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4-Substituted 2-Phenyl- and 2-Phenyl-3-Aryl Pyrroles by Reaction of Tosyl Benzyl Isocyanide (TosBIC) with Michael Acceptors

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SYNTHETIC COMMUNICATIONS, 25(6), 795-802 (1995)

4-SUBSTITUTED 2-PHENYL- AND 2-PHENYL-3-ARYL PYRROLES BY REACTION OF TOSYL BENZYL ISOCYANIDE (TosBIC) WITH MICHAEL ACCEPTORS

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Abstract: Synthesis of 2-phenyl and 2,3-diphenylpyrroles bearing at the 4 position electronwithdrawing groups by reaction of tosylbenzylisocyanide (TosBIC) with various Michael acceptors was investigated. Sodium hydride and *n*-butyllithium were used as deprotonating agents for the synthesis of monophenyl and diphenylpyrroles, respectively.

Preparation of pyrroles *via* tosylmethylisocyanide (TosMIC) reaction is a very simple, expeditious and high yielding procedure, which can be used with suxcess for the synthesis of useful intermediates in a searching for new biologically active compounds.[1-3]

By this method we prepared recently various 3-aroyl-4-arylpyrroles **1**, which were easily transformed into highly potent imidazole antifungal agents **2**[4] with chemical features resembling bifonazole **3** and pyrrolnitrin **4**, two antimycotics marketed for clinical use.

A further example is the reaction between TosMIC and 1-aryl-2-nitroethene, which afforded by an one-step procedure *neo*-isopyrrolnitrin **5**[5], a product strictly related to pyrrole antibiotics **4** and **6** (pyrrolomycin A).

Pursuing our decennial structure-activity relationships studies on bioisosteres of bifonazole **3**, we needed 2-phenyl-4-benzoylpyrrole **7a** as a key intermediate for the synthesis of the imidazole derivative **8**.

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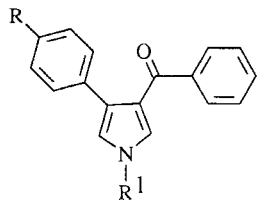
Preparations of **7a** by standard procedures would very likely result in multi-step pathways and low overall yields. Therefore, we decided to prepare the pyrrole ketone **7a** *via* the isocyanide method starting from α-tosylbenzylisocyanide (TosBIC)[6,7].



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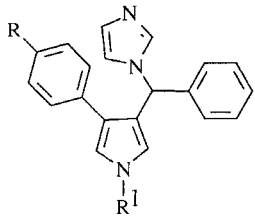

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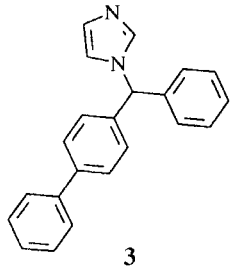

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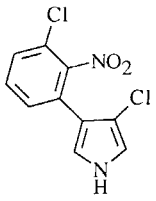

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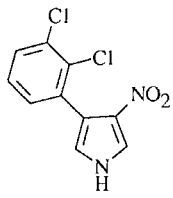

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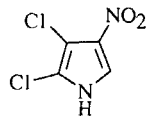

6

Reaction between this reagent and methyl 3-phenylacrylate as Michael acceptor with formation of 2,3-diphenyl-4-methoxycarbonylpyrrole **9e** was to our knowledge the sole example reported up to-day in the chemical literature[2].

For this reason, we were induced to explore the reactivity of TosBIC versus other Michael acceptors, such as phenyl vinyl ketone (prepared *in situ* from 1-benzoyl-2-chloroethane), methyl vinyl ketone and acrylonitrile. This reaction would provide a simple and convenient one-step procedure for preparing 2-phenylpyrroles **7a-d** substituted at 4-position by electronwithdrawing groups and could be easily extended to the synthesis of their 2,3-diphenyl analogues **9a-f**. Such compounds are relatively inaccessible otherwise and their preparations are generally obtained by either unusual or multi-step pathways. For example, 4-acetyl-2-phenylpyrrole **7c** has been prepared in 73% yield by photoreaction of thiobenzamide with 2-methylfuran in methanol[8] and 2-phenylpyrrole **7f** has been synthesized by a four-step sequence starting from 3-phenylacrolein[9].

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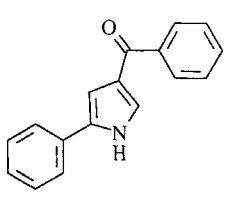
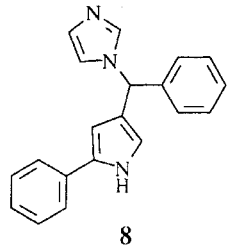


7a



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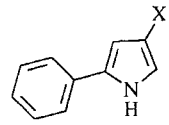
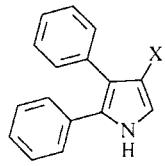


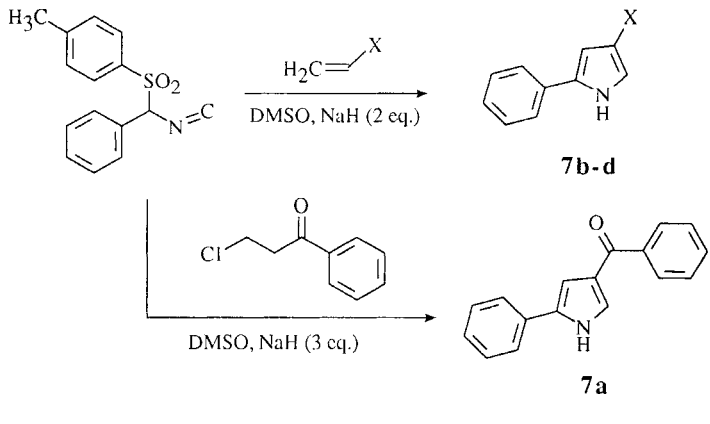
7b X = $COOC_2H_5$
7c X = $COCH_3$
7d X = CN
7e X = COOH
7f X = H



9a X = COC_6H_5
9b X = $COOC_2H_5$
9c X = $COCH_3$
9d X = CN
9e X = $COOCH_3$
9f X = NO_2

Reaction of TosBIC with the proper Michael acceptor or its precursor to obtain **7a-d** was performed in DMSO in the presence of sodium hydride (Scheme 1). However, these conditions did not permit to obtain the 2,3-diphenylpyrroles **9a-f** in good yields when styryl phenyl ketone, styryl methyl ketone, ethyl

SCHEME 1



7b-d

7a

X = $COOC_2H_5$, $COCH_3$, CN

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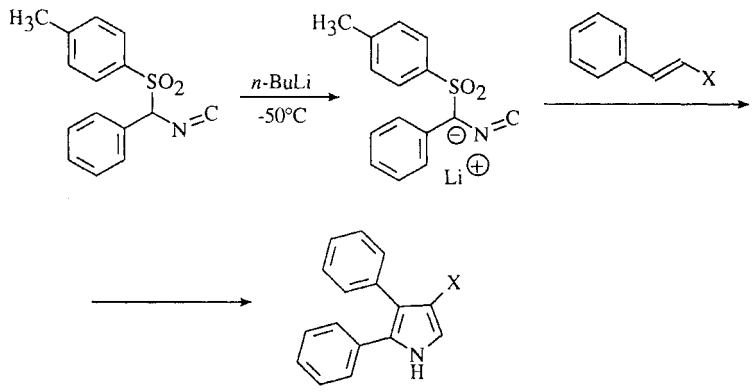
3-phenylacrylate and 3-phenylacrylonitrile were used as Michael acceptors. Generally, yields were lower than 10% or of no use. The previously reported yield for **9e**[2] was 23%.

We were able to improve significantly the yields of **9a-f** by treating the related Michael acceptors with the lithium salt of TosBIC, obtained by deprotonation of this reagent with *n*-butyllithium at -50°C (Scheme 2) (Table 1).

SCHEME 2



9a-f

X = COC_6H_5, $COOC_2H_5$, $COOCH_3$, $COCH_3$, CN, NO_2

Hydrolysis of **7b** in alkaline medium afforded **7e**, which easily was decarboxylated to 2-phenylpyrrole **7f**. Starting from ethyl acrylate and TosBIC, preparation of **7f** involves a three-step procedure, which appears to be competitive with those previously reported in the literature.[9-15]

In conclusion, TosBIC procedure provides a simple general method for the synthesis of 2-phenyl- and 2-phenyl-3-arylpyrroles bearing at the 4 position electronwithdrawing groups, such as acyl, aroyl, alkoxycarbonyl, cyano and nitro. These compounds are relatively inaccessible otherwise and some of them (**9b,d,e**) can be suitably used as intermediates for the synthesis of 2-phenyl-3-arylpyrroles. For example, hydrolysis of **9b** followed by decarboxylation of the intermediate acid **9g** gave 2,3-diphenylpyrrole **9h** (Scheme 3).

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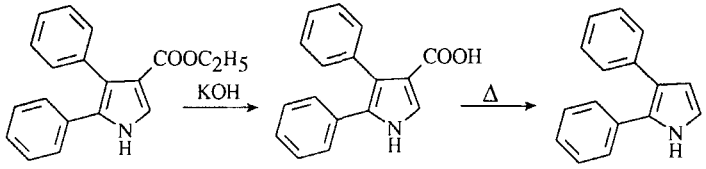
SCHEME 3



9b **9g** **9h**

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EXPERIMENTAL PART

Melting points were determined on a Büchi 510 apparatus and are uncorrected. IR spectra (nujol mulls) were obtained on a Perkin-Elmer 1310 spectrophotometer . ^{1}H-NMR spectra were recorded with a Varian EM-390 (90 MHz) spectrometer (a Varian Gemini 200 for derivative **9b**) using tetramethylsilane as internal standard. NMR spectra were in full accordance with the assigned structures. Column chromatographies were performed on alumina Merck (70-230 mesh). Aluminum oxide/TLC-cards Fluka (aluminum oxide precoated aluminum cards with fluorescent indicator 254 nm) were used for thin layer chromatography. Developed plates were visualized by UV light. Organic solutions were dried over anhydrous sodium sulfate. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator (Büchi) operating at reduced pressure (approx. 20 bar). Elemental analyses were performed by the Microanalytical Laboratories of Prof. A Pietrogrande, University of Padova (Italy). Microanalytical data were within ±0.4% of the theoretical values for C, H and N.

Preparation of phenylpyrroles ***7a-d***

A solution of the proper Michael acceptor (4 mmol) and tosylbenzylisocyanide (TosBIC) (1.19 g, 4.4 mmol) in dry dimethylsulfoxide-ethyl ether (15:35 ml) mixture was added by dropping onto a well-stirred suspension of sodium hydride (55% in white oil ; 380 mg, 8.8 mmol) in anhydrous ethyl ether (15 ml) under nitrogen atmosphere. The mixture was stirred at room temperature for the proper time (see Table 1), then diluted with water (50 ml) and the precipitate which formed was filtered, washed with light petroleum ether and recrystallized from suitable solvent. In presence of oily products (**7b** and **7c**) the mixture was extracted with ethyl acetate (3x20 ml) and the collected extracts were washed with brine (3x30 ml) and dried; evaporation of the

Table 1. Chemical and Physical Data of Pyrroles **7a-f** and **9a-f** [a]

compd	formula	yield (%)	m.p. (°C)	reaction time	crystallization solvent
7a	C17H13NO	85	220-222	5 min	DMF-H2O
7b	C13H13NO2	80	149-151	30 min	benzene
7c	C12H11NO	64	176-178	40 min	DMF-H2O
7d	C11H8N2	60	161-163	20 min	benzene
7e	C11H9NO2	93	180 (dec.)	-	EtOH-toluene
7f	C10H9N	75	128-130	-	cyclohexane
9a	C23H17NO	80	276-278	3h 20 min	DMF
9b	C19H17NO2	43	191-193	8 days	benzene-cyclohexane
9c	C18H15NO	65	210-212	1 h	benzene
9d	C17H12N2	24	139-141	5 days	benzene-cyclohexane
9e	C18H15NO2	45	183-185	8 days	benzene-cyclohexane
9f	C16H12N2O2	100	176-178	25 min	benzene

[a] All derivatives were analyzed for C, H, N.

solvent gave crude **7b** and **7c**, which were purified by passing through an alumina column (chloroform and ethyl acetate as eluents for **7b** and **7c**, respectively).

Preparation of diphenylpyrroles ***9a-f***

A solution of TosBIC (510 mg, 1.87 mmol) in anhydrous tetrahydrofuran (4 ml) was added, under nitrogen atmosphere, to a cooled (-45°C) well-stirred solution of *n*-butyllithium (2.5 M in *n*-hexane; 0.75 ml, 1.87 mmol) in anhydrous tetrahydrofuran (8 ml). After 10 min lithium bromide (870 mg, 10 mmol) was added and the mixture was stirred for 0.5 h. Michael acceptor (1.7 mmol) dissolved in anhydrous tetrahydrofuran (4 ml) was then added dropwise and the mixture was stirred at room temperature (at -45°C for **9c** and **9f**) for the proper time (Table 1). Treatment with water (40 ml) gave a solid (**9a**), which was filtered, washed with petroleum ether and recrystallized from suitable solvent. Oily products (**9b-f**) were extracted with ethyl acetate (3x20 ml), the extracts were collected, washed with brine (3x30 ml), dried and evaporated. The residue was recrystallized (**9b** and **9e**) or chromatographed (**9c** and **9d**) on an alumina column (chloroform as eluent) to obtain pure products.

2-Phenyl-1H-pyrrole-4-carboxylic acid ***7e***

A solution of **7b** (800 mg, 4 mmol) in ethanol (8 ml) was treated with 20% sodium hydroxide (8 ml) and refluxed for 3h. Treatment with crushed ice (50 g) followed by acidification with conc.

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hydrochloric acid till pH 2 and extraction with ethyl acetate (3x25 ml) gave an organic solution,which was dried and then evaporated to afford pure **7e** (300 mg, 93% yield).

*2-Phenyl-1*H*-pyrrole* ***7f***

Compound **7e** (200 mg, 1.1 mmol) was dissolved in ethanolamine (2 ml) and refluxed for 2 h. Treatment with water (20 ml) afforded a precipitate, which was filtered and then purified by passing through an alumina column (chloroform as eluent). Removal of solvent from eluates furnished **7f** (110 mg, 75% yield).

*2,3-Diphenyl-1*H*-pyrrole-4-carboxylic acid* ***9g***

A solution of **9b** (60 mg, 0.2 mmol) in ethanol (1.5 ml) was treated with 20% sodium hydroxide (0.5 ml) and refluxed for 3h. Treatment with crushed ice (20 g) followed by acidification with conc. hydrochloric acid till pH 2 and extraction with ethyl acetate (3x10 ml) gave an organic solution, which was dried and then evaporated to afford pure **9g** (40 mg, 76 % yield), m.p. 223-225°C (dec.) from toluene. Anal. C, H, N.

*2,3-Diphenyl-1*H*-pyrrole* ***9h***

Compound **9g** (289 mg, 1.1 mmol) was dissolved in ethanolamine (2 ml) and refluxed for 2 h. Treatment with water (20 ml) afforded a precipitate, which was filtered and then purified by passing through an alumina column (chloroform as eluent). Removal of solvent from eluates furnished **9h** (182 mg, 76 % yield), m.p. 127-128°C from cyclohexane (lit.[16]: m.p. 129°C, 60% yield). Anal. C, H, N.

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