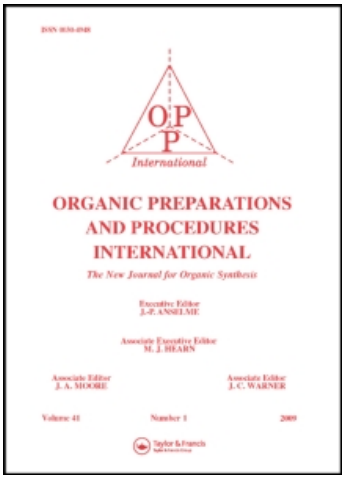

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SYNTHESIS OF INDOLOSULFONYLUREAS, POTENT ACETOLACTATE SYNTHASE INHIBITORS

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SYNTHESIS OF INDOLOSULFONYLUREAS, POTENT ACETOLACTATE SYNTHASE INHIBITORS

Submitted by (01/17/06)

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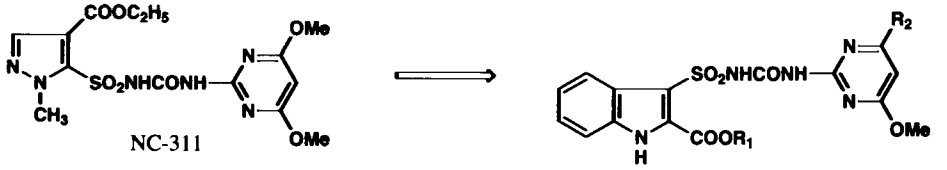
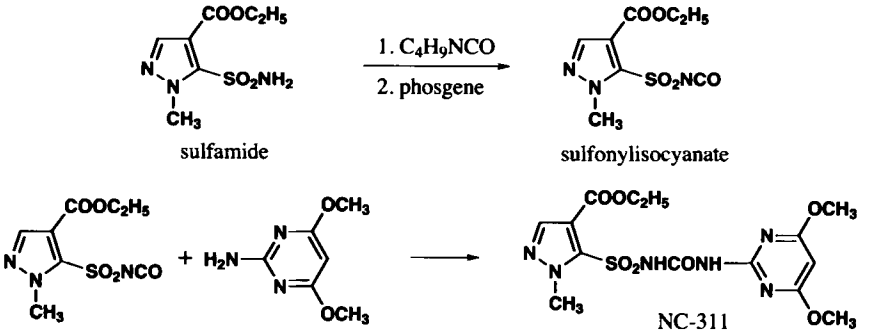
Sulfonylurea is one of the four classes of herbicides which inhibit *acetolactate synthase* (ALS), a key enzyme in the biosynthesis of branched-chain amino acids in plants.[1] However, a common problem is that sulfonylureas sometimes harm the plants or the next stubble crops

because of their long residual life.[2-4] Current research in our laboratories directed at the synthesis and biological evaluation of indole derivatives as pesticides is in progress. Because plants have oxidases[5] which can easily degradate the indole derivatives and moreover, because of the fact that indole-containing compounds often possess unexpected biological activity, it was thought that the replacement of a phenyl group or heterocycle with a indole moiety in a bioactive compound would induce great changes in its molecular properties, such as the solubility and hydrophobicity. Therefore, we designed new sulfonylureas similar to pyrazosulfuron-ethyl (NC-311) by replacing the diazole ring with an indole moiety, which might overcome the disadvantage of traditional sulfonylureas.



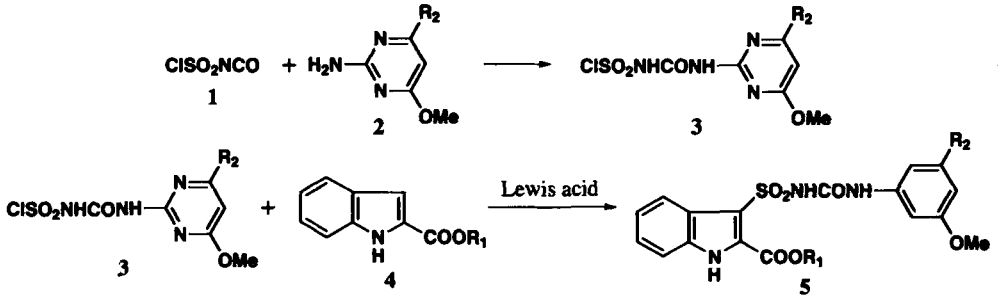
The conventional approach[6] for the synthesis of sulfonylureas is from sulfonylisocyanates prepared by treatment of the sulfamide with phosgene or oxalyl chloride, followed by reaction with pyrimidine or triazine to give the sulfonylurea as shown for NC-311 in *Scheme 1*.[7]



Scheme 1

However, in order to replace the diazole ring with an indole moiety, another route (*Scheme 2*) had to be devised because indole has an active hydrogen atom which can react with phosgene and oxalyl chloride making it difficult to obtain the isocyanates in high purity and yields. The key step of this route is the Friedel-Crafts reaction between chlorosulfonylureas (**3**), obtained by treatment of chlorosulfonylisocyanate (**1**) with 4,6-disubstituted-2-aminopyrimidines (**2**), and alkyl indole-2-carboxylates (**4**) to afford the indolosulfonylureas (**5**).

Then, the alkyl indole-2-carboxylates (**4**) were acylated by chlorosulfonylurea (**3**) to generate the target compounds **5**. The acylation of alkyl indole-2-carboxylate (**4**) with chlorosulfonylurea (**3**) was examined under several reaction conditions. Although the highest yield was obtained when $InBr_3$[8] was used as catalyst (yield 70% for **5d**), it seemed that the inexpensive, commonly used Lewis Acid $TiCl_4$ though having a slightly lower catalytic effect in preparing



a) $R_1 = CH_3, R_2 = Cl$; b) $R_1 = C_2H_5, R_2 = Cl$; c) $R_1 = C_2H_5, R_2 = OCH_3$; d) $R_1 = CH_3, R_2 = OCH_3$

Scheme 2

this kind of sulfonylureas (yield 66% for **5d**), was the best choice for future application. Other catalysts as $AlCl_3$ or $FeCl_3$ proved to be less efficient. The best results were achieved when a mixture of alkyl indole-2-carboxylate (**4**), chlorosulfonylurea (**3**), using $TiCl_4$ as a catalyst in 1,2-dichloroethane (molar ratio: 4: 3: $TiCl_4$ = 1:1:2) were heated at 40-65°C for 12h.

The herbicidal activity of the new compounds was evaluated. The result indicates that the indolosulfonylureas, especially compound **5d**, displayed better herbicidal activity compared to the commercial sulfonylureas.[9]

EXPERIMENTAL SECTION

Commercially available reagents were purchased from Aldrich and used without further purification. Alkyl indole-2-carboxylates were prepared according to the literature.[10] All melting points were recorded using capillary melting point apparatus and are uncorrected. The IR spectra were determined neat or as KBr pellets on a Shimadzu FTIR-8300 spectrometer. ^1H NMR were acquired using Varian-INOVA600 spectrometer in DMSO-d_6 solution with TMS as the internal standard. The elemental analyses were performed at the Institute of Chemistry, Chinese Academy of Sciences. Analytical thin layer chromatography (TLC) was carried out using MN Kieselgel G/ UV 254 (Art. 816320) glass-backed plates. Yields were not optimized.

General Procedure for the Preparation of Products 5a-d. To a solution of the substituted 2-aminopyrimidine **2** (0.08 mol) in 1,2-dichloroethane (200 mL) was added chlorosulfonyl-isocyanate (**1**) (0.08 mol) at 5-10°C. The reaction mixture was warmed up to rt, stirred for 30 min and then a solution of alkyl indole-2-carboxylate **4** (0.08 mol) in dichloroethane (60 mL), $TiCl_4$ (0.16 mol) was successively added to the reaction mixture which was then warmed up to 40-65°C and stirred for 12 h. After completion of the reaction (monitored by TLC), the brownish-orange slurry was poured into ice water (150 mL) and stirred. The grayish-white solid formed was collected and purified by recrystallization from ethanol to give white needle crystals.

Table 1. Yields, Melting Points and Elemental Analyses of **5**

Cmpd	mp. (°C)	Yield (%)	Elemental Analyses (Found) C	H	N
5a	218-220	59	43.69 (43.83)	3.21 (3.40)	15.92 (15.81)
5b	232-235	42	44.99 (45.23)	3.55 (3.74)	15.43 (15.43)
5c	224-226	50	48.10 (47.96)	4.26 (4.42)	15.58 (15.61)
5d	218-220	66	46.90 (46.73)	3.94 (4.08)	16.08 (16.27)

Table 2. Spectral Data of Compounds **5**

Cmpd	IR(KBr) (cm^{-1})	^1H NMR (DMSO-d_6/TMS) (δ), J (Hz)
5a	3350, 3200, 1740,1700, 1580, 1360, 1260, 1160, 740, 580	3.90 (s, 3H), 4.04 (s, 3H), 6.80 (s, 1H), 7.30-7.49 (m, 2H), 7.60 (d, 1H, J = 8.0Hz), 8.19 (d, 1H, J = 7.6Hz), 10.76 (s, 1H), 12.04 (s, 1H), 13.20 (s, 1H)
5b	3280, 3200, 1730, 1710, 1570, 1350, 1250, 1210, 750, 580	1.30 (t, 3H), 4.04 (s, 3H), 4.40 (q, 2H), 6.88 (s, 1H), 7.40 (m, 2H), 7.60 (m, 1H) 8.18 (d, 1H, J = 7.8Hz), 10.76 (s, 1H), 12.00 (s, 1H), 13.12 (s, 1H)
5c	3340,3260, 1730, 1710, 1610, 1580, 1380, 1350, 1200,1150, 750, 580	1.31 (t, 3H), 4.02 (s, 6H), 4.37 (q, 2H), 5.58 (s, 1H), 7.34 (m, 2H), 7.57 (m, 1H), 8.16 (m, 1H), 10.30 (s, 1H), 12.61 (s, 1H), 13.00 (s, 1H)
5d	3300, 3180, 1740, 1700, 1600, 1580, 1360, 1220, 1160, 750, 580	3.72 (s, 3H), 4.00 (s, 6H), 6.01 (s, 1H), 7.22-7.42 (m, 2H), 7.60 (d, 1H, J=8.0Hz) 8.20 (d,1H, J=7.8Hz), 10.42 (s, 1H), 12.64 (s, 1H) 13.09 (s, 1H)

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DIRECT α-HYDROXYLATION OF ARYL KETONES USING A HYPERVALENT IODINE(III) SULFONATE

Submitted by (01/25/06)

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α-Hydroxyketones are widely used intermediates and are important constituents of many biologically important natural products.[1] The methods used for their synthesis involve the direct α-hydroxylation of ketones under basic[2] or acidic conditions.[3] Only a few reports in the literature account for the direct α-hydroxylation of ketones under neutral conditions.

Recently, hypervalent iodine(III) reagents have been used extensively in organic synthesis due to their low toxicity, ready availability and easy handling.[4] As a part of our on-going studies to utilize hypervalent iodine (III) reagents in organic synthesis, we report here a new and direct method for the synthesis of α-hydroxy aryl ketones by the reaction of aryl ketones with [hydroxy-(2,4-dinitrobenzenesulfonyloxy)iodo] benzene (HDNIB) under mild conditions. The required HDNIB was prepared in satisfactory yields from the reaction of 2,4-dinitrobenzenesulfonic acid with phenyliodine (III) diacetate (PIDA).[5] Treatment of aryl ketones (**1**) with HDNIB in CH_3CN at reflux for 1 h produced the α-(2,4-dinitrobenzenesulfonyloxy)-ketone intermediates (**2**),[5] which can then undergo hydrolysis with DMSO-H_2O system at room temperature for 2 h to give α-hydroxyaryl ketones (**3**) in good yields as shown in the *Scheme*.