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An atom-economic green approach: oxidative synthesis of functionalized 1,4-dihydropyridines from *N,N*-dimethylenaminones and amines

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ABSTRACT

We report the first oxidative condensation between *N,N*-dimethylenaminones with amines to form 1,4-dihydropyridines in moderate to good yields, promoted by oxone and trifluoroacetic acid in PEG-400. This reaction features an unusual oxidation of in situ formed dimethylamine to efficiently provide the 4-methylene of 1,4-dihydropyridines, and a highly environment-friendly reaction condition.

Introduction

1,4-Dihydropyridines (1,4-DHPs) are an important class of heterocyclic compounds and are attractive targets both in medicinal chemistry and in organic synthesis in recent years. Calcium channel blockers containing 1,4-DHP subunit, such as felodipine, amlodipine, nifedipine, nicardipine and isradipine (Fig. 1), are widely used as cardiovascular and antihypertensive drugs.[1] Other pharmacological activities of 1,4-DHPs include anti-HIV,[1c,2] anti-bacterial,[3] anti-convulsant,[4] anti-tumour,[5] neuroprotection,[6] radioprotection[7] and others.[8] Synthetically, 1,4-DHPs like Hantzsch ester[9] (Fig. 1) are very useful reducing agents, and are valuable intermediates.[9f,10]

In view of its high significance, tremendous efforts have been taken to develop efficient synthetic methods for this privileged structure. Conventionally, the preparation of 1,4-DHPs mainly relies on the Hantzsch reaction,[11] a three-component condensation reaction of a 1,3-dicarbonyl compound, an aldehyde and an amine or ammonium salt. While this process remains a gold standard to access structurally diverse 1,4-DHPs and an emblematic example of multicomponent reactions (MCRs), new methods based on enaminones have been devised recently.[12] For instance, the group of Wan reported a one-pot reaction of *N,N*- dimethylenaminones **1**, amines **2** and aromatic aldehydes **5** to directly afford 4-substituent 1,4-DHPs **6** (Scheme 1).[12b–e]

Alternatively, the group of Li developed an effective two-component reaction between enaminones **4**, which are derived from *N,N*-dimethylenaminones **1**,[11j,13] and aromatic aldehydes **5** to obtain 4-substituent 1,4-DHPs **6** (Scheme 1).[12f] Notably, an aldehyde

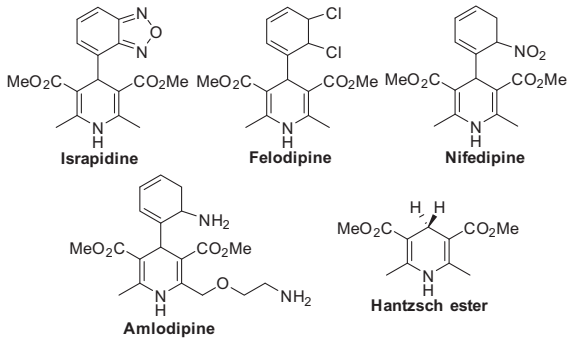

Figure 1. Representative 1,4-DHPs.

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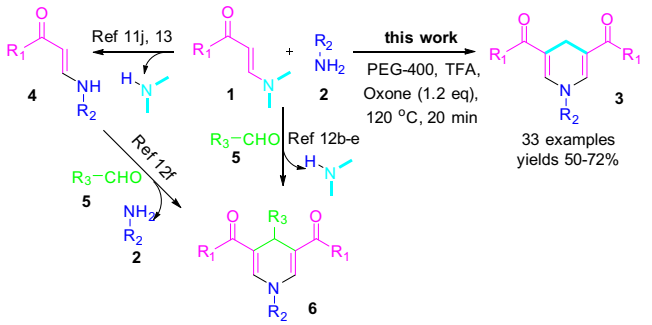


Scheme 1. Current synthesis of 1,4-DHPs.

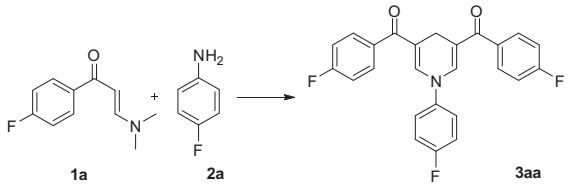
partner is required for these methods. 4-Substituent 1,4-DHPs could not be prepared from the condensation of *N*,*N*-dimethylenaminones **1** and amines **2**. Based on our previous work on enaminone-based heterocycle synthesis,[14] we wish to report here an oxone/TFA-promoted direct synthesis of 1,4-DHPs **3** from *N*,*N*-dimethylenaminones **1** and amines **2** in PEG-400 (Scheme 1). Our protocol involves a unique oxidation of dimethylamine released from the amine-exchange of *N*,*N*-dimethylenaminones **1**. To the best of our knowledge, this is the first example of 1,4-DHPs synthesis with an in situ-formed aldehyde partner.

Results and discussion

In the beginning of our study, *N*,*N*-dimethylenaminone **1a** and 4-fluoroaniline (**2a**) were selected as model substrates for screening the reaction conditions. As shown in Table 1, different solvents, oxidants, catalysts and reaction temperatures were tested. First, oxidants were investigated in the presence of AcOH. 1,4-Benzoquinone (BQ), DDQ and iodobenzene diacetate (IBD) afforded only trace amounts of the desired 1,4-DHPs **3aa** in DMF at 120 °C (entries 1–3), whereas $AgNO_3$, H_2O_2 and TBHP was ineffective (entries 4–6). To our delight, formation of **3aa** were observed for reactions with CAN and $K_2S_2O_8$ (entries 7–8), and oxone was found more efficient (entry 9). Next, the role of the acid was studied using oxone as the oxidant. Among the acids tested, TFA was more efficient (entries 9, 11–12 vs entry 10). Various solvents were then screened in the presence of TFA and oxone (entries 10, 13–22). The reaction in PEG-400 provided an increased yield of the desired product **3aa** (55%, entry 21).[15] After further investigation of the oxone amount and reaction temperature, we found that the reaction with 1.2 equiv oxone to the amine in the presence of TFA in PEG-400 at 120 °C provided the best result (68%, entry 24 vs entries 23, 25–28). Various reaction times have also been tested. The reaction could not reach complete conversion while the reaction time is less than 20 min (5, 10 or 15 min). But for longer reaction times (25 and 30 min), the desired product **3aa** decomposed significantly. A 20-min reaction time was thus adopted.

With the optimal reaction condition in hand (Table 1, entry 24), the scope of substrates was explored. The results are summarized in Table 2. *N*,*N*-Dimethylenaminones **1** with various R_1 group, including electron-poor (**1a**–**1b**), electron-neutral (**1c**) and electron-rich (**1d**–**1e**), proceeded smoothly and afforded the desired 1,4-DHPs **3** in moderate to good yields. Similarly, variation of the amine partner **2** showed little impact on the results, although cyclohexylamine tends to give lower yields than arylamines. All of electron-rich and electron-poor anilines (**2a**–**2g**) are effective substrates and able to generate the expected **3** in moderate to good yields. Moreover, cyclohexylamine **2h** is also a suitable substrate. The structure of **3ce** was further confirmed by X-ray single-crystal diffraction studies (Fig. 2, CCDC 1026867).[16]

Table 1
Optimization of reaction conditions[a]



Entry	Solvent	Oxidant (equiv)	Catalyst	*T* (°C)	Yield[b] (%)
1	DMF	BQ (0.5)	AcOH	120	Trace
2	DMF	DDQ (0.5)	AcOH	120	Trace
3	DMF	IBD (0.5)	AcOH	120	Trace
4	DMF	$AgNO_3$ (1.0)	AcOH	120	–
5	DMF	H_2O_2 (1.5)	AcOH	120	–
6	DMF	TBHP (0.5)	AcOH	120	–
7	DMF	CAN (1.0)	AcOH	120	20
8	DMF	$K_2S_2O_8$ (1.0)	AcOH	120	28
9	DMF	Oxone (1.0)	AcOH	120	32
10	DMF	Oxone (1.0)	TFA	120	42
11	DMF	Oxone (1.0)	Lactic acid	120	28
12	DMF	Oxone (1.0)	TMSCl	120	Trace
13	1,4-Dioxane	Oxone (1.0)	TFA	Reflux	Trace
14	*p*-Xylene	Oxone (1.0)	TFA	120	22
15	Toluene	Oxone (1.0)	TFA	Reflux	20
16	DMSO	Oxone (1.0)	TFA	120	30
17	EG	Oxone (1.0)	TFA	120	26
18	Glycerol	Oxone (1.0)	TFA	120	27
19	PEG-200	Oxone (1.0)	TFA	120	48
20	PEG-300	Oxone (1.0)	TFA	120	50
21	PEG-400	Oxone (1.0)	TFA	120	55
22	PEG-600	Oxone (1.0)	TFA	120	40
23	PEG-400	Oxone (0.8)	TFA	120	43
24	**PEG-400**	**Oxone (1.2)**	**TFA**	**120**	**68**
25	PEG-400	Oxone (2.0)	TFA	120	37
26	PEG-400	Oxone (1.2)	TFA	110	34
27	PEG-400	Oxone (1.2)	TFA	130	67
28	PEG-400	Oxone (1.2)	TFA	140	63

[a] Reagents and conditions: *N*,*N*-dimethylenaminone **1a** (1.0 mmol), 4-fluoroaniline **2a** (0.5 mmol), catalyst (0.2 mL), solvent (5.0 mL).
[b] Isolated yield based on *N*,*N*-dimethylenaminone **1a**.

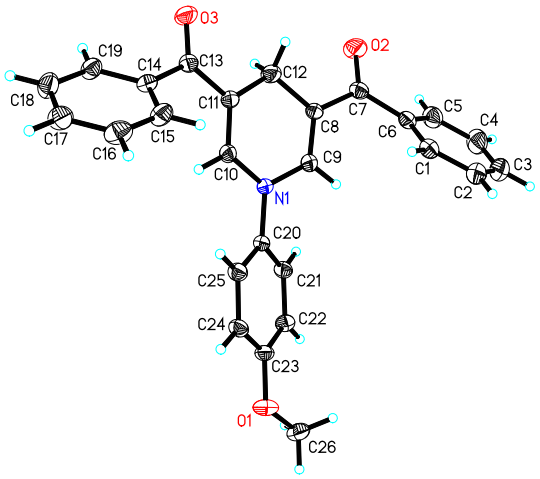
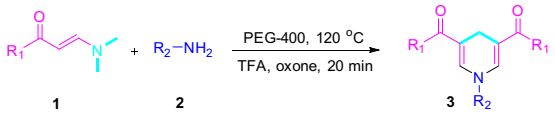


Figure 2. ORTEP diagram of **3ce**; ellipsoids are drawn at the 30% probability level.

To provide insights into the reaction mechanism, several control experiments were carried out (Scheme 2). For the reaction of *N*,*N*-dimethylenaminone **1c** and aniline **2c** in the absence of oxone, no **3cc** was detected. Instead, *N*-phenylenaminone **4a**[13a] was isolated in 95% yield (Scheme 2, Eq. 1). *N*-Phenylenaminone **4a** could react with **1c** under the standard condition to give **3cc** in an impressive 45% yield (Scheme 2, Eq. 2). Furthermore, while **4a**

Table 2
Substrate scope of the 1,4-DHPs **3**[a,b]



1 2 3

1a, R_1 = 4-FC_6H_4; **1b**, R_1 = 4-ClC_6H_4; **1c**, R_1 = Ph; **1d**, R_1 = 4-MeC_6H_4; **1e**, R_1 = 4-OMeC_6H_4;
2a, R_2 = 4-FC_6H_4; **2b**, R_2 = 4-ClC_6H_4; **2c**, R_2 = Ph; **2d**, R_2 = 4-MeC_6H_4; **2e**, R_2 = 4-OMeC_6H_4;
2f, R_2 = 3,5-(Me)2 C_6H_3; **2g**, R_2 = 3,4,5-(OMe) $_3C_6H_2$; **2h**, R_2 = cyclohexyl;

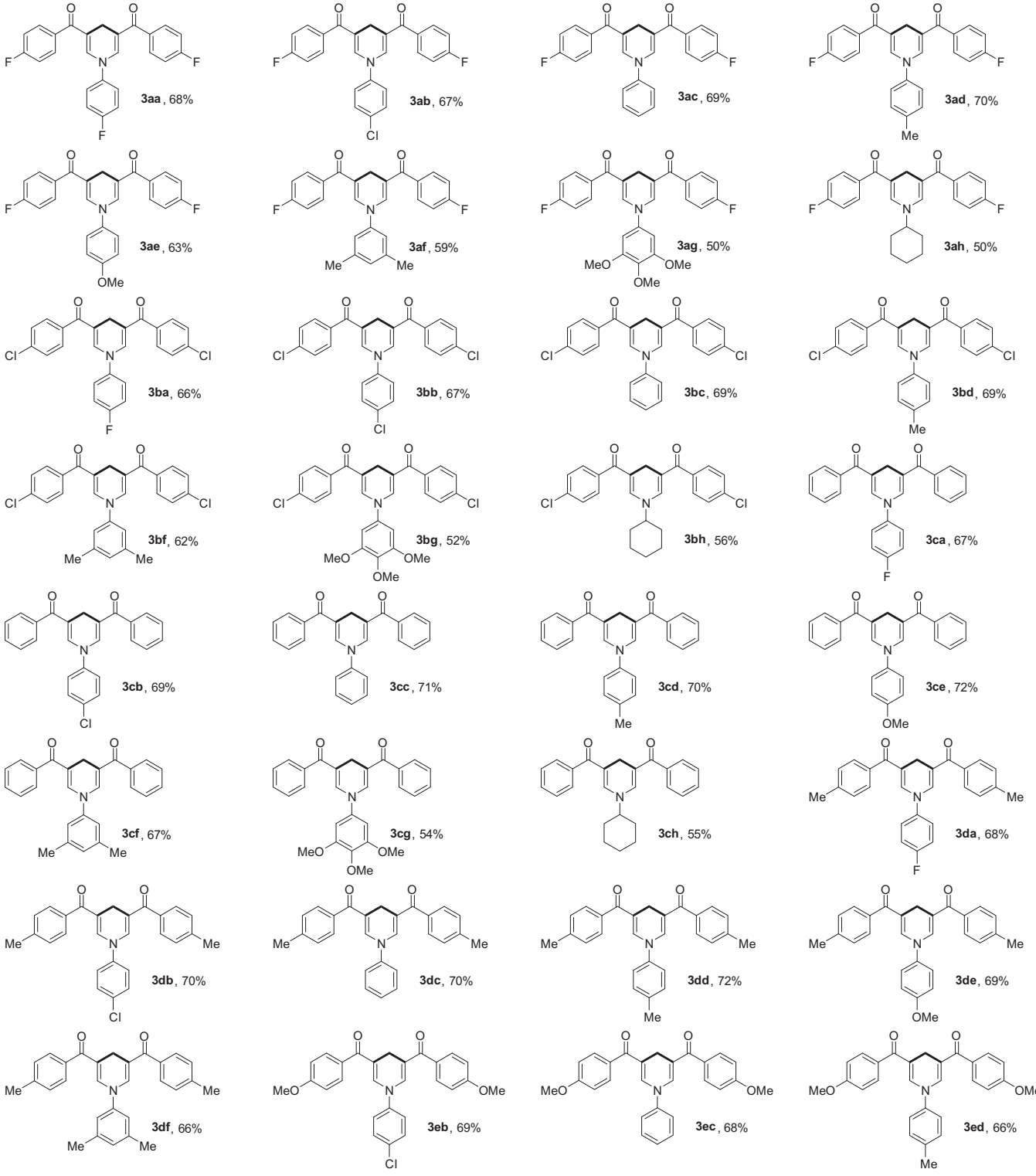


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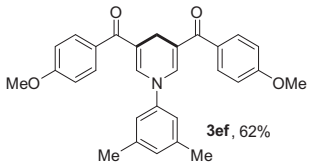
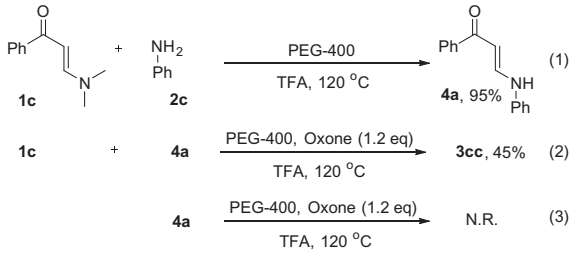
Table 2 (*continued*)



[a] Reagents and conditions: *N*,*N*-dimethylenaminones **1** (1.0 mmol), amines **2** (0.5 mmol), TFA (0.2 mL), oxone (1.2 equiv), PEG-400 (5.0 mL).
[b] Isolated yield based on *N*,*N*-dimethylenaminones **1**.



Scheme 2. Control experiments.

was subjected to react under the standard condition, no formation of **3cc** was detected (Scheme 2, Eq. 3). These results clearly indicated that oxone plays an important role in this reaction, and the 4-methylene of **3cc** is derived from dimethylamine formed in situ.

Based on these observations, it is safe to propose that in our system, oxone reacts with dimethylamine released from the amine-exchange of *N*,*N*-dimethylenaminone **1c**, giving rise to formaldehyde through the fragmentation of an unclear oxidized species. Afterwards, the in situ formed formaldehyde participates in a three-component condensation similar to the ones reported by the group of Wan.[12b–e]

Conclusion

In summary, we successfully developed an atom-economic method for the synthesis of structurally diverse 1,4-DHPs, from *N*,*N*-dimethylenaminones **1** and amines **2** via a unique oxidative three-component reaction under a green condition. Attempts to further understand the reaction mechanism and applications are underway in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization data and ^{1}H and ^{13}C NMR spectra of the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.118. These data include MOL files and InChiKeys of the most important compounds described in this article.

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15. *General Procedure for the synthesis of compounds* ***3aa****: N,N*-Dimethylenaminone **1a** (1.0 mmol), 4-fluoroaniline **2a** (0.5 mmol), PEG-400 (5 mL), oxone (1.2 equiv) and trifluoroacetic acid (TFA) (0.2 mL) were charged into a 25 mL round-bottom flask, and the mixture was stirred at 120 °C for 20 min until the *N,N*dimethylenaminones **1a** were completely consumed. The mixture was cooled to room temperature, neutralized with a saturated solution of Na_2CO_3 to pH 8–9, and then EtOAc (30 mL × 2) was added. The organic phase was washed with water (20 mL), dried over Na_2SO_4, concentrated and purified by flash column chromatography to afford 1,4-DHPs **3aa**. (*1-(4-Fluorophenyl)-1,4-dihydropyridine-3,5-diyl)bis((4-fluorophenyl)methanone*) (**3aa**): yellow solid; mp 164–166 °C; IR (KBr): 1662, 1632, 1599, 1505, 1396, 1232, 1147, 1105, 837, 751, 596 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.60 (s, 2H, CCH_2C), 7.03 (s, 2H, C=CHN), 7.06–7.14 (m, 8H, ArH), 7.61–7.65 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 116.0, 116.0 (d, J = 21.6 Hz), 117.3, 117.4 (d, J = 22.9 Hz), 123.4 (d, J = 8.4 Hz), 131.1 (d, J = 8.7 Hz), 135.3 (d, J = 2.7 Hz), 139.7, 141.5, 161.4 (d, J = 246.6 Hz), 164.8 (d, J = 250.5 Hz), 193.5; HRMS (TOF ES^+): m/z calcd for $C_{25}H_{17}F_3NO_2$ [$(M+H)^+$], 420.1206; found, 420.1209.
16. CCDC 1026867 contains the supplementary crystallographic data of compound **3ce**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.