, which underwent cyclization to quinoxaline **34** under the reaction conditions. Thiocyanate **34** was converted to the corresponding thiosulfonate **36** via thiol **35** as described above in 64% overall yield.

These heterocylclic thiosulfonates were coupled successfully to the 5,6-dihydropyran-2-one ring system in the presence of a mild base like potassium carbonate. The HIV protease activity and anti-HIV activity of the final compounds will be discussed elsewhere.

Acknowledgment. I thank Dr. John M. Domagala for his encouragement and the Analytical Chemistry Department for spectral data.

OL0056170

(13) Kher, S. M.; Cai, S. X.; Weber, E.; Keana, F. W. *J. Org. Chem.* **1995**, *60*, 5838.
(14) Devlin, T. A.; Jebaranam, D. J. *Synth. Commun.* **1995**, *25*, 711.
(15) Grivass, S.; Tian, W. *Acta Chim. Scand.* **1992**, *46*, 1109.