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Graphical Abstract

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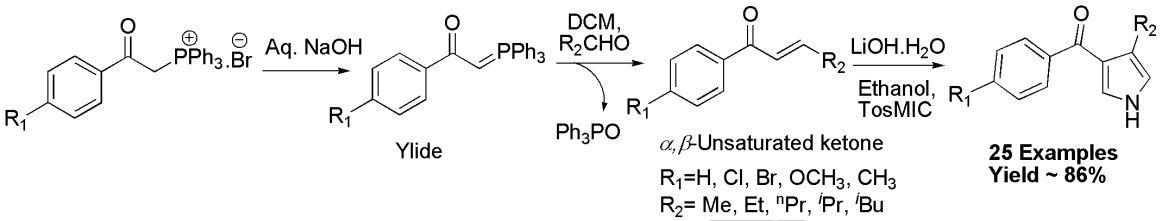

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ABSTRACT

A convenient synthesis of 4-alkyl-3-benzoyl pyrrole was achieved from *α,β*-unsaturated ketones and tosylmethylisocyanide in presence of mild base $LiOH.H_2O$. This method is very economical and was successfully utilized for the synthesis of various 4-alkyl-3-benzoylpyrrole derivatives with good to excellent yields.

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1. Introduction

Among heterocyclic compounds, pyrrole[1] is one of the most explored heterocycles because of its therapeutic importance which includes antibacterial,[2] antifungal,[3] antiviral,[4] anti-inflammatory[5] and anticancer[6] properties. The structural motif is also an integral part of several natural products comprising of bilins, bilanes, phycobilin, porphyrin and chlorophyll (**Figure 1**).[7] This scaffold has also found use in supramolecular chemistry and material science.[8]

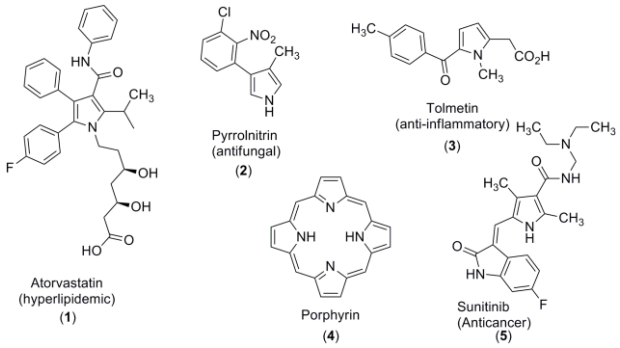


Figure 1. Important molecules with pyrrole skeleton.

Synthesis of substituted pyrroles always pose challenges due to functional group complexity and stability issues.[1] Among the various methods, a few strategies are widely employed for the synthesis such as (i) condensation reactions of *α*-aminocarbonyl compounds with activated ketones (Knorr pyrrole synthesis),[9] (ii) reactions of *α*-halocarbonyl compounds with *β*-ketoesters and ammonia (Hantzsch pyrrole synthesis),[10] (iii) reactions of 1,4-dicarbonyl compounds with primary amines (Paal–Knorr synthesis).[11] Functionalization of pyrrole skeleton by substitution reactions has also provided new strides in accessing the desired scaffolds.[12] Recent advancements in the synthesis of pyrroles involve reaction between enamines and nitroalkenes.[13] Jadhav *et al*. have developed three-component one-pot reaction by reacting amines, nitrostyrenes and (diacetoxyiodo)benzene.[14] Coupling reactions were explored with iron(III) salts as catalysts for highly functionalized pyrroles involving 1,3-dicarbonyl compounds, amines, aromatic aldehydes and nitroalkanes.[13a] Polysubstituted pyrroles were synthesized from ketones using *N*-iodosuccinimide, amines, *β*-dicarbonyl compounds on a high-speed vibration mill in presence of cerium (IV) ammonium nitrate and silver nitrate.[15] Meshram *et al*. developed a greener method by utilizing four-component reaction of amines, aldehydes, nitromethane and *β*-diketones employing an ionic liquid.[16] Another four-component one-pot reaction involving aryl aldehydes, benzyl amines, *β*-ketoesters and nitroalkanes was reported using $NiCl_2.6H_2O$ as a catalyst.[13d] Various substituted pyrroles were synthesized using *β*-nitrostyrene, *β*-diketones and aryl amines employing $CeCl_3.7H_2O$ as catalyst under microwave irradiation.[17] A one-pot coupling reaction of amines, 1,3-diketones and phenacyl bromide was reported recently for the synthesis of pyrroles using $Yb(OTf)_3$.[18] In spite of the vast amount of literature available, synthetic methodologies for substituted pyrroles have encountered several drawbacks such as incompatibility of functional groups, lack of regioselectivity, non-availability of suitable starting materials for desired reactions, harsh reaction conditions and use of costly reagents as well as involvement of tedious purification procedures with poor yields.[19]

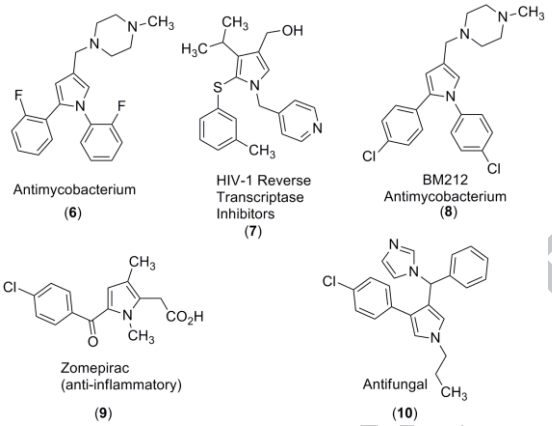
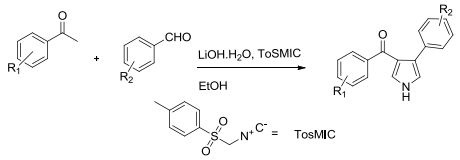


Figure 2. A few biologically important 4-alkyl substituted pyrrole derivatives

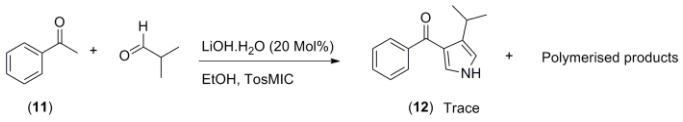
2. RESULTS AND DISCUSSION

Our interests in the synthesis of heterocyclic compounds as well as exploration of these compounds in stereoselective C-C bond forming reactions[20] motivated us to investigate a convenient synthetic methodology for the synthesis of alkyl substituted pyrroles.[21] Recently we reported the van Leusen reaction for aryl pyrroles using tosylmethyl isocyanide (TosMIC)[22] and aromatic aldehydes under mild basic condition in a one-pot reaction with high yields (**Scheme 1**).[21d]



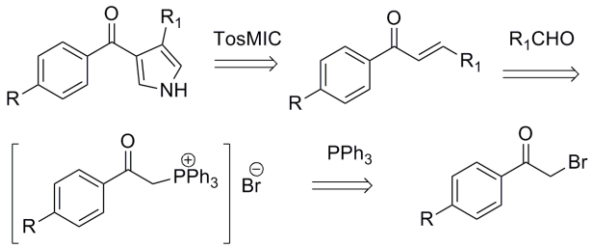
Scheme 1. Synthesis of phenyl(4-aryl-1*H*-pyrrol-3-yl)methanones

However the methodology could not be extended to provide the desired alkyl substituted pyrroles, employing aliphatic aldehydes. It was observed that enolisable aliphatic aldehydes polymerizes in presence of a base and this results in only trace amounts of aliphatic *α*,*β*-unsaturated ketone intermediate which affords poor yields of the desired pyrroles (**Scheme 2**). Synthesis of 4-alkyl pyrroles derivatives therefore is more challenging but robust procedures need to be developed considering their biological properties.[23-25]



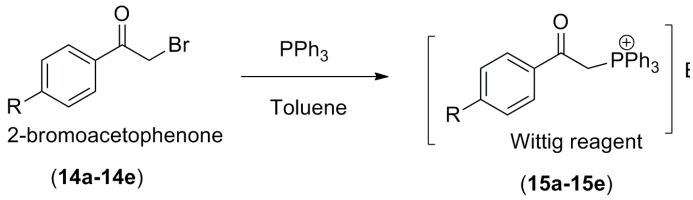
Scheme 2. Problem associated with aliphatic aldehyde by $LiOH.H_2O$ catalyzed reaction.

A retrosynthetic scheme is depicted in **Scheme 3** incorporating the Wittig reaction with van Leusen reaction for the synthesis of 4-alkyl pyrroles. It can be fairly expected that the Wittig reaction would provide access to *α*,*β*-unsaturated carbonyl compound which upon reaction with $LiOH.H_2O$ and TosMIC affords the desired products (**Scheme 3**).



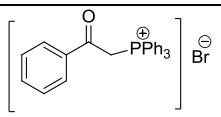
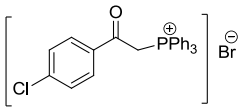
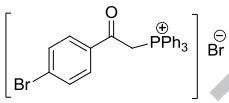
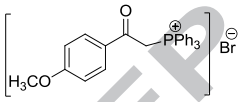
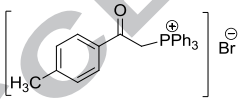
Scheme 3. Retrosynthesis of 4-alkylpyrroles.

To standardize the reaction condition, we synthesized various phosphonium salts by treating substituted 2-bromoacetophenones with triphenylphosphine in toluene (**Scheme 4**).[26] Various substrates containing electron withdrawing as well as electron donating groups were chosen to understand the substitution effects on the course of reactions (**Table 1**).



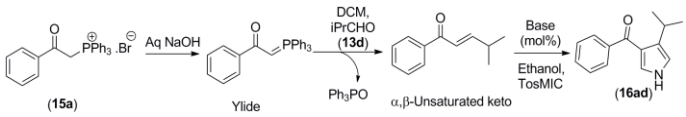
Scheme 4. Synthesis of phosphonium salts.

Table 1. Synthesis of phosphonium salts[a]

Entry	R	Phosphonium salt	Yield[b](%)	Product
1	H		95	**15a**
2	Cl		96	**15b**
3	Br		97	**15c**
4	OCH_3		93	**15d**
5	CH_3		90	**15e**

[a]2-Bromoacetophenone (1.0 mmol), triphenylphosphine (1.0 mmol), toluene (5.0 mL), 1.0h; [b]Isolated yield.

The phosphonium salt **15a** was neutralised with aqueous NaOH and extracted with dichloromethane to afford 1-phenyl-2-(triphenylphosphoranylidene) ethanone. Further the compound was reacted with isobutyraldehyde in dichloromethane to generate the corresponding *α,β*-unsaturated ketone. Upon completion of the reaction, dichloromethane was evaporated and reaction mixture was triturated with hexane to remove triphenylphosphine oxide (**Scheme 5**). Thereafter the product obtained was treated with TosMIC in presence of various bases in stoichiometric amounts (**Table 2**). Among the different bases employed $LiOH.H_2O$ gave good yield of the desired product comparatively. This might be due to better coordination power of lithium. A stoichiometric analysis of $LiOH.H_2O$ (**Entries 10-13, Table 2**) indicated that a catalytic quantity of 20 mol% is sufficient to afford the desired product with good yield. However, below 20 mol% product yield diminished.



Scheme 5. Synthesis of 4-alkyl-3-benzoylpyrroles.

Table 2. Effect of base in convenient synthesis of 4-alkyl-3-benzoylpyrrole[a]

Entry	Reaction condition		Yield[b] (%)
	Base (mol%)	Time (h)	
1	KOH (100)	2	78
2	NaOH (100)	2	80
3	$LiOH.H_2O$ (100)	0.5	88
4	$CsCO_3$ (100)	4	65
5	DBU (100)	6	c
6	DIPEA (100)	6	c
7	TEA (100)	6	c
8	$ZrCl_4$ (100)	10	d
9	$AlCl_3$ (100)	10	d
10	$LiOH.H_2O$ (50)	0.5	87
11	**$LiOH.H_2O$ (20)**	**0.5**	**85**
12	$LiOH.H_2O$ (10)	2.0	42
13	$LiOH.H_2O$ (0)	5.0	d

[a]1-Phenyl-2-(triphenylphosphoranylidene) ethanone (1.0 mmol), isobutyraldehyde (1.0 mmol), TosMIC (1.1 mmol), Ethanol (5.0 mL); [b]Isolated yield. [c]undesired product, [d]α,β-unsaturated ketone remained intact.

The reaction was examined by carrying out in various solvents (**Table 3**). Nonpolar solvents such as toluene was found to be ineffective (**Entry 1, table 3**) whereas polar solvents showed better results. In comparison, ethanol proved to be the most suitable solvent which may be attributed to the better stabilisation of the intermediate generated by the 1,3-dipolar addition reaction. Thus a combination of $LiOH.H_2O$ as a base and ethanol as a solvent gave the best condition for the synthesis of various 4-alkyl-3-benzoylpyrroles (**Table 4**).

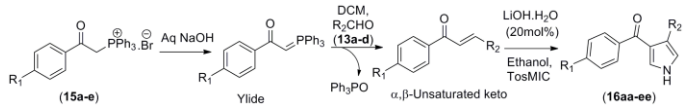
Table 3. Effect of solvent in convenient synthesis of 4-alkyl- 3-benzoylpyrrole[a]

Entry	Reaction condition		Yield[b] (%)
	Solvent	Time (h)	
1	Toluene	6.0	c
2	Diethylether	6.0	20
3	1,4 dioxane	6.0	30
4	Tetrahydrofuran	1.0	70
5	Chloroform	5.0	22
6	Dichloromethane	5.0	20
7	Acetonitrile	5.0	25
8	Water	4.0	c
9	Isopropylalcohol	4.0	50
10	Methanol	2.0	65
11	**Ethanol**	**0.5**	**85**

[a]1-Phenyl-2-(triphenylphosphoranylidene)ethanone (1.0 mmol), isobutyraldehyde (1.0 mmol), TosMIC (1.1 mmol), $LiOH.H_2O$ (0.2 mmol); [b]Isolated yield. [c]*α,β*-unsaturated ketone remained intact.

The reaction is assumed to proceed through 1,3-dipolar addition of TosMIC to *α,β*-unsaturated ketones generated by the reaction of the ylides and aldehydes. Further this strategy was applied for the synthesis of various 4-alkyl-3-benzoylpyrrole derivatives. Thus the reaction condition has been successfully used for the synthesis of *α,β*-unsaturated carbonyl compounds followed by reaction with $LiOH.H_2O$ (20 mol%) and TosMIC to get the

desired compounds (**Scheme 6**). The aldehyde substituent (R^2) was found to significantly affect the course and yield of the reaction (**Table 4**).



Scheme 6. A convenient synthesis of 4-alkyl-3-benzoylpyrrole derivatives

Table 4. Synthesis of 4-alkyl-3-benzoylpyrroles[a]

Entry	R^1	R^2	Product	Yield[b] (%)
1	H	$-CH_3$	**16aa**	75
2	H	$-CH_2CH_3$	**16ab**	76
3	H	$-CH_2CH_2CH_3$	**16ac**	80
4	H	$-CH(CH_3)_2$	**16ad**	85
5	H	$-CH_2CH(CH_3)_2$	**16ae**	81
6	Cl	$-CH_3$	**16ba**	73
7	Cl	$-CH_2CH_3$	**16bb**	75
8	Cl	$-CH_2CH_2CH_3$	**16bc**	79
9	Cl	$-CH(CH_3)_2$	**16bd**	86
10	Cl	$-CH_2CH(CH_3)_2$	**16be**	81
11	Br	$-CH_3$	**16ca**	74
12	Br	$-CH_2CH_3$	**16cb**	77
13	Br	$-CH_2CH_2CH_3$	**16cc**	78
14	Br	$-CH(CH_3)_2$	**16cd**	82
15	Br	$-CH_2CH(CH_3)_2$	**16ce**	79
16	OCH_3	$-CH_3$	**16da**	68
17	OCH_3	$-CH_2CH_3$	**16db**	70
18	OCH_3	$-CH_2CH_2CH_3$	**16dc**	73
19	OCH_3	$-CH(CH_3)_2$	**16dd**	83
20	OCH_3	$-CH_2CH(CH_3)_2$	**16de**	78
21	CH_3	$-CH_3$	**16ea**	69
22	CH_3	$-CH_2CH_3$	**16eb**	72
23	CH_3	$-CH_2CH_2CH_3$	**16ec**	76
24	CH_3	$-CH(CH_3)_2$	**16ed**	85
25	CH_3	$-CH_2CH(CH_3)_2$	**16ee**	84

[a]1-Phenyl-2-(triphenylphosphoranylidene)ethanone (1.0 mmol), aldehyde (1.0 mmol), ethanol (5.0 mL), TosMIC (1.1 mmol), $LiOH.H_2O$ (0.2 mmol), room temperature; [b]Isolated yield.

3. CONCLUSION

A convenient method for the synthesis of 4-alkyl-3-benzoylpyrroles in good to excellent yields is reported. The course of the reaction is influenced by the nature of the alkyl substituents. This methodology also allows a cost effective synthesis of 4-alkyl-3-benzoylpyrroles with ease in purification.

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SUPPLEMENTARY DATA

Supplementary data (experimental procedures, compound data and scanned spectra (^{1}H NMR, ^{13}C NMR and HRMS)) associated with this article can be found, in the online version.

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Highlights:

- A convenient synthesis of 4-alkyl-3-benzyolpyrrole from α,β-unsaturated ketones.
- $LiOH.H_2O$ with ethanol work as a dual activator.
- Synthesis of various 4-alkyl-3-benzoylpyrrole derivatives with excellent yields.
- Cost effective synthesis of 4-alkyl-3-benzoylpyrroles with ease in purification.