Synthetic Methods

Direct Coupling of Pyrroles with Carbonyl Compounds: Short Enantioselective Synthesis of (*S*)-Ketorolac**

Phil S. Baran, Jeremy M. Richter, and David W. Lin*

Pyrroles and indoles are the foundation of innumerable medicines, natural products, and synthetic materials.[1] Alkylations, acylations, and transition-metal-mediated couplings are the staple reactions for intermolecular C–C bond formation between these heterocycles and other organic substrates.[1–3] Typically, organometallic couplings require that one[3] or both entities are prefunctionalized (i.e. halogenation or any other disposable functionality).[2] Simple and practical methods that eliminate this prerequisite in synthetic design are rare.[4]

Inspired by a family of naturally occurring indole alkaloids, we recently reported a remarkably simple method for the direct coupling of the C-3 carbon of indoles with the α-carbon of carbonyl compounds as shown in Figure 1.[5] We imagined that these results could be extended to the analogous coupling of pyrroles (at C-2) with carbonyl compounds. Herein, we demonstrate the coupling of pyrroles with ketones, esters, amides, lactones, and lactams. An intramolecular variant of this methodology has also been

[*] Prof. Dr. P. S. Baran, J. M. Richter, D. W. Lin
Department of Chemistry
The Scripps Research Institute
10650 North Torrey Pines Road
La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-7375
E-mail: pbaran@scripps.edu

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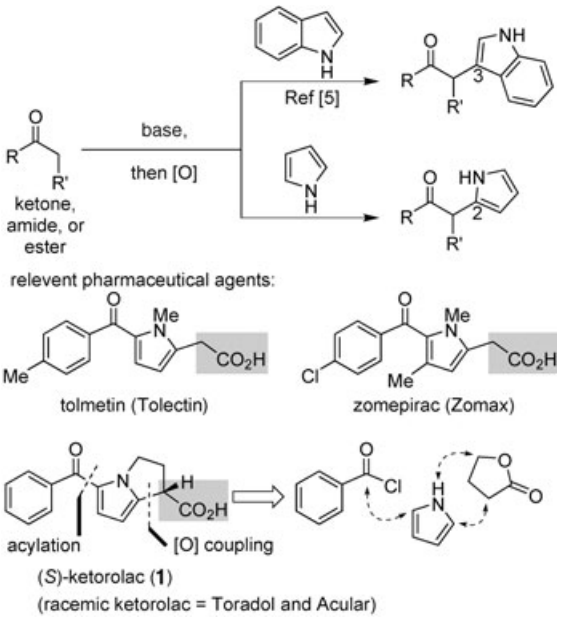
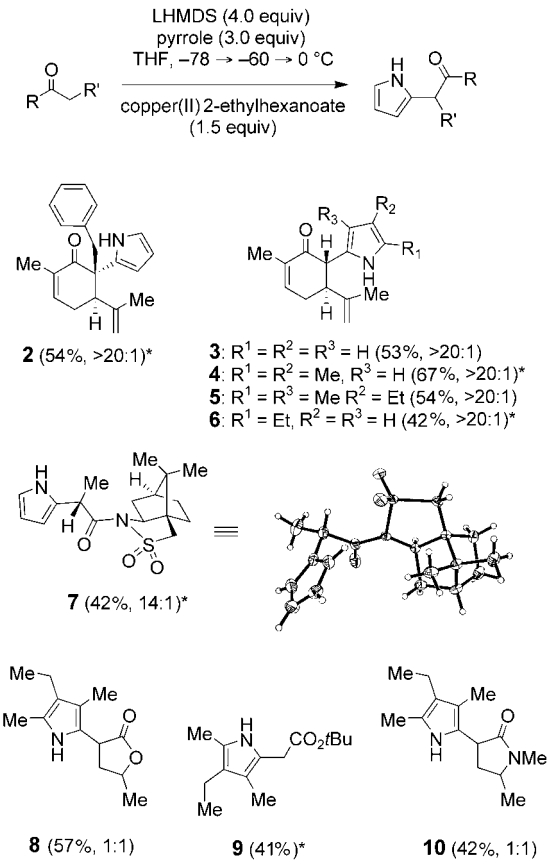


Figure 1. Direct coupling of indoles and pyrroles to carbonyl compounds and retrosynthetic analysis of (*S*)-ketorolac.

developed and applied to a concise, enantioselective synthesis of the nonsteroidal anti-inflammatory drug (*S*)-ketorolac (**1**) that can be performed without the need for protecting groups. The underlying mechanisms of these processes are also discussed.

Whereas the locus of nucleophilicity of the indole anion is at C-3, it resides at C-2 for the pyrrole anion,[1] and it was expected that direct coupling would link pyrroles to carbonyl compounds at that site. By slight modification of our previously reported conditions,[5] this proved to be the case as shown in Scheme 1. As with most electron-rich pyrroles, the products shown in Scheme 1 are quite sensitive to air and light. Nevertheless, both the pyrrole and indole[5] couplings can be performed on a multigram scale (>100 mmol). Further, complex pyrrolidines, pyrrolidinones, and pyridines are accessible from the pyrrole adducts.[1] A range of substitution patterns are tolerated on the pyrrole subunit (**3**–**6**) and, as with indoles,[5] highly congested pyrroles fused at a quaternary center are easily prepared with complete diastereocontrol (**2**). Sultam **7** was prepared as a 14:1 mixture of diastereomers, and the structure was confirmed by X-ray crystallographic analysis (colorless needles (1:1 cyclohexane/Et_2O), mp 131–133 °C). Although lactones (**8**) and lactams (**10**) are easily joined with pyrroles, esters (**9**) generally couple in lower yield (see Supporting Information for details), and pyrroles that bear electron-withdrawing groups either do not couple or do so in low yield. However, efforts to overcome these limitations are underway.

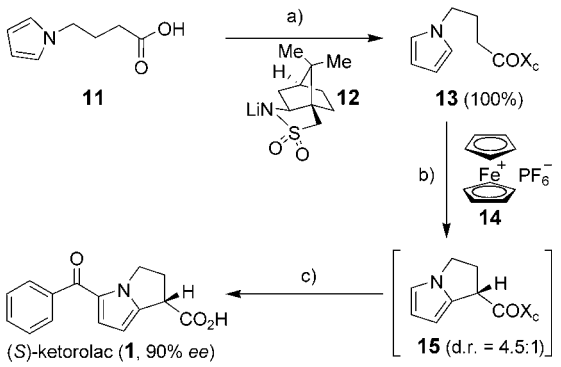
As shown in Figure 1, the pyrroleacetic acid scaffold is found in the widely marketed pharmaceutical agents tolmetin and ketorolac and the previously marketed agent zomepirac. Our retrosynthetic analysis of ketorolac (**1**, Toradol and Acular) was influenced strategically by the pioneering syntheses patented in the literature[6,7] and by the fact that the *S* antipode of ketorolac is more potent and causes fewer



Scheme 1. Preparation of pyrrole–carbonyl compounds (LHMDS = lithium hexamethyldisilazide). Yields (%, isolated after chromatography unless otherwise stated) and d.r. values of the products are indicated in parentheses. [*] Yield based on recovered starting material.

side effects.[8] Our aim was not to improve upon the extremely efficient and practical five-step Syntex route[7] ($\approx 45\%$ yield from pyrrole, racemic); an enantioselective synthesis[9] of **1** would merely serve as an ideal proving ground for the versatility of the current method.

Our synthesis (Scheme 2) commences with pyrrole acid **11**, which results from the near-quantitative union of pyrrole with butyrolactone on a multigram scale.[10] The stage was set for an intramolecular pyrrole–carbonyl coupling after installing the chiral auxiliary to afford **13** (Et_3N, MeOCOCl, then **12**, 100%).[11] In the event, we were unable to achieve the oxidative annulation of **13** with many standard oxidants (Cu^{II}, Fe^{III}, Ag^{I}, Ag^{II}, Ti^{IV}, Mn^{III}, Ce^{IV}). After considerable exploration, ferrocenium hexafluorophosphate (**14**, a practical, recyclable, and commercially available oxidant)[12] was found to elicit the cyclization of **13** to **15** in 65% yield (based on recovered starting material and determined by ^{1}H NMR spectroscopy) as a 4.5:1 mixture of diastereomers. The isolated yield of **15** was about 35%, however, as **15** was quite sensitive to air and moisture, so the crude reaction mixture that contained **13**, **15**, and ferrocene was carried forward without purification (benzoyl chloride, 70 °C, remaining **13** and ferrocene easily separable).[13] Hydrolysis of the resulting benzoylated pyrrole by using tetrabutylammonium



Scheme 2. Short, enantioselective synthesis of (*S*)-ketorolac. Reagents and conditions: a) Et_3N (1.1 equiv), MeOCOCl (1.0 equiv), THF (0.1 M), 0 °C, 1 h; then **12**, 100%; b) LHMDS (1.2 equiv), Et_3N (2.0 equiv), THF (0.01 M), −78 °C, 30 min; then 12 °C, **14** (0.75 equiv), 5 min, 65% bsm; (c) BzCl, 70 °C, 4 h; then TBAH (2.0 equiv), H_2O_2 (2.0 equiv), 2-methylbut-2-ene (3.0 equiv), DME (0.25 M), −10 °C, 3 h, 38%. X_c = camphor sultam auxiliary, bsm = based on recovered starting materials, Bz = benzoyl, TBAH = tetra-*n*-butylammonium hydroperoxide, DME = 1,2-dimethoxyethane.

hydroperoxide[14] furnished *S*-ketorolac (**1**, 90% *ee* determined by chiral HPLC, 38% isolated yield over 2 steps) along with recovered auxiliary. From the vantage point of synthetic design, certain details are worth noting: 1) the oxidation state of **11** is conserved (reduction, decarboxylation, and halogenation processes avoided),[15] 2) protecting groups are absent, 3) decent stereocontrol is observed in the ring closure despite the readily enolizable[9] nature of the newly formed stereocenter, and 4) overall brevity of the sequence (≈25% overall unoptimized yield from pyrrole in four operations).

Although conceptually similar, the direct coupling of carbonyl compounds with pyrroles (Scheme 1) by using a Cu^{II} oxidant probably differs mechanistically from the intramolecular cyclization (**13**→**15**) by using Fe^{III}-based **14**. As shown in Figure 2, we believe that in the former case an intermediate

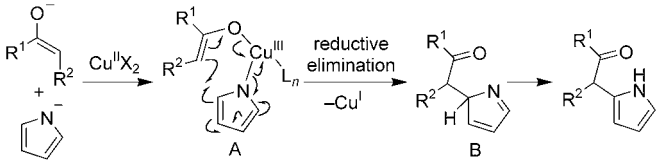


Figure 2. Proposed mechanism for the direct coupling of pyrroles with carbonyl compounds by using Cu^{II}.

Cu^{III}-chelated species (A) may be involved.[16] Reductive elimination and loss of Cu^{I} should lead to B, followed by tautomerization to yield the product. Several observations support this tentative mechanistic model: 1) dimerization of the pyrrole is never observed, as expected from geometrical constraints, 2) N-protected pyrroles do not react, 3) only 1 equivalent of oxidant is necessary, although the use of 1.5 equivalents gives a slight improvement in yield, and 4) the characteristic red-brown color of copper(I) salts is often observed at the end of the reaction. The same trends are seen for the analogous coupling with indoles and implies that a similar mechanism may be active.[5] To effect the conversion of **13** into **15**, oxidant **14** was employed because it has been firmly established by the scholarly studies of Jahn et al. to convert enolates into radical species by an outer-sphere single-electron-transfer pathway.[12] Remarkably, Fe^{III}-based oxidant **14** is ineffective for the couplings in Scheme 1 as are Cu^{II}-based oxidants for the annulation (**13**→**15**).

In summary, we have developed a new method for the one-step construction of a variety of pyrroles that would ordinarily require multistep sequences to synthesize. The method is scalable, practical, and reliable. The intermolecular heteroarylation of enolates (Scheme 1) uses a Cu^{II}-based oxidant, whereas the intramolecular variant proceeds by a different mechanism that functions using the Fe^{III}-based oxidant **14** (Scheme 2). The waste associated with protecting groups, prior modification of the substrates (such as halogenation or any other disposable functionalities), and expensive metals is eliminated. These studies point to a unique approach for the synthesis of π-electron-rich heterocyclic systems through coupling of unfunctionalized $C(sp^2)$ and $C(sp^3)$ atoms.[17]

Experimental Section

General Procedure for Direct Pyrrole Coupling: The carbonyl compound (0.25 mmol) was dissolved in benzene (1.0 mL) and the solvent was removed in vacuo. Pyrrole (0.75 mmol) was then added and the starting materials were dissolved in THF (8.0 mL). The solution was cooled to −78 °C and a solution of LHMDS (0.50 M, 2.0 mL) was added. The reaction mixture was allowed to stir for 30 min, after which time the septum was removed and copper(II)-2-ethylhexanoate (131 mg, 0.38 mmol) was rapidly added as a solid and then the septum was replaced. The reaction was allowed to warm to −60 °C and stirred for 3 h. The reaction was subsequently warmed slowly to ambient temperature and quenched by pouring into 5% aqueous NH_4OH (15 mL). The aqueous layer was partitioned with EtOAc (20 mL). The organic layer was separated and washed successively with water (15 mL) and then brine (15 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. Flash chromatography (silica gel) of the crude reaction mixture afforded pure coupled product. With the exception of compound **2**, all the pyrroles began to darken in color immediately after concentration, but NMR spectroscopic analysis showed no loss in purity. In general it was found that the couplings of ketones, amides, lactones, and lactams worked well with the exception of esters, which proved to be more unpredictable.

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[17] Detailed experimental procedures, copies of all spectral data and full characterization are contained in the Supporting Information. CCDC 251395 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif..

