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A VERSATILE AND EFFICIENT PROCESS TO 3-SUBSTITUTED INDOLES FROM ANILINES

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Abstract: Borane-mediated reductive elimination of α-thiomethyl-, α-hydroxy-, or α-alkoxy-, α'-substituted oxindoles affords 3-substituted indoles in high yield. Isatins, available via several routes from oxindoles, also afford indoles.

Indoles have been a key feature in many syntheses as well as the object of new synthetic methods[1,2] because of their relative abundance and importance in natural product and medicinal chemistry. Our recent synthesis of a novel indole-containing antitumor agent incorporated new chemistry to a 3-substituted indole.[3] The development and generality of this chemistry is described herein.

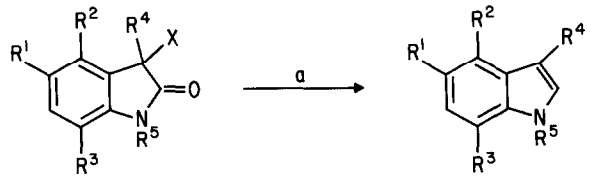
We chose the overall approach of aniline → oxindole → indole, since the Gassman and van Bergen procedure[9b] of preparing oxindoles had general precedent and since Wieland and Grimm[9a] had disclosed the conversion of an α-substituted oxindole to an indole with lithium aluminum hydride (LAH)[10]. It was quickly apparent, however, that the first step had some restrictions and the latter procedure was unacceptable for general use. In searching for alternatives and yet accommodate this general scheme, we found solutions to both of these problems.

Reduction of oxindoles with hydride reagents has been reported usually to afford indolines[5] but also indoles[4] (N-substituted only) as a function of hydride reagent or substrate substitution pattern. An alternative two-step reductive procedure to indoles has been devised[6] but appears unsatisfactory as a general approach.[7] Treatment of a 3-substituted-2-ethoxy indole, available from the oxindole and triethyloxonium salts, with THF·BH_3 afforded the indole in moderate yield.[8] These procedures lacked general utility.

We have found that Me_2S·BH_3 (BMS) or THF·BH_3[11] converts 3-substituted-3-thiomethyloxindoles to 3-substituted indoles in high yield under mild conditions[12] (Table I)[13]. This procedure tolerates a variety of substitution patterns (including N-CH_3, entry 8) as well as groups that would be reduced by LAH (entries 6, 7). In further contrast with LAH, we found that refluxing LAH/THF was required for efficient conversion of 7-methoxy-3-methyl-3-thiomethyl oxindole (entry 1) to 7-methoxy-3-methyl indole. If this reaction was run at room temperature a dioxindole (12%) and oxindole (24%) were produced as by-products. Furthermore, the LAH procedure on entry 4 resulted only in recovered starting material and on entry 7 none of the desired indole was produced.

The BMS process is equally adaptable to the conversion of 3-substituted-3-hydroxy and 3-methoxyoxindoles (dioxindoles) to the respective indole (entries 11-16). The yield of indole is poor or nonexistent with 3-bromo or 3-phenylselenyl oxindoles (entries 17, 18). If there is no 3-substituent (entry 9), the product is the 3-thiomethylindole. This can be converted to the 3-unsubstituted indole with Raney nickel.[9b]

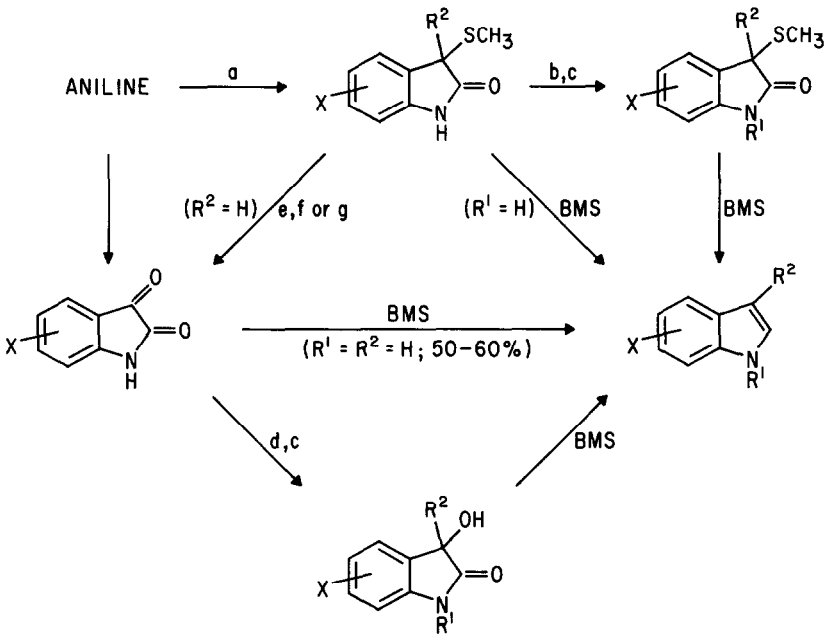
Table I



Entry	R^1	R^2	R^3	R^4	R^5	X	% Yield
1	H	H	OCH_3	CH_3	H	SCH_3	92%
2	H	H	Cl	CH_3	H	SCH_3	82%
3	H	H	H	CH_3	H	SCH_3	58%[b]
4	H	CH_3	OCH_3	CH_3	H	SCH_3	86%
5	H	Cl	OCH_3	CH_3	H	SCH_3	83%
6	NO_2	Cl	OCH_3	CH_3	H	SCH_3	95%
7	$MsNCH_2CHCH_2OAc$		OCH_3	CH_3	H	SCH_3	90%
8	H	H	OCH_3	CH_3	CH_3	SCH_3	92%
9	H	H	H	H	H	SCH_3	c
10[d]	H	H	H	H	H	$SOCH_3$	50%[e]
11	H	H	Cl	CH_3	H	OH	90%
12	H	H	CH_3	Ph	H	OH	88%
13	H	H	CH_3	CH_3	H	OH	91%
14	H	H	CH_3	CH_3	CH_3	OH	93%
15	H	H	Cl	CH_3	H	OCH_3	89%
16	H	H	CH_3	CH_3	CH_3	OCH_3	88%
17	H	H	Br	CH_3	H	Br	25%[f]
18	H	H	Cl	CH_3	H	SePh	g

a Reactions condition: 2.3 equiv. of $Me_2S{\cdot}BH_3$ or $THF{\cdot}BH_3$ in dry THF under N_2 at room temperature for 24 hr followed by 1 N HCl quench and work-up.
b Also isolated 9% indolinine and 9% starting material.
c Product is 3-SCH_3-indole.
d Prepared by MCPBA treatment of 3-methylthio-2-oxindole in CH_2Cl_2 at room temperature.
e Product is 3-$SOCH_3$ indole; also isolated 20% 3-SCH_3 indole and 7% indole.
f Also isolated 50% of oxindole (X = H).
g Product exclusively oxindole (X = H).

Scheme



a: R^2 $CH(CO_2CH_3)SCH_3 \cdot Cl_2$, proton sponge, -78°, CH_2Cl_2; Et_3N (-78° to 0°); AcOH, R.T., 12 hr; b: R^2 X, Na_2CO_3, DMF, R.T.; c: R^1 X, Na_2CO_3, DMF; d: R^2 MgX (2.5 eq), THF, 0°; e: NCS; $BF_3 \cdot Et_3O$, HgO; f: MCPBA; $(CF_3CO)_2O/Ac_2O$; HCl (1 N), HgO, acetone, R.T.; g: SO_2Cl_2(3.0 eq), silica gel (wet), CH_2Cl_2, R.T., 3 hr (1 N HCl, 70°, 2 hr)

A postulated mechanism involves reduction and elimination of H_2O to the indolinine. This is then further reduced to the 3,3-disubstituted indoline which then eliminates HX to the indole. In following the reaction by GC-MS (entry 3), we identified an intermediate material as indolinine when the reaction was not allowed to go to completion. An attempt to enhance the leaving group capacity of the thiomethyl (entry 10), and thus the yield of indole, was unsuccessful.

The utility of this process in preparing indoles is dependent on the ready availability of the 3-substituted-3-thiomethyl or 3-hydroxyoxindoles. In fact, these are readily available from the appropriate anilines (Scheme).[13] The 3-thiomethyloxindoles are efficiently derived in high yield *via* a modified Gassman procedure.[14] The group R can be introduced in this operation or subsequently *via* alkylation chemistry.[15]

The 3-hydroxyoxindoles can be prepared in high yield from the addition of Grignards to isatins.[16] Isatins are readily obtained *via* the Sandmeyer or related procedures[16] and can also be efficiently produced from the 3-thiomethyloxindoles employing three different procedures. In addition to the Gassman procedure[17], we successfully utilized an oxidation-Pummerer rearrangement procedure (reaction f) as well as a one-pot chlorination-hydrolysis procedure (reaction g) employing sulfuryl chloride.[18]

Although all of the procedures afforded isatins from α-thiomethyloxindoles in good yields (> 65%)[19], the latter procedure is recommended in view of the economics. BMS or BH_3·THF treatment of isatins affords indoles directly[20] in yields comparable or greater than LAH[16] again with the added advantage of greater substituent group compatibility. Thus, these alternative pathways from anilines (Scheme) allow for the introduction of R^2 either electrophilically or nucleophilically to provide a general, high yield route to 3-substituted indoles.

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10. Gassman and van Bergen reported the reduction of 3-methyl-3-methylthio-2-oxindole to 3-methylindole in 76% yield; this same reaction was done previously by Wieland and Grimm in unreported yield.
11. Borane trimethylamine was ineffective.
12. Extensive exposure of the product indole to excess borane will yield the indoline. Details will be reported elsewhere.
13. All new compounds reported were homogeneous by TLC and gave satisfactory IR, NMR, MS and exact mass and/or combustion analysis.
14. We have realized > 80% yields consistently by using one equiv. of proton sponge (1,8-bis(dimethylamino)naphthalene) with one equiv. of the aniline in the first step coupled with employing neat acetic acid to induce the cyclization to the oxindole. We have also utilized the chlorosulfonium ion rather than the chloramine route to the intermediate azasulfonium species for stability reasons and, in that regard, find the use of sulfuryl chloride much more convenient than chlorine. This 3-step sequence can be accomplished in a one-pot, 24 hr operation.
15. Either employing the dianion approach of Kende and Hodges[22] or utilizing Na_2CO_3/DMF/RX for accomplishing regioselective C-alkylation.
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19. For example, o-anisidine afforded 7-methoxyisatin in 49% overall yield; isatin and 4-methyl-7-methoxy isatin and 7-fluoroisatin were also prepared by this procedure; note that the latter example has not yielded to synthesis yet by classical procedures.[21]
20. 7-Methylindole (55% yield), 1,7-dimethylindole (56% yield).
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