The Preparation of 2-Substituted Indole Sulfonamides and Subsequent Conversion to Indole-2-carboxylic Acids, Indole-2-carbonitriles, and 2-Acylindoles

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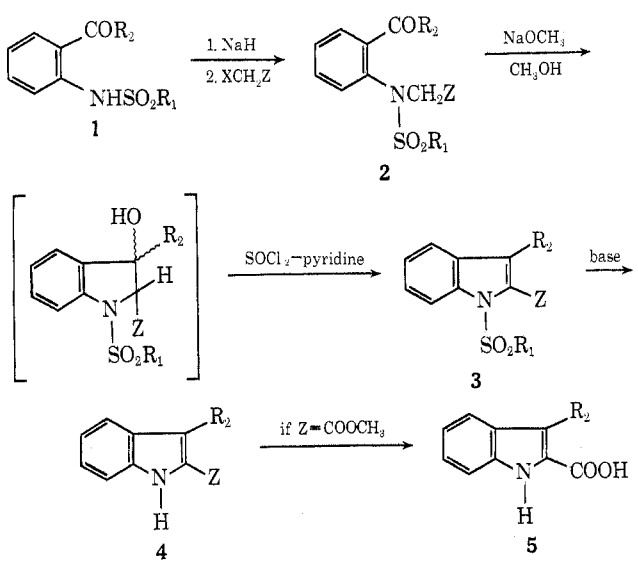
A convenient and general synthesis of indole-2-carboxylic acids, indole-2-carbonitriles, and 2-acylindoles is described. Sulfonamides of *o*-aminocarbonyl compounds (**1**) are N-alkylated by active halides to provide compounds of type **2**. On base-catalyzed aldol condensation of **2**, and subsequent dehydration, crystalline 2-substituted indole sulfonamides (**3**) are obtained. Hydrolysis of **3** removes the tosyl moiety to yield the corresponding 2-acylindoles and indole-2-carbonitriles. The synthesis of indole-2-carboxylic acids from 2-carbomethoxyindole sulfonamides was also achieved in a similar manner.

In an accompanying paper,[1] a method was described for the preparation of 2-acylindoles by the direct condensation of *o*-amino ketones with α-halo ketones. As an extension of this investigation, we wish to discuss the use of an analogous alkylation–condensation route to 2-acylindoles which we have applied successfully to the preparation of synthetically more useful derivatives (*i.e.*, indole-2-carboxylic acids and indole-2-carbonitriles).

Although *o*-amino ketones and aldehydes do not yield indolic products on direct reaction with methyl bromoacetate or bromoacetonitrile under conditions analogous to those described earlier[1] (DMF, 80–90°), we have found that the corresponding *N*-sulfonyl derivatives can be converted into the desired indoles in excellent yield (Chart I). In this method sulfonamides

CHART I



1, prepared by sulfonylation of *o*-amino ketones or by Rosenmund reduction of *N*-sulfonylanthranilic acid halides, are alkylated by active halides to provide **2** (Table I). On base-catalyzed aldol condensation of **2** and subsequent dehydration of the intermediate carbinol(s), crystalline 2-substituted indole sulfonamides (**3**) are obtained in excellent yield. This indole-forming reaction is generally applicable to the R and Z substituents listed in Table II.

Hydrolysis of the resultant 2-substituted indole sulfonamides (**3**) with aqueous NaOH removes the tosyl moiety and provides the 2-substituted indole (**4**) in nearly quantitative yield (Table III). If a 2-carboxylic ester group is initially present in **3**, saponification also occurs under conditions of excess base to provide the corresponding indole-2-carboxylic acid (**5**), also in excellent yield (Table III).

In summary, N-alkylation of *o*-amino ketone sulfonamides by active halo compounds, followed by cyclization and hydrolysis of the resultant indole sulfonamides, provides a convenient route to 2-acylindoles, indole-2-carbonitriles,[2] and indole-2-carboxylic acids. The indole-forming reactions proceed readily under quite mild conditions and the overall sequence permits isolation of the various intermediates enroute to the final products. Since decarboxylation of indole-2-carboxylic acids proceeds in virtually quantitative yield on simple heating, the parent indoles are also easily accessible *via* this sequence.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Nmr spectra were recorded on a Varian T-60 spectrometer in $CDCl_3$ or DMSO-d_6 using TMS as internal reference. Mass spectra were taken on a CEC 21–110 spectrometer. All compounds included in this report gave correct molecular ions and satisfactory analytical and spectral data.

General Procedure for Alkylation of *N*-Sulfonyl-*o*-aminocarbonyl Compounds by Methyl Bromoacetate, Phenacyl Bromides, and Chloroacetonitrile.—The appropriate sulfonamide **1** (0.25 mol) was suspended in anhydrous DMF (100 cc) at 0°. With stirring, NaH (6.0 g, 0.25 mol) was added in small portions and the mixture was kept at 0° for an additional 30 min. The resulting yellow amide anion solution was added dropwise over a 30-min period to a stirred solution of the appropriate halide (0.25 mol) in 20 cc of DMF. (In the alkylation of *N*-*p*-toluenesulfonyl-*o*-aminobenzaldehyde and *N*-*p*-toluenesulfonyl-*o*-aminoacetophenone, a 5-fold excess of methyl bromoacetate was advantageous.) After the solution was stirred for 1 hr at room temperature, the DMF was evaporated, and H_2O was added. The precipitated product (**2a–i**) (Table I) was collected on a filter and recrystallized from MeOH or MeOH–H_2O.

Cyclization of 2a–i. General Procedure for Preparation of 2-Substituted Indole Sulfonamides.—To the alkylated sulfonanilide **2a–h** (0.025 mol) suspended in MeOH (400 ml) was added NaOMe (0.025 mol). (In the case of **2i**, 0.025 mol of potassium *t*-butoxide in 300 ml of *t*-BuOH was used in lieu of NaOMe–MeOH.) After the suspension was stirred for 2 hr, the solvent was evaporated on a rotary, and the residue was dissolved in a mixture of H_2O (300 ml) and $CHCl_3$ (200 ml). The chloroform layer was washed with H_2O (50 ml), dried over $MgSO_4$, and evaporated to dryness.

(1) C. D. Jones and T. Suárez, *J. Org. Chem.*, **37**, 3622 (1972).

(2) While this manuscript was in preparation an example of synthesis of an indole-2-carbonitrile by a similar sequence appeared in the literature; see M. Oklobdzija, M. Japelj, and T. Fajdiga, *J. Heterocycl. Chem.*, **9**, 161 (1972).

TABLE I[a]

Compd	R_1	Z	R_2	Recrystn solvent	Mp, °C	% yield
2a	C_6H_4-*p*-CH_3	$COOCH_3$	H	MeOH–H_2O	115–116	85
2b	C_6H_4-*p*-CH_3	$COOCH_3$	CH_3	MeOH	90–91	90
2c	C_6H_4-*p*-CH_3	$COOCH_3$	Ph	MeOH	126–127	86
2d	C_6H_4-*p*-CH_3	$COCH_3$	Ph	MeOH	109–110	82
2e	C_6H_4-*p*-CH_3	COPh	Ph	MeOH	159–160	96
2f	C_6H_4-*p*-CH_3	COC_6H_4-*p*-OCH_3	Ph	$CHCl_3$–MeOH	199–200	90
2g	CH_3	COC_6H_4-*p*-Cl	Ph	MeOH	157–158	75
2h	CH_3	COC_6H_4-*p*-CH_3	Ph	MeOH	135–136	88
2i	C_6H_4-*p*-CH_3	CN	Ph	MeOH	95–96	91

[a] Satisfactory analytical values (±0.4) for C, H, N, and O) were reported for all compounds in this table and in Tables II and III: Ed.

TABLE II

Compd	R_1	Z	R_2	Recrystn solvent	Mp, °C	% yield
3a	C_6H_4-*p*-CH_3	$COOCH_3$	H	MeOH	83–84	95
3b	C_6H_4-*p*-CH_3	$COOCH_3$	CH_3	MeOH	114–115	89
3c	C_6H_4-*p*-CH_3	$COOCH_3$	Ph	MeOH	93–94	92
3d	C_6H_4-*p*-CH_3	$COCH_3$	Ph	MeOH	75–77	80
3e	C_6H_4-*p*-CH_3	COPh	Ph	Acetone	192–193	89
3f	C_6H_4-*p*-CH_3	COC_6H_4-*p*-OCH_3	Ph	MeOH	156–157	76
3g	CH_3	COC_6H_4-*p*-Cl	Ph	MeOH	149–150	64
3h	CH_3	COC_6H_4-*p*-CH_3	Ph	MeOH	164–165	63
3i	C_6H_4-*p*-CH_3	CN	Ph	Acetone–H_2O	147–148	31

TABLE III

Compd	R	Z	Recrystn solvent	Mp, °C	% yield
4d	Ph	$COCH_3$	MeOH	151–152 (lit.[a] 151)	92
4e	Ph	COPh	MeOH	203–204 (lit.[b] 203.4–5.0)	98
4f	Ph	COC_6H_4-*p*-OCH_3	MeOH	155–156	94
4g	Ph	COC_6H_4-*p*-Cl	MeOH	179–180	79
4h	Ph	COC_6H_4-*p*-CH_3	MeOH	148–149	84
4i	Ph	CN	MeOH–H_2O	145–146	99
5a	H		Et_2O–hexane	205 (lit.[c] 205)	90
5b	CN_3		Benzene–hexane	164–165 (lit.[d] 166)	85
5c	Ph		MeOH	186–187 (lit.[e] 186)	96

[a] R. H. F. Manske, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 1 (1927). [b] D. Y. Curtin and M. L. Poutsma, *J. Amer. Chem. Soc.*, **84**, 4887 (1962). [c] S. Gabriel, W. Gerhard, and R. Wolter, *Ber.*, **56**, 1024 (1923). [d] W. B. Whalley, *J. Chem. Soc.*, 1651 (1954). [e] A. R. Kidwai and N. H. Khan, *C. R. Acad. Sci.*, **256**, 3709 (1963).

The residue was dissolved in benzene (100 ml), and pyridine (0.05 mol) was added. After the mixture was chilled to 5°, $SOCl_2$ (0.025 mol) was added dropwise, and the mixture was stirred at room temperature for 1 hr. Ice and water were then added; the benzene layer was separated, washed with 5% $NaHCO_3$ (50 cc) and with H_2O (50 cc), and dried over $MgSO_4$. Evaporation of the benzene, trituration with MeOH, and recrystallization from the appropriate solvent provided the *N*-sulfonylindole (**3a–i**) in good yield (Table II).

Hydrolysis of 2-Substituted Indole Sulfonamides.—The appropriate indole sulfonamide (**3a–i**, 5 mmol) was dissolved in 50 ml of MeOH containing 10 ml of 2 *N* aqueous NaOH and refluxed on a steam bath until tlc revealed no remaining starting material. (In the case of **3a**, cleavage was accomplished using 1 *M* $NaOCH_3$ in refluxing MeOH with gradual introduction of moisture.) The MeOH was then evaporated, and H_2O was added. In those cases (**3d–i**) in which a neutral product was obtained, it was collected by filtration and purified by recrystallization from MeOH or MeOH–H_2O to provide pure **4–i** (Table III).

When the hydrolysis product was an H_2O-soluble carboxylate salt, as in the cases **3a–c**, the alkaline solution was washed with ether (50 cc), and the aqueous layer was then acidified. The precipitated indole-2-carboxylic acid was collected by filtration or extracted into ethyl acetate. Recrystallization of the crude product from the solvent indicated in Table III gave rise to **5a–c** in excellent yield.

Registry No.—**2a**, 36004-63-4; **2b**, 36004-64-5; **2c**, 36004-65-6; **2d**, 36004-66-7; **2e**, 36004-67-8; **2f**, 36004-68-9; **2g**, 36004-69-0; **2h**, 36004-70-3; **2i**, 36004-71-4; **3a**, 36004-72-5; **3b**, 36004-73-6; **3c**, 36004-74-7; **3d**, 36004-75-8; **3e**, 36004-76-9; **3f**, 36004-77-0; **3g**, 36004-78-1; **3h**, 36004-79-2; **3i**, 36004-80-5; **4d**, 36015-23-3; **4e**, 36004-54-3; **4f**, 36004-82-7; **4g**, 36004-83-8; **4h**, 36004-84-9; **4i**, 36004-85-0; **5a**, 1477-50-5; **5b**, 10590-73-5; **5c**, 6915-67-9.