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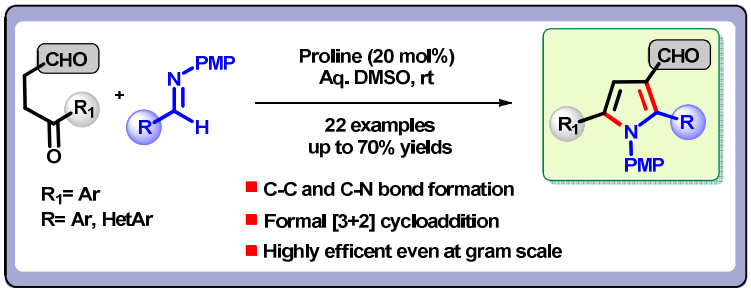

An organocatalytic formal [3+2] cycloaddition have been developed between 1,4-ketoaldehydes and imines to synthesize densely substituted 3-formylpyrroles in high yields (up to 70%) under mild conditions at room temperature.

Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Direct catalytic synthesis of densely substituted 3-formylpyrroles from imines and 1,4-ketoaldehydes†

Indresh Kumar,*[a] Nisar A. Mir,[a] Panduga Ramaraju,[a] Deepika Singh,[b] Vivek K. Gupta[c] and Rajnikant[c]

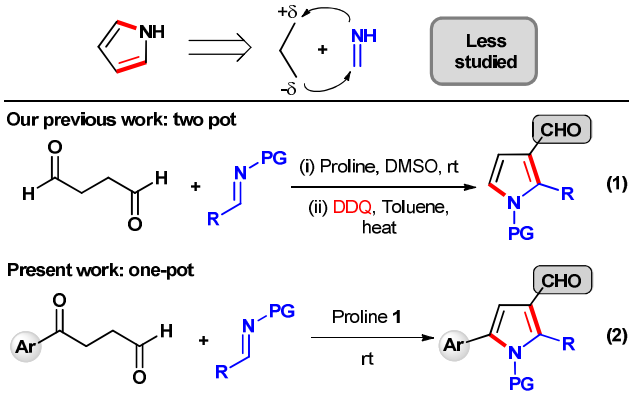
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A sustainable method for the direct access to highly substituted 3-formylpyrroles from 1,4-ketoaldehydes and imine via formal [3+2] cycloaddition is reported. This reaction involves one-pot amine catalyzed chemoselective Mannich-cyclization-aerobic oxidation sequence with good to high yields. Further application at gram scale reaction as well as synthesis of fully substituted 3-formylpyrrole is also shown.

Pyrroles are not only the essential structural units of many biologically active natural products and medicines,[1] but also broadly utilized in material science.[2] Highly substituted pyrroles have been identified as pharmacophores for the anti-inflammatory and anticancer drug: atorvastatin (Lipitor), a top-selling drug that is used as an antihyperlipidemic agent.[3] Due to high commercial impact of substituted pyrroles, a series of efficient methods including classical one's have been developed by synthetic chemists.[4] Cycloadditions,[5] Multi-component,[6] and metal-catalyzed[7] reactions are the predominantly applied strategies to provide easy access to pyrroles. However, most of these methods are limited to the use of elaborately designed starting materials, suffer from low efficiency and selectivity and sometimes required harsh conditions. Additionally, direct synthesis of C3-functionalized pyrroles is quite challenging[8] because it has conventional problem of regioselective substitution at C2 and C5 positions. In particular, the direct regioselective synthesis of substituted 3-formylpyrroles has been a stubborn problem and require the use of indirect methods involving several steps.[9] To the best of our knowledge, direct synthesis of exceedingly substituted 3-formylpyrroles has not been discussed. Therefore, the development of 'one pot' direct regioselective route to highly functionalized 3-formylpyrroles from simple and easy available materials is highly attractive.

On the other hand, involvement of imines in [3+2] cycloaddition/annulation with different C3 synthons to synthesize pyrroles has been little explored.[10] Few organocatalytic methods involving imines have been developed recently,[11] as imines are highly attractive partners for formal [3+2] cycloadditions to synthesize five membered *N*-heterocyclic ring systems.[12] Organocatalytic transformations have been considered as most effective ways of synthesis in asymmetric[13] as well as in relatively less studied non-asymmetric fashion.[14] Hence, the development of completely organocatalytic approach for highly functionalized non-chiral scaffolds would be very interesting from a synthetic as well as an environmental point of view.

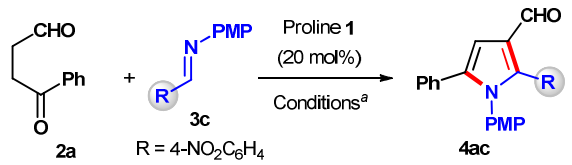


Scheme 1: Organocatalytic strategy for 3-formylpyrroles from 1,4-dicarbonyls and imines

We have recently presented the two pot synthesis of pyrrole-3-carboxaldehyde using organocatalytic [3+2] annulation between succinaldehyde and *N*-PMP aldimines (eqn. 1, Scheme 1).[11b] While the methodology resulted a rapid construction of pyrrole ring, it required DDQ as harsh reagent for oxidative aromatization. In addition, the novelty and clear synthetic potential of this method prompted us to explore similar transformation with 1,4-ketoaldehydes to direct access of tetrasubstituted pyrroles having formyl functionality at C3 position under mild condition. Since a wider variety of ketoaldehyes are easily accessible, this can increase the potential diversity of the resulting polysubstituted pyrroles. Interestingly, Paal-Knorr strategy is the only method to synthesize pyrroles from 1,4-dicarbonyl compounds and ammonia or primary amines, and the development of alternative method is highly inspiring. Here, we describe our success on fully organocatalytic one-pot direct synthesis of densely substituted 3-formylpyrroles as most rational and straightforward route from versatile starting materials (eqn. 2, Scheme 1). The initial screening of best reaction condition with *N*-PMP aldimine **3c** as model substrate was investigated and summarized in Table 1.

Based on our previous experience on amine catalyzed annulation reaction,[15] we tried our initial experiment in DMSO using proline **1** as amine catalyst. To our delight, tetra-substituted pyrrole **4ac** was obtained directly with moderate yield in a one pot sequence (entry 1, table 1). The reaction proceed through the chemoselective Mannich reaction of 1,4-ketoaldehyde **2a** with

Table 1 Optimization of reaction conditions [a]



Entry	Conditions[a]	Yield (%)[b]
1	DMSO, rt, 48 h	58
2	DMF, rt, 26 h	45
3	CH_3CN, rt, 30 h	41
4	Toluene, rt, 24 h	n.r.
5	THF, rt, 28 h	34
6	CH_2Cl_2, rt, 28 h	<20
7[c]	**DMSO, rt, 24 h**	**70**
8[d]	DMSO, rt, 24 h	62

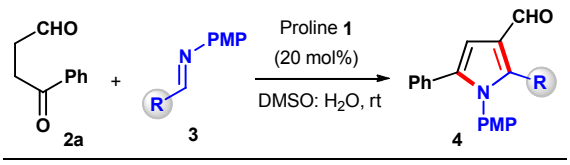
[a] Imine **3c** (0.3 mmol), **2a** (0.9 mmol), proline **1** (20 mol%), solvent (3.0 mL). [b] Isolated yield refer to **4ac**. [c] With addition of H_2O (100 µL). [d] With addition of water (200 µL).

imine **3c**, followed intramolecular cyclization and aerobic oxidative aromatization. Next we made efforts to optimize the reaction condition to improve the reaction yields. Screening the reaction solvents exposed that most of them afforded reactions yields lower than that in DMSO (20-45%, entries 2-6, Table 1). Addition of water enhance the rate of reaction, similar to that discussed earlier by Barbas and others for direct Mannich reactions.[16] Pyrrole **4ac** was obtained with high yield (70%) in the presence of water (100 µL) (entry 7, Table 1), whereas any increment in the amount of water (200 µL) further reduced the reaction yields (entry 8, Table 1). Thus, we preferred to perform this one pot strategy with the optimized conditions (entry 7, Table 1).

With the established reaction conditions in hand, a series of imines **3** were investigated for extending the substrate scope (Table 2). In general, all the *N*-PMP aldimines derived from corresponding aromatic aldehydes worked well in the reaction, provided a series of 2,5-biaryl-3-formylpyrroles **4** in moderate to high yields (up to 70%). In case of electron-deficient arylimines reactions proceeded nicely (entries 1-14, Table 2), however the reactions were rather slow in case of imines preformed from 2-substituted aldehydes (entries 1, 4, 7, and 10, Table 2) and naphthaldehydes (entries 16, 17, Table 2) lead to lower yields, perhaps because of the steric crowding. Not only simple aryl imine (entry 15, Table 2), but hetero-aryl imines also resulted in products with good yields (entry 18–21, Table 2). In the case of slightly electron-rich aryl imine (entry 22, Table 2), the corresponding pyrrole **4av** was obtained with moderate yield (45%). Single crystal X-ray diffraction analysis of functionalized pyrrole **4aq** further established the structure (Scheme 2).[17]

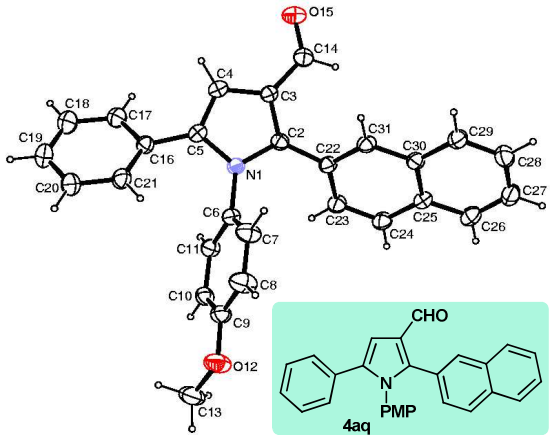
Next, differently substituted 2,5-biaryl-3-formyl pyrroles **4ac**–**4ec** were prepared in good yields to show the substrate scope of 1,4-ketoaldehyde **2** (Table 3). It was found that the protocol work efficiently regardless to both electron deficient and electron rich aromatic ring R of **2**. Based on our previous study on amine catalyzed annulation reaction,[15] a tentative mechanism is proposed for this protocol. We speculate here that aromatic part of 1,4-ketoaldehyde **2** comprise positive effect on aerobic oxidative aromatization (for details: see ESI). Further application

Table 2: Scope study with various imines **3**



Entry[a]	(**3**) R =	time (h)	**4**	Yield (%)[b]
1	2-$NO_2C_6H_4$	32	**4aa**	67
2	3-$NO_2C_6H_4$	27	**4ab**	65
3	4-$NO_2C_6H_4$	24	**4ac**	70
4	2-FC_6H_4	30	**4ad**	69
5	3-FC_6H_4	28	**4ae**	65
6	4-FC_6H_4	28	**4af**	70
7	2-Cl-C_6H_4	35	**4ag**	61
8	3-ClC_6H_3	30	**4ah**	63
9	4-ClC_6H_4	30	**4ai**	67
10	2-BrC_6H_4	38	**4aj**	60
11	3-BrC_6H_4	30	**4ak**	65
12	4-BrC_6H_4	28	**4al**	67
13	3-Br-4-FC_6H_3	28	**4am**	65
14	4-$CF_3C_6H_4$	26	**4an**	69
15	Ph	35	**4ao**	58
16	1-Naphthyl	38	**4ap**	56
17	2-Naphthyl	35	**4aq**	60
18	2-pyridyl	24	**4ar**	62
19	3-pyridyl	28	**4as**	55
20	4-pyridyl	24	**4at**	61
21	2-thiophene	28	**4au**	52
22	4-$CH_3C_6H_4$	35	**4av**	45

[a](i) Imine **3** (0.3 mmol), **2a** (0.9 mmol), proline **1** (20 mol%), DMSO (3.0 mL), H_2O (100 µL). [b] Isolated yield of **4**; about ≤10% of corresponding aldehyde was obtained in all the cases due to cleavage of imine **3**).

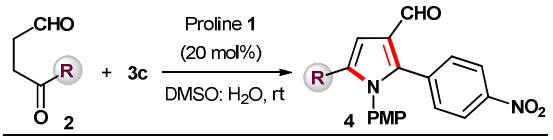


Scheme 2: X-ray crystal structure of **4aq** (ORTP-diagram). Thermal ellipsoids are drawn at the 40% probability level

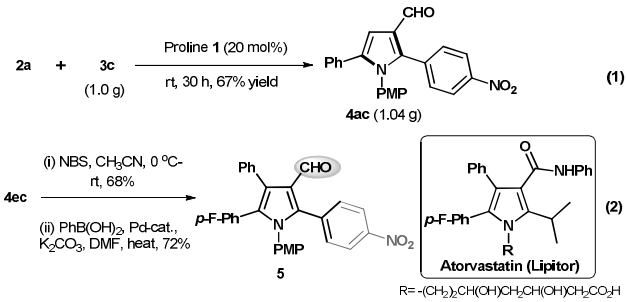
of this method was established; (*i*) gram scale synthesis of pyrrole **4ac** (1.04 g, 67% yield) from aldimine **2c** (1.0 g) with an extended reaction time (eqn. 1, Scheme 3), (*ii*) a quick synthesis of fully substituted 3-formylpyrrole **5** through coupling sequence (eqn. 2, Scheme 3). Fully substituted pyrroles are versatile building blocks in organic synthesis and can be readily converted to biologically important products. For example; compounds **5** contains the similar pyrrole skeleton of atorvastatin, a clinically approved drug.[3]

In summary, we have developed a straightforward synthesis of

Table 3: Scope study with different 1,4-keto-aldehydes **2**



Entry	(**2**) R =	time (h)	**4**	Yield (%)
1	C_6H_5	24	**4ac**	70
2	4-$CH_3C_6H_4$	27	**4bc**	69
3	3-$OCH_3C_6H_4$	24	**4cc**	64
4	4-$OCH_3C_6H_4$	30	**4dc**	65
5	4-FC_6H_4	28	**4ec**	62



Scheme 3: Application at gram-scale (eqn. 1) and synthesis of fully substituted pyrrole (eqn. 2)

densely substituted 3-formylpyrroles in a modular fashion from 1,4-dicarbonyl compounds and aldimines under very mild condition.This one-pot cascade sequence involves chemoselective Mannich-cyclization-aerobic oxidation as formal [3+2] cycloaddition. The viability of this method was established; (*i*) at gram scale, and (*ii*) synthesis of fully substituted 3-formylpyrrole. We believe that this method provides a rapid access to highly substituted 3-formylpyrroles, which are difficult to access by alternate approaches. Further application of this method is under investigation and will be presented in due course.

We acknowledge the financial support from BITS-Pilani and DST-New Delhi. Mr. N. A. Mir and P. Ramaraju thanks to DST-New Delhi and UGC-New Delhi for their Research Fellowships.

[a] *Department of Chemistry, Birla Institute of Technology and Science, Pilani 333 031, (Rajasthan) India. Tel:+91 1596 515707; Fax: +91 1596 244183; E-mail: indresh.chemistry@gmail.com, indresh.kumar@pilani.bits-pilani.ac.in;*
[b] *Instrumentional Division, IIIM-CSIR Lab, Jammu 180 001, India.*
[c] *X-ray Crystallography Laboratory, Post-Graduate Department of Physics & Electronics, University of Jammu, Jammu 180 006, India.*
† Electronic Supplementary Information (ESI) available: CCDC 1007133 (***4aq***). *For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/*

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