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N-Acyl pyrroles: chemoselective pyrrole dance vs. C–H functionalization/aroylation of toluenes

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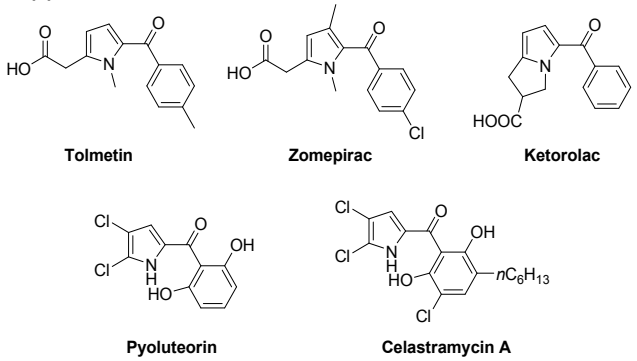
Chemoselectivity is one of the most challenging issues facing the chemical sciences. In this study, the first highly chemoselective reactions of *N*-acylpyrroles via either an anionic Fries rearrangement (pyrrole dance) or a C–H functionalization of toluene to provide aryl benzyl ketones are advanced. This efficient and operationally simple approach enables the synthesis of either 2-aroylpyrroles or aryl benzyl ketones in good to excellent yields under transition metal-free conditions. The choice of base plays a crucial role in controlling the chemoselectivity. The aroylation of toluene derivatives was observed with *N*-acylpyrroles when subjected to $KN(SiMe_3)_2$, while anionic Fries rearrangement products were produced with $LiN(SiMe_3)_2$. Surprisingly, cross-over experiments indicate that the anionic Fries rearrangement is an intermolecular process. The aroylation reaction has the advantage over Weinreb amide chemistry in that it does not require preformed organometallic reagents or cryogenic temperatures.

Pyrroles are among the most well-known heterocyclic compounds and are ubiquitous motifs in bioactive molecules, organic materials and natural products.[1] In particular, 2-aroylpyrrole derivatives are core structures in the pharmaceutical industry and present in a variety of biologically active compounds.[2] Representative examples are shown in Scheme 1 and include Tolmetin, Zomepirac and Ketorolac as non-steroidal anti-inflammatory drugs (NSAID) that exhibit excellent anti-inflammatory activity by reducing hormones that cause pain and swelling, as well as antipyretic actions.[2g, 3] The pyrrolomycin alkaloids *Pyoluteorin* and *Celastramycin* A, isolated from Pseudomonas[4] and Streptomyces,[5] respectively, have demonstrated high activity against a series of multiresistant bacteria and mycobacteria. The latter has also been identified as an innate immune suppressor.



Scheme 1 Biologically important structures containing 2-aroylpyrrole motifs.

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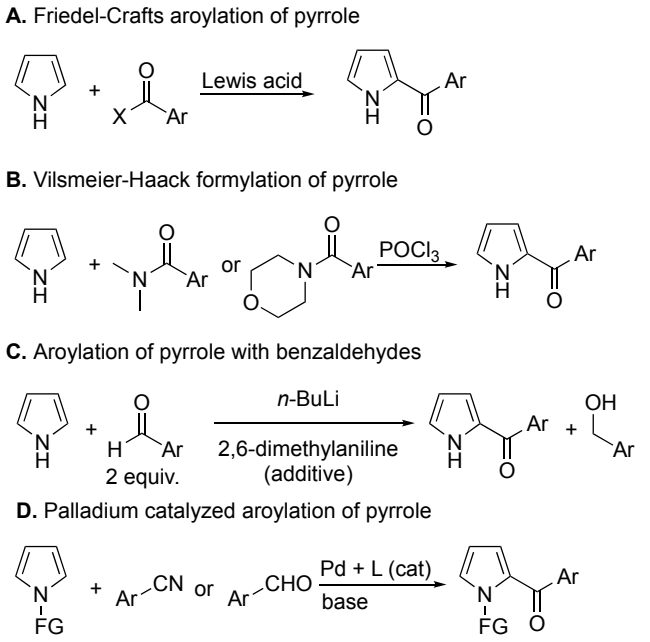
Given their desirable biological activities, the development of efficient and practical methods for the synthesis of 2-aroylpyrroles is of significant value.[6] The traditional route for the synthesis of these privileged heterocycles largely relies on two approaches: (1) Friedel-Crafts aroylation of pyrrole at the 2-position (Scheme 2A)[7] and (2) Vilsmeier-Haack reaction of pyrrole with amide or acylmorpholine (Scheme 2B).[8] A complementary approach to the Vilsmeier-Haack reaction employs strongly basic conditions with *n*-BuLi, pyrrole, two equivalents of a benzaldehyde derivative and 2,6-dimethylaniline as additive to provide good yields of the aroylated products (Scheme 2C).[2h] This method is suboptimal, particularly if the aldehyde coupling partner is valuable, as 1 equiv is lost in the oxidation process. In addition, several other methods based on the use of seleno- or thio-esters,[9] *N*-acylbenzotriazoles,[10] nitrilium salts,[11] carboxylic acids,[12] benzaldehydes,[13] and arylglyoxylic acids[14] as alternate acyl sources have been reported. The requirement of stoichiometric amounts of Lewis acids or strongly acidic conditions, and the resulting poor selectivity that gives rise to formation of mixtures of mono- and diacylated products, are among the drawbacks of the abovementioned methods. Moreover, these approaches frequently suffer from competitive site selectivity at the *N*- and C-3 positions and extensive polymerization under acidic conditions.[15] Recently, several palladium-catalyzed acylations of pyrroles with aldehydes, nitriles and allyl esters as aroyl electrophiles have been reported (Scheme 2D).[16] Despite notable progress, there remains room for improvement, including reducing the excess of a valuable coupling partner, the elimination of metals that ultimately generate waste, the use of expensive ligands and limited substrate scope.

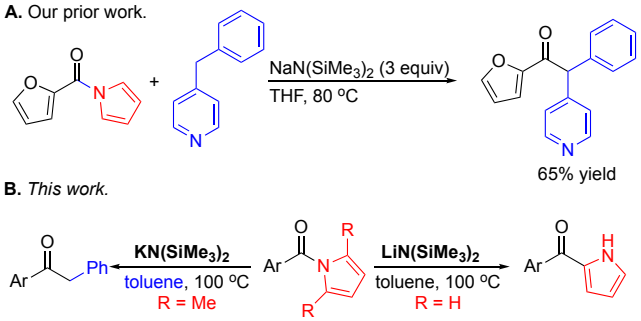


Scheme 2 Synthetic methods for 2-aroylpyrroles. a. Friedel-Crafts, b. Vilsmeier-Haack, c. Aroylation with organolithium reagents, d. Palladium catalyzed aroylation.

Another class of important synthetic intermediates and biologically active targets are aryl benzyl ketones. A popular method to prepare these valuable compounds is the transition metal catalyzed α-arylation of acetophenones. Despite the impressive scope of the α-arylation reaction, it does have drawbacks. These include the use of expensive precatalysts and difficulty in controlling the extent of arylation.[17] This latter issue arises because monoarylation of ketones, for example, results in an increase in acidity of the remaining α-C–H's by about 6 orders of magnitude, facilitating the formation of enolate intermediates and subsequent arylation. To circumvent these shortcomings, efforts have been made to use base metal catalysts and to develop transition metal free processes.[18]

Our team has also worked to develop more efficient and economical methods to generate arylated ketones. We recently introduced a simple approach toward the synthesis of 1,2,2-triarylethanones based on transition metal-free aroylation of diarylmethane derivatives with *N*-acylpyrroles (Scheme 3A)[19] as part of a larger program on the functionalization of weakly acidic pronucleophiles.[20] This chemistry has the advantage over the Weinreb ketone synthesis[21] in that it begins from a pronucleophile rather than a preformed organometallic reagent and it also does not require cryogenic temperatures.

In the present study, we have developed conditions to significantly broaden the scope of the aroylation strategy to include toluene pronucleophiles (Scheme 3B). Compared to the weakly acidic (pK_a 25−35) benzylic C−H bonds of diarylmethanes, the benzylic C−H bonds of toluene have pK_a values of ~43 (in DMSO[22]). Surprisingly, when the silylamide base $KN(SiMe_3)_2$, which is selective for toluene deprotonation, was replaced with $LiN(SiMe_3)_2$, an unexpected rearrangement (anionic Fries rearrangement[23] that we call the pyrrole dance in analogy to halogen dance reactions[24]) occurred and 2-aroylpyrroles are formed in high yields. Herein we describe the development of these two useful synthetic methods.

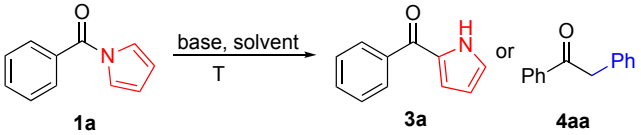


Scheme 3 A. Aroylation of diarylmethanes with *N*-acylpyrroles. B. This work.

Results

Reaction development and optimization. Initial screens were conducted with *N*-benzoylpyrrole (**1a**) in toluene with five different bases [$LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$, KO^{t}Bu, and NaO^{t}Bu] at 80 °C for 3 h (Table 1, entries 1–5). $NaN(SiMe_3)_2$, NaO^{t}Bu and KO^{t}Bu failed to afford product (entries 2, 4 and 5). When $LiN(SiMe_3)_2$ was employed, the pyrrole dance product **3a** was produced in 67% yield (entry 1). Interestingly, $KN(SiMe_3)_2$ generated the aroylation product **4aa** in 36% isolated yield (entry 3). Focusing on the pyrrole dance first, in place of toluene, four solvents were next examined [1,4-dioxane, DME, THF, and CPME (cyclopentyl methyl ether)] with $LiN(SiMe_3)_2$ at 80 °C. These solvents failed to produce the desired pyrrole dance product. Concentrating on reactions in toluene, excess base was found to be essential for high conversion. When 2 equiv of $LiN(SiMe_3)_2$ was used, the rearrangement product was obtained in 55% yield (entry 11), whereas only trace product was observed with 1 equiv of $LiN(SiMe_3)_2$ (entry 10). We next examined the impact of reaction temperature. At 100 °C, the pyrrole dance product **3a** was obtained in 81% yield after 3 h (entry 13), while 46% yield was observed at 60 °C (entry 12). Further elevation of the reaction temperature to 120 °C was deleterious, yielding only 53% of the product (entry 14). Thus, the optimized conditions entail 3 equiv $LiN(SiMe_3)_2$ in toluene at 100 °C for 3 h.

Table 1. Reaction Optimizationa

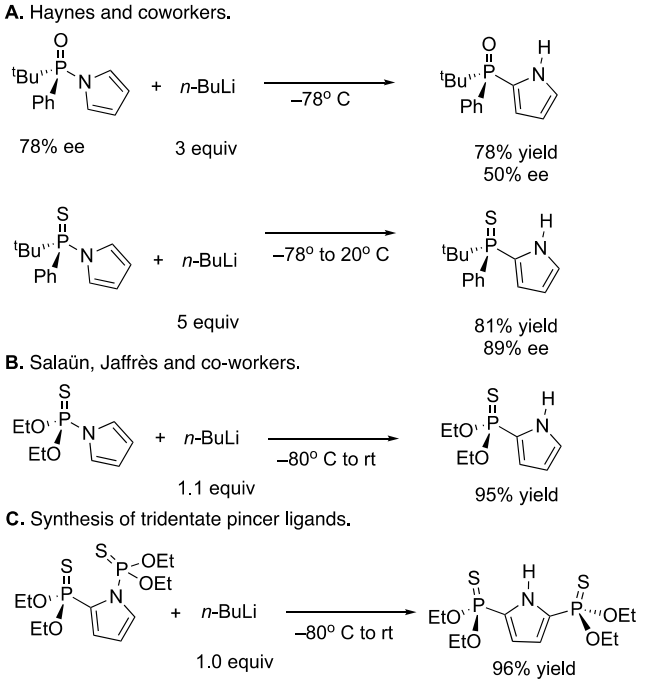


entry	solvent	base	temp.	3a/4aa

1	toluene	$LiN(SiMe_3)_2$	80 °C	**3a** (67)
2	toluene	$NaN(SiMe_3)_2$	80 °C	–
3	toluene	$KN(SiMe_3)_2$	80 °C	**4aa** (36)
4	toluene	NaO^tBu	80 °C	–
5	toluene	KO^tBu	80 °C	–
6	1,4-	$LiN(SiMe_3)_2$	80 °C	–
7	DME	$LiN(SiMe_3)_2$	80 °C	–
8	THF	$LiN(SiMe_3)_2$	80 °C	–
9	CPME	$LiN(SiMe_3)_2$	80 °C	–
10[c]	toluene	$LiN(SiMe_3)_2$	80 °C	trace
11[d]	toluene	$LiN(SiMe_3)_2$	80 °C	**3a** (55)
12	toluene	$LiN(SiMe_3)_2$	60 °C	**3a** (46)
13	toluene	$LiN(SiMe_3)_2$	100 °C	**3a** (81)
14	toluene	$LiN(SiMe_3)_2$	120 °C	**3a** (53)

[a]Reactions were conducted with **1a** (0.1 mmol) base (0.3 mmol), solvent (1 mL), for 3 h. [b] Isolated yields. [c]1 equiv of $LiN(SiMe_3)_2$. [d]2 equiv of $LiN(SiMe_3)_2$.

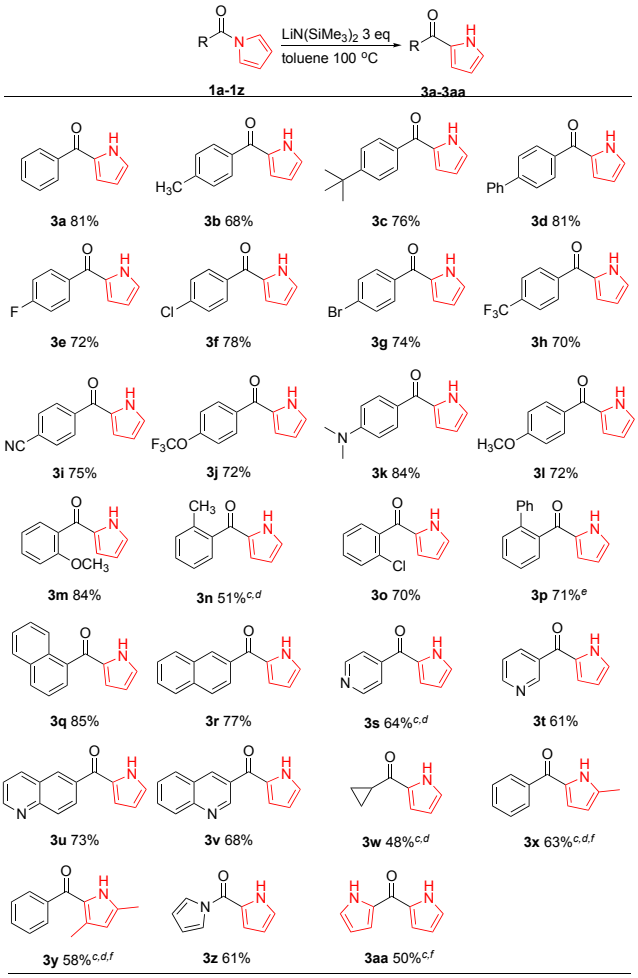
The closest reported reaction to the pyrrole dance in Table 1 of which we are aware was initially reported by Haynes and coworkers.[25] This group demonstrated that treatment of the enantioenriched pyrrole phosphinoamidate or thionophosphinoamidate with excess *n*-BuLi at –78 °C resulted in formation of P–C bonds, as shown in Scheme 4A. Later, Salaün, Jaffrès and their co-workers investigated the rearrangement of achiral thionophosphinoamidates as a route to prepare *N*,*S*-based chelating ligands[26] (Scheme 4B). Extension to the synthesis if tridentate pincer ligands was later explored. Although the synthesis of the thionophosphinoamidate starting material in Scheme 4C was formed in only 18% yield, the rearrangement to install the second *O*,*O*-diethylthiophosphonyl group proceeded in 96% yield.



Scheme 4 Prior examples of 1,2-rearrangements of pyrrole derivatives. a. Use of enantioenriched phosphorus derivatives, b. Preparation of ligands.

Given the under-developed state of the rearrangement with pyrroles, and the utility of pyrroles in medicinal chemistry, we decided to pursue the pyrrole dance as a method to form C–C bonds. The scope of the 1,2-rearrangement reaction with *N*-acylpyrroles was, therefore, explored. As shown in Table 2, a broad range of *N*-acylpyrroles can serve as suitable substrates in this protocol. Aryl *N*-acylpyrroles possessing diverse substituents on the *N*-benzoyl group formed products in 68−84% yield, including those with alkyl (**3b**, **3c**), phenyl (**3d**), electron-withdrawing (**3e**, **3f**, **3g**, **3h**, **3i**, and **3j**), and electron-donating (**3k**, **3l**) substituents. Notably, sterically hindered N-acylpyrroles, such as 2-OMe (**3m**), 2-Me (**3n**), 2-Cl (**3o**), or 2-Ph (**3p**), were also found to be excellent substrates, giving the desired product in 58−84% yield. Furthermore, *N*-(1-naphthoyl)pyrrole and *N*-(2-naphthoyl)pyrrole provided **3q** and **3r** in 85% and 77% yield, respectively. It is noteworthy that electron-deficient heterocycles, such as pyridines (**1s**, **1t**) and quinolines (**1u**, **1v**), were well-tolerated in this reaction, giving the corresponding products in 61−73% yield. Aliphatic derivative **1w**, which was prepared from cyclopropane carboxylic acid, reacted to give **3w** in 48% yield. On the other hand, sterically hindered *N*-acylpyrrole derivatives that bear a 2-methyl group on the pyrrole (**1x**, **1y**) were also suitable substrates in this transformation, affording the products in 63% and 58% yield respectively. Interestingly, subjecting pyrrole-1-carboxamide (**1z**), bearing two pyrroles, to $LiN(SiMe_3)_2$ in toluene at 100 °C for 3 h resulted in mono-rearranged product **3z** in 61% yield, while di-rearrangement product **3aa** was produced in 50% yield at higher temperature (120 °C) for 13.5 h.

Table 2. Scope of pyrrole dance[a,b]

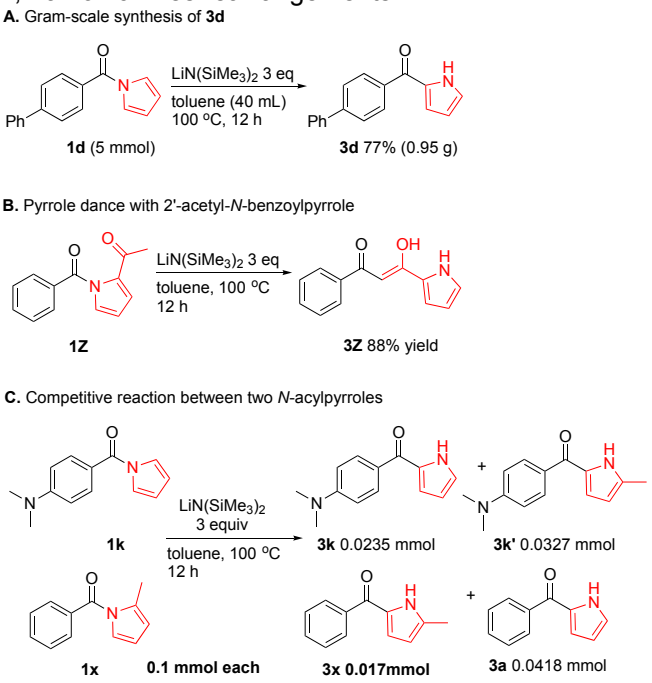


[a]Reactions were conducted with **1a** (0.1 mmol), $LiN(SiMe_3)_2$ (1.0 mol/L in THF, 0.3 mL, 0.3 mmol), solvent (1 mL), 3 h. [b]Isolated yields. [c]120 °C. [d]6 equiv of 12-crown-4. [e]6 h. [f]13.5 h.

To be practical, a method must be scalable. To illustrate the scalability of this 1,2-rearrangement reaction, 5 mmol of *N*-(4-phenyl)-benzoylpyrrole was treated with $LiN(SiMe_3)_2$ in toluene at 100 °C for 12 h (Scheme 5A). The rearranged product **3d** was isolated in 77% yield.

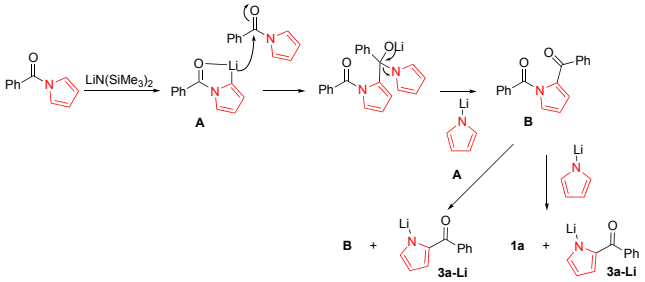
We were curious if the course of the migration could be altered by introduction of more acidic C–H bonds that would be deprotonated more readily than the *N*-acyl pyrrole. The deprotonated carbon would then attack the *N*-acylpyrrole. When 2'-acetyl-*N*-benzoylpyrrole **1Z** was treated with $LiN(SiMe_3)_2$ under standard the conditions, the 1,3-diketone (enol form) product **3Z** formed in 88% yield (Scheme 5B). This compound might be an interesting ligand, serving as an acac derivative with an additional pyrrole that could be used for the synthesis of bimetallic complexes.

Finally, we wanted to learn more about the rearrangement reaction pathway by conducting a crossover experiment. It is noteworthy that anionic 1,2-Fries rearrangements have been found to proceed by an *intramolecular* pathway.[23, 27] In our case, we used a competitive reaction between *N*-(4-dimethylamino)-benzoylpyrrole (**1k**) and 2'-methyl-*N*-benzoylpyrrole (**1x**) under the optimized conditions with $LiN(SiMe_3)_2$. As shown in Scheme 5C, in addition to the expected intramolecular products **3k** and **3x**, two rearranged crossover products (**3k'** and **3a**) were also observed. The observation of crossover products indicates that this pyrrole dance is an intermolecular process, unlike 1,2-anionic Fries rearrangements.



Scheme 5 Reaction characteristics. A. Scale up of the pyrrole dance. B. Application of the pyrrole dance with 2'-acetyl-*N*-benzoylpyrrole to the synthesis of acac ligands. C. Cross-over experiments.

Based on the results above, we propose a reaction pathway for this 1,2-rearrangement process (Scheme 6). The first step is directed metallation of the *N*-acyl pyrrole (**1a**) to afford **A**. Next, organolithium **A** acts as a nucleophile toward the carbonyl group of another *N*-benzoylpyrrole (**1a**) to give a dibenzoyl intermediate **B** with loss of the pyrrolide anion. The intermediate **B** is then attacked by a second carbanion A to give **3a-Li** and another molecule of **B**. Alternatively, **B** could be attacked at the *N*-acyl pyrrole by the pyrrolide anion to liberate the deprotonated product **3a-Li** and form an equivalent of *N*-acylpyrrole **1a**. Finally, it is possible that the pyrrolide anion reacts at the 2-position directly with **B** to generate 2 equiv. **3a-Li** (not shown).

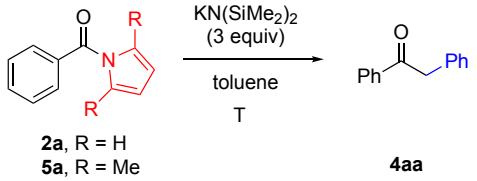


Scheme 6 Possible reaction pathways for the pyrrole dance.

Aroylation of toluene derivatives. We next turned our attention to the aroylation of benzylic methyl groups. The functionalization of the benzylic C–H bonds of toluene and its derivatives has attracted significant recent attention, because toluenes are chemical feedstocks, representing plentiful and inexpensive starting materials. Most methods to engage the benzylic hydrogens involve transition metal catalysts.[28] In contrast, our approach relies on the ability of silyl amide bases [$MN(SiMe_3)_2$, M = Na, K & Cs] to reversibly deprotonate the weakly acidic benzylic methyl groups. Based on this approach, we developed the aminobenzylation of toluenes,[29] a convergent indole synthesis using 2-fluoro toluenes and benzonitriles,[20c] and a palladium catalyzed arylation of toluenes with aryl bromides and chlorides.[20d, 30] We hypothesize that the alkali metal cations form cation pi-interactions[30b, 31] with the toluene ring, thereby acidifying the benzylic hydrogens. Despite this experience, we were still surprised that switching base from $LiN(SiMe_3)_2$ to $KN(SiMe_3)_2$ changed the reaction outcome from the pyrrole dance to aroylation (Table 1, entry 13 vs. 3). We therefore explored the optimization of the aroylation reaction to prepare aryl benzyl ketones under transition metal-free conditions.

The initial results on the aroylation from Table 1 have been transferred to Table 3, entry 1. Heating the reaction with 3 equiv $KN(SiMe_3)_2$ to 100 °C improved the yield of aroylation product **4aa** (48%, entry 2). Unfortunately, extensive effort to raise the yield of this reaction over 50% were unsuccessful (41% yield at 120 °C, entry 3). We rationalized that blocking the 2,5-positions of the pyrrole would shut down the pyrrole dance and might render the *N*-acyl pyrrole more electrophilic by forcing the pyrrole out of planarity with the carbonyl group. Thus, we chose 2,5-dimethyl-*N*-benzoylpyrrole **5a** as starting material (R = Me, entry 4). In this case, conducting the aroylation in toluene at 100 °C with 3 equiv $KN(SiMe_3)_2$ furnished the aroylation product in 83% yield. Temperature screening indicated that 100 °C was most suitable for this transformation (entries 5−7). Additionally, the excess base is critical in this reaction. The aroylation product was collected in 51% yield with 2 equiv of $KN(SiMe_3)_2$, while only 26% product was produced when the amount of base was lowered to 1 equiv. Use of 3 equiv $LiN(SiMe_3)_2$ as base led to recovery of most of the stating *N*-acylpyrrole **5a**.

Table 3. Reaction Optimization[a]



2a, R = H
5a, R = Me

4aa

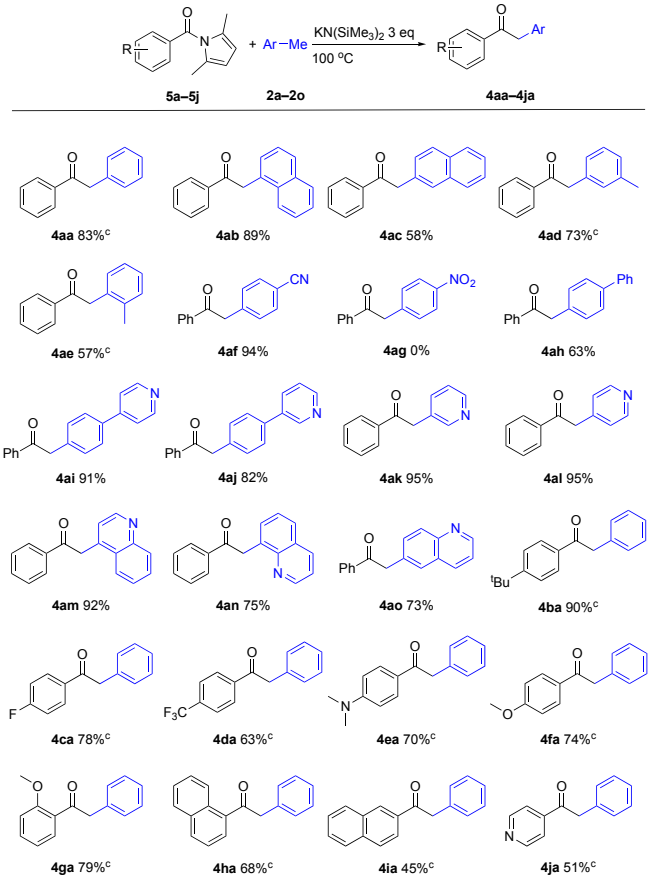
entry	solvent	R	temp.	4aa (%)[b]
1	toluene	H	80 °C	**4aa** (36)
2	toluene	H	100 °C	**4aa** (48)
3	toluene	H	120 °C	**4aa** (41)
4[c]	toluene	Me	100 °C	**4aa** (83)
5[c]	toluene	Me	120 °C	**4aa** (68)
6[c]	toluene	Me	80 °C	**4aa** (56)
7[c,d]	toluene	Me	100 °C	**4aa** (51)
8[c,e]	toluene	Me	100 °C	**4aa** (26)
9[f]	toluene	Me	100 °C	**4aa** (trace)

[a]Reactions were conducted with **1a** (0.1 mmol), $KN(SiMe_3)_2$ (1.0 mol/L in THF, 0.3 mL, 0.3 mmol), toluene (1 mL), 12 h. [b]Isolated yields. [c]2a was replaced with **5a** (0.1 mmol). [d]0.2 mmol of $KN(SiMe_3)_2$. [e]0.1 mmol of $KN(SiMe_3)_2$. [f]0.3 mmol of $LiN(SiMe_3)_2$ led to mostly recovered **5a**.

Employing the conditions in Table 3 (entry 4) with $KN(SiMe_3)_2$ at 100 °C, a series of toluene derivatives were successfully used, affording 1,2-diarylethanones in good to excellent yields after workup. Beyond the parent reaction to give **4aa** with toluene, 1-methylnaphthalene and 2-methylnaphthalene furnished the desired products **4ab** and **4ac** in 89% and 58% yield, respectively. Substrates bearing alkyl (**4ad**, **4ae**), electron-withdrawing (**4af**), phenyl (**4ah**), and heterocyclic (**4ai**, **4aj**) groups were all tolerated in this protocol. In contrast, 4-nitrotoluene decomposed under the reaction conditions. Interestingly, heterocyclic 3-methylpyridine, 4-methylpyridine, 4-methylquinoline, 8-methylquinoline, and 6-methylquinoline were also suitable coupling partners, giving the products **4ak**−**4ao** in 73−95% yield.

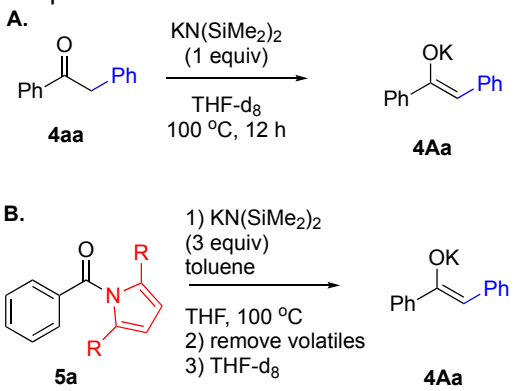
The substrate scope of 2,5-dimethyl-*N*-acylpyrroles in the aroylation of toluene (**2a**) was subsequently examined. As shown in Table 3, 2,5-dimethyl-*N*-acylpyrroles derived from benzoyl groups bearing substituents such as 4-^{t}Bu, 4-F, 4-CF_3, 4-NMe_2, and 4-OMe reacted to give the corresponding products in 63−90% yield. Notably, the sterically hindered 2-methoxy 2,5-dimethyl-*N*-benzoylpyrrole showed a reaction efficiency similar to less hindered substrates, affording the product **4ga** in 79% yield. Additionally, substrates with extended π-systems, such as 2,5-dimethyl-*N*-acylpyrroles bearing 1- and 2-naphthyl groups, furnished products **4ha** and **4ia** in 68% and 45% yield, respectively. Additionally, a heterocyclic substrate, which bears a pyridyl group, gave a 51% yield of product **4ja**.

Table 4. Scope of aroylation of toluene derivatives[a,b]



[a]Reactions were conducted with 2,5-dimethyl-*N*-acylpyrrole (0.1 mmol), $KN(SiMe_3)_2$ (1.0 mol/L in THF, 0.3 mL, 0.3 mmol), toluene derivatives (0.12 mmol) in 1 mL THF for 12 h. [b]Isolated yields. [c]THF was replaced with toluene derivative as solvent (1 mL).

To understand the reason that over addition is not observed in Table 4, we first subjected compound **4aa** to reaction with $KN(SiMe_3)_2$ in THF-d_8 (Scheme 7A). The solution was warmed to 100 °C for 12 h, cooled to rt, and ^1H and $^{13}C\{^1H\}$ NMR spectra acquired. Next, the reaction of *N*-acyl pyrrole derivative **5a** with toluene and $KN(SiMe_3)_2$ was conducted under the standard aroylation conditions. The crude reaction mixture was not subjected to standard aqueous work up, but instead was placed under reduced pressure to remove the volatile materials. Under a nitrogen atmosphere, the crude reaction mixture was dissolved in THF-d_8, filtered through a pad of Celite and transferred to an NMR tube for analysis. As shown in the Supporting Information (Mechanism Study, pg. S17), deprotonation of **4aa** leads to the expected enolate **4Aa**, with a characteristic ^{13}C resonance for the carbon attached to oxygen of the enolate at 167.2 ppm. In the case of the reaction with the *N*-acyl pyrrole, the ^{13}C resonance at 167.2 was again observed. Thus, the initially formed product of this reaction is the enolate, which arises from the addition of the benzylic carbanion to the *N*-acyl pyrrole. At 100 °C, it is likely that the tetrahedral intermediate looses the pyrrole anion to generate the ketone, which is rapidly deprotonated by the $KN(SiMe_3)_2$ to afford the enolate **4Aa**. Of course, the enolate does not undergo further nucleophilic addition.



Scheme 7 Investigation of the direct product. A. Independent synthesis of the enolate, B. Formation of enolate 4Aa from addition of toluene.

Conclusions

In summary, we have introduced a chemoselective approach for the synthesis of either benzyl phenyl ketones or 2-aroylpyrroles, both of which are important structural motifs in medicinal chemistry and distributed widely in natural products. Despite the remarkable similarity of the reaction parameters for these two processes, which are both promoted by silylamide bases, the key to achieving high selectivity is the choice of main group metal (K vs. Li) and *N*-acylpyrrole. This novel method for the synthesis of 2-aroylpyrroles complements traditional routes, such as the Friedel-Crafts aroylation and Vilsmeier-Haack reaction. Among these, our synthesis stands out for its convenience, avoidance of strongly acidic conditions, excellent regioselectivity, and high functional group compatibility. In the case of the aroylation reaction, standard methods would involve use of Weinreb amides with preformed organometallic reagents at cryogenic temperatures. In contrast, this method used pro-nucleophiles to in situ generate the needed organometallics and requires only heating. Compared to enolate arylation, our method does not use transition metal catalysts. Thus, the aroylation approach outlined herein represents the most straightforward and practical method for the generation of a host of aryl benzyl ketones.

Conflicts of interest

There are no conflicts to declare.

Author contributions

The work was conceptualized by JL and PJW. Experiments were performed by HW, JM, SS, SC, and DZ. The first draft of the manuscript was prepared by JL and the final draft was edited by PJW.

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