Tetrahedron Letters, Vol. 34, No. 13, pp. 2059-2062, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A General Non-Reductive Method for the Desulfenylation of 3-Indolyl Sulfides

Pierre Hamel*, Nicolas Zajac†, Joseph G. Atkinson and Yves Girard

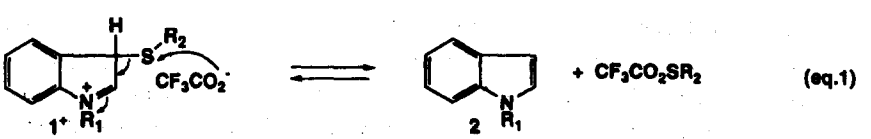
Merck Frosst Centre for Therapeutic Research, P.O. Box 1005, Pointe-Claire - Dorval, Québec H9R 4P8

Abstract: In trifluoroacetic acid, in the presence of thiosalicylic acid as a trapping agent, 3-indolyl sulfides bearing a wide variety of substituents are smoothly and rapidly desulfenylated to the corresponding 3-unsubstituted indoles.

The 3-position is the most nucleophilic center of the indole nucleus. Over the years, many novel and elegant procedures have been developed for the synthesis of 2-substituted indoles without a substituent on this highly reactive 3-position. [1]

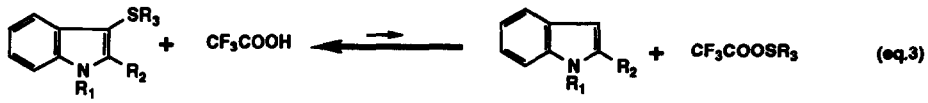
One of the now classical methods, developed almost 20 years ago by P.G. Gassman et al,[2] involves the initial synthesis of a 3-methylthio indole, followed by reductive desulfurization with Raney Nickel. This method has the disadvantage of being limited to substrates bearing substituents which are compatible with the reductive conditions of the process. We present here a novel, general, non-reductive procedure for the desulfenylation of 3-indolyl sulfides which greatly broadens the applicability of this very convenient 2-step synthesis of 2-substituted indoles.

Recently,[3] we demonstrated that the trifluoroacetic acid (TFA)- catalyzed isomerization of 3-indolyl sulfides (**1**) to the corresponding 2-indolyl sulfides, previously thought to occur via an intramolecular shift,[4] actually proceeds mainly via a more complex multi-step process. This intermolecular series of events features an initial, quite rapid disproportionation of the substrate into a 2,3-unsubstituted species (**2**) and a corresponding 2,3-disubstituted analog (**3**) (eq. 1 and 2):

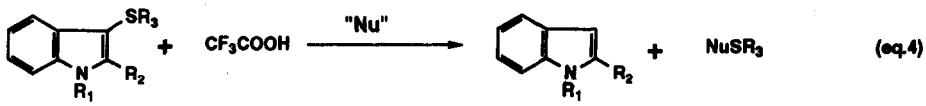


In an initial step, the protonated substrate 1+ suffers an attack by trifluoroacetate anion to afford the desulfenylated species 2 along with an acyloxy sulfide, which is a potent sulfenylating agent.[5] This reagent is rapidly trapped by the unprotonated substrate to afford the 2,3-bis sulfide 3. This disproportionation process is rapid, usually accomplished within minutes at room temperature. By rapid quenching of the reaction mixture, the two disproportionation products 2 and 3 have been isolated.[3]

In cases where a substituent is present at the 2-position of a 3-indolyl sulfide, this disproportionation is blocked, and a slow, low-yielding desulfenylation occurs (eq. 3), the main driving force being the slow decomposition of the acyloxy sulfide.[5] We reasoned that if an exogenous trapping agent for the acyloxy sulfide were present, the process could be greatly accelerated, leading to improved yields for the desulfenylated products 4 (eq. 4).



1 4



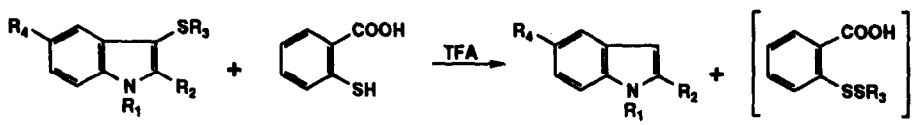
1 4

We have found that thiols are excellent trapping agents and give rise to high yields of desulfenylated indoles 4. Our preferred thiol is thiosalicylic acid which offers the advantages of being non-volatile and not very odorous, inexpensive and easily removed, along with the corresponding trapping product, by extraction with dilute aqueous base. An analogous desulfenylation of stable 3-methylthio indolenines by external mercaptans has been reported by Dmitrienko et al.[6]

In a typical procedure, a mixture of 1 mmole of a 3-indolyl sulfide 1 and 2 mmoles of thiosalicylic acid in 7 mL of TFA is stirred at room temperature or at reflux, until the reaction is complete, as monitored by TLC, usually within minutes to a few hours. The excess TFA is evaporated, the residue is taken up in ethyl acetate and washed with 1N aq. NaOH and water. The product from the organic phase is purified by silica gel chromatography to afford the desulfenylated product 4 in good to excellent yield. The Table illustrates the wide scope of the process. This process offers several advantages over the Raney Nickel desulfurization, the most notable of which is its non-reductive nature, so that functionalities such as nitro, halogen (even iodide), nitrile, olefin, etc., are unaffected. In addition, there is no handling of messy, pyrophoric materials and the desulfenylation occurs exclusively at the 3-position of the ring, so that a sulfide at another position remains untouched (e.g. substrate **1d**). It should also be noted that substrate **1i** bearing the electron-withdrawing carbomethoxy substituent in the 2-position also undergoes smooth desulfenylation.

Table

Desulfenylation of 3-Indolyl Sulfides in TFA with 2 eq. of Thiosalicylic Acid



1 4

Substrate	R_1	R_2	R_3	R_4	T(°C)	Time(h)	% 4*	mp(°C)
1a	Me	Ph	t-Bu	H	72	1.5	84	97-99
1b	H	Me	Me	NO_2	72	0.25	67	169-171
1c	H	Me	Ph	COMe	rt	0.25	50	139-141
1d	H	Me	Ph	SMe	rt	0.25	93	51-53
1e	H	Me	Ph	CN	rt	0.25	83	134-135
1f	H	Me	Ph	O-Allyl	rt	1.5	94	40-42
1g	H	Me	Ph	I	72	0.25	81	89-91
1h	CH_2Ph	Me	Ph	H	rt	1	86	oil
1i	H	CO_2Me	Ph	H	60	0.25	91	148-150

* Isolated yield. All new compounds were fully characterized by IR and ^1H NMR data and elemental analysis.

The 3-indolyl sulfide starting materials can be obtained by coupling ß-keto sulfides with appropriately substituted anilines (Gassman synthesis)[2] or phenylhydrazines (Fischer indolization). The complementarity of these two methods provides a wide range of substituents on the phenyl portion of the indole ring. An interesting aspect of the preparation of these substrates is that the 3-sulfide group may be considered as a built-in protecting group for the 3-position of the indole. Indeed, various transformations can be effected at other positions on the ring without complications arising from the nucleophilicity of the 3-position. The concept of utilizing the sulfide as protecting group has had very limited application,[7] in view of the reductive conditions that were previously required for its removal. The desulfenylation method that we present herein, which permits the presence of a much wider array of substituents on the indole ring, allows novel flexibility in the manipulation of indole derivatives. As a possible extension to this concept, a 3-unsubstituted indole may be easily sulfenylated, transformations effected elsewhere on the molecule and the sulfide protecting group removed, liberating the 3-position for further modifications.

REFERENCES

† This paper is dedicated to the memory of Nicolas Zajac, who died in a tragic sports accident in June 1992. He performed a portion of this work during a student work term.

1. The following are representative of the many recent papers on the subject:
   a) Hirao, K.; Mohri, K.; Yonemitsu, O.; Tabata, M. and Sohma, J., *Tetrahedron Lett.*, **1992**, *33*, 1459.
   b) Kawasaki, T.; Kodama, A.; Nishida, T.; Shimizu, K. and Somei, M., *Heterocycles* **1991**, *32*, 221.
   c) Gharpure, M.; Stoller, A.; Bellamy, F.; Firnau, G. and Snieckus, V., *Synthesis*, **1991**, 1079.
   d) Gray, N.M.; Dappen, M.S.; Cheng, B.K.; Cordi, A.A.; Biesterfeldt, J.P.; Hood, W.F. and Monahan, J.B., *J. Med. Chem.*, **1991**, *34*, 1283.
   e) Bartoli, G.; Palmieri, G.; Petrini, M.; Bosco, M. and Dalpozzo, R., *Tetrahedron*, **1990**, *46*, 1379.
   f) Katritzky, A.R.; Fan, W.Q.; Akutagawa, K.; Wang, J., *Heterocycles*, **1990**, *30*, 407.
2. Gassman, P.G.; van Bergen, T.J.; Gilbert, D.P. and Cue, B.K. Jr, *J. Amer. Chem. Soc.*, **1974**, *96*, 5495.
3. Hamel, P.; Girard, Y. and Atkinson, J.G., *J. Org. Chem.*,**1992**, 57, 2694.
4. Plate, R. and Ottenheijm, H.C.J., *Tetrahedron*, **1986**, *42*, 451.
5. a. Barton, D.H.R.; Nakano, T. and Sammes, P.G., *J. Chem. Soc.(c)*, **1968**, *322*.
   b. Morishita, T.; Furukawa, N. and Oae, S., *Tetrahedron*, **1981**, *37*, 3115.
   c. Haas, A.; Lieb, M. and Zhang, Y., *J. Fluorine Chem*, **1985**, *29*, 297.
6. Friesen, R.W.; Vice, S.F.; Findlay, C.E. and Dmitrienko, G.I., *Tetrahedron Lett.*, **1985**, *26*, 161.
7. Mohan, B.; Nagarathnam, D.; Vedachalam, M. and Srinivasan, P.C., *Synthesis*, **1985**, 188.

(Received in USA 30 November 1992; accepted 20 January 1993)