ADDITION OF THIOLS TO ACETYLENE SUBSTITUTED INDOLES

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Abstract - The preparation of synthetically useful thio enol ether substituted indoles is described.

We have recently published a novel approach to prepare indole derivatives possessing an acetylene functionality at C-4.[1] In exploring the synthetic potential of this type of substituents we have established that addition of thiols can be performed in a satisfactory manner leading to thio enol ethers, the versatility of which is well precedented.[2]

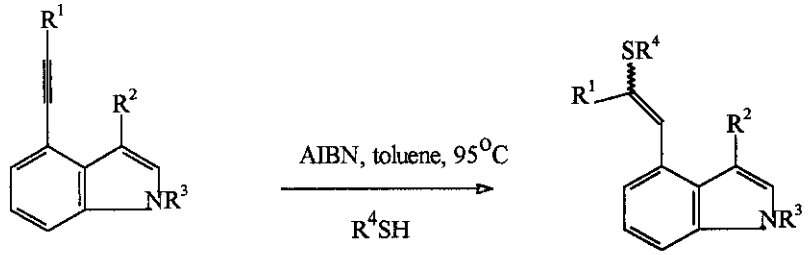
Despite the fact that radical addition of thiols to acetylenes has been known for decades,[3] the reaction attains relatively little attention in the numerous recent publications on synthetic applications of radical reactions.[4]

We have performed successful radical additions to terminal or internal acetylenes according to Scheme 1.

The majority of starting acetylenes has been described in our previous report.[1] Terminal acetylenes (**1a-c**) were prepared from the corresponding iodide with Pd-Cu(I) catalyzed coupling[1] followed by fluoride promoted desilylation[5] in good overall yields (Scheme 2). Protected propargylic derivative (**1g**) (TBS stands for dimethyl-*tert*-butylsilyl) was obtained by the standard method.[6]

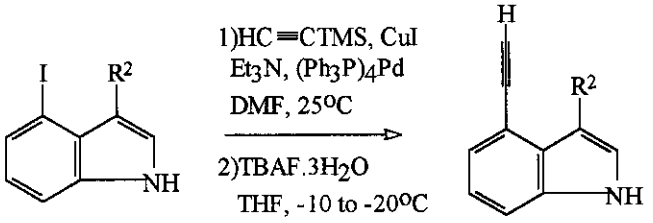
The results of the radical additions of thiols (**2a-e**) to indoles (**1a-i**) together with the tlc behaviour of the products are listed in Table 1. The reactions were routinely carried out immensing a stirred toluene solution of indole[7] (*ca* 30 mg of indole/ml of solvent), the thiol (1.2 equiv) and AIBN (0.2 equiv) into a preheated (90-

Scheme 1



1	R^1	R^2	R^3	2	R^4
a	H	CH=O	H	**a**	4-Me-C_6H_4
b	H	/*E*/-CH=$CHNO_2$	H	**b**	Ph
c	H	$(CH_2)_2NO_2$	H	**c**	4-Br-C_6H_4
d	TMS	$(CH_2)_2NO_2$	H	**d**	*n*-Bu
e	*n*-Bu	$(CH_2)_2NO_2$	H	**e**	*tert*-Bu
f	CH_2OH	$(CH_2)_2NO_2$	Me		
g	CH_2OTBS	$(CH_2)_2NO_2$	Me		
h	$(EtO)_2CH$	$(CH_2)_2NO_2$	H		
i	$Me_2C(OH)$	$(CH_2)_2NO_2$	H		

Scheme 2.



4	R^2	1	Y(%)
a	CH=O	**a**	74
b	/*E*/-CH=$CHNO_2$	**b**	67
c	$(CH_2)_2NO_2$	**c**	71

Table 1.

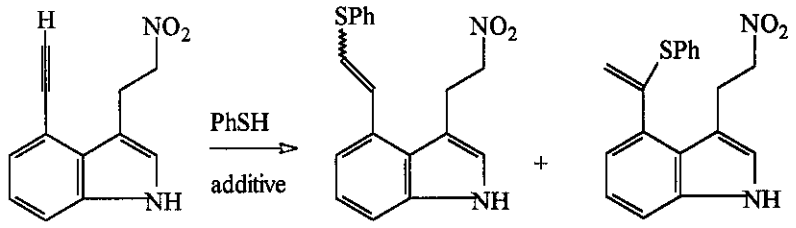
Radical Addition Reaction of Indole (1) with Thiol (2)

Run	Startg. Compd.		Thiol		Product[9]	Yield[a]		Tlc[b]	
	1	R^1	2	R^4	3	%	E/Z[c]	Eluent	R_f
1	**a**	H	**a**	4-Me-C_6H_4	**aa**	85	*E* only	1H1E	0.18
2	**a**	H	**e**	*tert*-Bu	no reaction[d]				
3	**b**	H	**a**	4-Me-C_6H_4	complex mixture				
4	**c**	H	**a**	4-Me-C_6H_4	**ca**	88	4:1	K	0.51
5	**c**	H	**b**	Ph	**cb**	87	5:1	K	0.41
6	**c**	H	**c**	4-Br-C_6H_4	**cc**	82	4:1	K	0.46
7	**c**	H	**d**	*n*-Bu	**cd**	82	3:1	K	0.50
8	**c**	H	**e**	*tert*-Bu	**ce**	86	1:2	K	0.54
9	**d**	TMS	**a**	4-Me-C_6H_4	no reaction[e]				
10	**e**	*n*-Bu	**a**	4-Me-C_6H_4	**ea**	70	3:2[f]	K	0.63
11	**f**	CH_2OH	**a**	4-Me-C_6H_4	**fa**	82	1:3	K	0.16(*E*)
									0.13(*Z*)
12	**f**	CH_2OH	**b**	Ph	**fb**	76	1:2	30K1M	0.61(*E*)
									0.56(*Z*)
13	**f**	CH_2OH	**e**	*tert*-Bu	**fe**	61	1:8	30K1M	0.56(*E*)
									0.41(*Z*)
14	**g**	CH_2OTBS	**a**	4-Me-C_6H_4	**ga**	97[g]		K	0.57
15	**h**	$(EtO)_2CH$	**a**	4-Me-C_6H_4	complex mixture				
16	**i**	$Me_2C(OH)$	**a**	4-Me-C_6H_4	**ia**	35[h]		20K1M	0.49

a. Isolated yields **b**. Abbreviations: K: $CHCl_3$, M: MeOH, H: *n*-hexane, E ethyl acetate. **c**. Determined by ^1H nmr of the purified product **d** 40% of the starting material was recovered unchanged. **e**. 90% of the starting material was recovered unchanged. **f**. The minor component is a 25/15 mixture of isomers, their stereochemistry has not been determined **g**. The major isomer is (*Z*)-**3**. We could not determine, however, the accurate isomer ratio. **h**. The stereochemistry has not been determined.

105°C) oil bath[8] under argon. The stereochemical outcome of the reactions was determined by ^{1}H nmr spectroscopy of the chromatographically purified products.[9] In the case of disubstituted olefins the vicinal coupling constants were indicative, while the geometry of trisubstituted olefins was established from NOE experiments With three exceptions (Runs 10, 14, 16) we could detect only one regioisomer, which is depicted in Scheme 1. Usually we were unable to separate the isomers by chromatography. In the case of the products derived from **1f** (Runs 11-13), however, the two isomers could be distinguished and partially separated, which is indicated in Table 1 by giving the different R_f values of the isomers. In most of the cases terminal acetylenes gave good preparative yields with every thiol examined (Runs 1-8). The unsuccessful coupling described in Run 2 can be the consequence of the poor solubility of **1a** in toluene, while the complex reaction mixture in Run 3 is attributed to the participation of the vinyl group affording a product too sensitive under these harsh reaction conditions. The reactions of internal acetylenes were less predictable. Some correlation, however, exists between steric congestion and the efficiency of coupling.[10] When the propargylic carbon of the starting acetylene was monosubstituted, the addition became more sluggish, but good preparative yields could be achieved (Runs 10-14). A further increase in the steric demand of R^1, however, resulted in either no reaction (Run 9) or complex reaction mixtures (Runs 15, 16). The stereochemical outcome of these reactions deserves comment. Usually the additions to terminal acetylenes (**1a-c**) exhibited good selectivities in favour of the thermodynamically more stable *E* isomers. In the cases of the sterically more demanding *tert*-butyl mercaptan (**2e**), or disubstituted acetylenes (**1e-i**) the ratio of isomer *Z* increased to varying extent. In the reaction of **1f** with **2e** (Run 13) the *Z* selectivity became significant.

Scheme 3.



1c **3cb** **4**

We performed some preliminary experiments to check the possibility of changing the regioselectivity of the addition (Scheme 3, Table 2). Until now, however, we have achieved only limited success, which we attribute

to the unexpected difficulty to suppress the radical addition either under acidic or noble metal catalyzed[11] conditions.

Table 2.[a]

Run	Temp. °C	Solvent	Additive	Yield[b] %	4/3cb[c]	E/Z[d]
1	25	$CHCl_3$	$BF_3.Et_2O$	53	0/1	7/3
2	25	MeCN/H_2O (4:1)	$HClO_4$	52	0/1	3/2
3	60	THF	$Pd(OAc)_2$	85	1/1	1/2
4	25	benzene	$Pd(OAc)_2$	23	1/0	

a. Typical experiment: To a solution of **1c** in the solvent indicated (20-30 mg/ml concentration) is added 1.2 equiv of thiol (2 equiv was used in Run 1), 0.2 equiv of additive under argon at the temperature indicated. **b**. Isolated yield. **c**. None of the isomers could be separated by chromatography, the values were determined by ^{1}H nmr. **d**. Refers to the isomer ratio of **3cb**, determined by ^{1}H nmr.

Further research in this area is underway.[13]

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3. For leading references see: **a**. K. Griesbaum, *Angew. Chem.*, **1970**, *82*, 276; **b**. The Chemistry of the Thiol Group, ed. by S Patai, John Wiley and Sons, **1974**.
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5. *Typical reaction conditions:* 20 mg of indole/ ml of THF, 1.2 equiv of TBAF.$3H_2O$ at -10 to -20°C. It is important to note that elevation of temperature resulted in significant reduction of the yield.

6. *Reaction conditions:* 50 mg of indole/ml of DMF, 5 0 equiv of imidazole, 2.0 equiv of dimethyl-*tert*-butylsilyl chloride, room temperature. Purification with flash chromatography. Yield: 83%. See : E. J. Corey, A Venkateswarlu, *J. Am. Chem. Soc.*, **1972**, *94*, 6190.

7. Compound (**1a**) is not soluble in toluene. Runs 1 and 2 were performed with suspensions.

8. In an experiment when the reaction of **1c** with **2a** was performed with gradual heating from 60 to 95°C, the preparative yield dropped to 65%, and the *E/Z* ratio to 3:2 (compare with Run 4 in Table 1).

9 All new compounds were characterized by ir, ^{1}H nmr, ^{13}C nmr (Varian VXR-300) and EI ms (Kratos MS-902) spectra. For selected spectroscopical data of the new thio enol ethers see ref. 12.

10. We do not claim that this trend is a consequence of the steric bulk of the substituents on the propargylic atom, since we do not have sufficient experimental evidence to arrive at this conclusion.

11. H. Kuniyasu, A. Ogawa, K -I Sato, I. Ryu, N Kambe and N. Sonoda, *J. Am. Chem. Soc.*, **1992**, *114*, 5902

12 *Abbreviations*: δ: for disubstituted thio enol ethers. ^{1}H Nmr (300 MHz) chemical shift of SC<u>H</u>=CH (J in Hz) in $CDCl_3$ (ppm, TMS internal standard), for trisubstituted thi enol ethers: ^{1}H Nmr (300 MHz) chemical shift of SCR=C<u>H</u> in $CDCl_3$ (ppm, TMS internal standard), unless otherwise indicated. *Ms*: % abundance of M^{+}/z, m/z of base peak in the 70 eV EI spectra. Since we observed no difference between the fragmentations of *E* and *Z* isomers, the values are given only for the former isomers. **3aa:** δ: 7.06 (d, J=15.4 Hz), *ms*: 46, 170; (*E*)-**3ca:** δ: 6.86 (d, J=15.0 Hz), *ms*: 100, 338; (*Z*)-**3ca:** δ: 6.67 (d, J=10.3 Hz); (*E*)-**3cb:** δ: 6.82 (d, J=15.0 Hz), *ms*: 100, 324, (*Z*)-**3cb:** δ 6.71 (d, J=10.2 Hz); (*E*)-**3cc:** δ: 6.82 (d, J=14.9 Hz), *ms*: 87, 168, (*Z*)-**3cc:** δ: 6.64 (d, J=10 2 Hz); (*E*)-**3cd:** δ: 6.70 (d, J=15.4 Hz), *ms*: 97, 168, (*Z*)-**3cd:** δ: 6.44 (d, J=10.2 Hz); (*E*)-**3ce:** δ. 6.84 (d, J=15.0 Hz), *ms*: 64, 248, (*Z*)-**3ce:** δ: 6.65 (d, J=10.7 Hz); (*E*)-**3ea:** δ: 6.50 (br s), *ms*: 100, 394; (*E*)-**3fa:** δ: 6.91 (br s), *ms*: 100, 382, (*Z*)-**3fa:** δ: 7.52 (br s); (*E*)-**3fb:** δ. 7 03 (br s), (*Z*)-**3fb:** δ: 7.62 (br s); (*E*)-**3fe:** δ: 7.58 (br s), *ms*: 64, 248, (*Z*)-**3fe:** δ: 7.73 (br s); (*E*)-**3ga:** δ 6 55 (br s), *ms*: 68, 304, (*Z*)-**3ga:** δ: 7.62 (br s); **3ia:** δ: 6.47 (s), *ms*: 100, 396; **4:** δ (C<u>H</u>$_2$=CSPh): 4.99 (s), 5 22 (s), δ (<u>C</u>H$_2$=CSPh, ^{13}C): 111.0.

13. Part of the ms work was conducted by Prof. József Tamás who deceased in 1993. The technical assistance of Éva Papp-Borsos is acknowledged here. Full paper with experimental and spectroscopical details will be published later on

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