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Cascade synthesis of 1,2-dihydropyridine from dienaminodioate and an imine: a three-component approach

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ABSTRACT

A convenient synthesis of 1,2-dihydropyridine (1,2-DHP) has been developed from dienaminodioate and an imine mediated by trifluoroacetic acid in a one-pot cascade synthesis. The advantages associated with this transformation include conditions that are metal-free, room temperature, undistilled solvent, and expeditious in excellent yields. The substrate scope has been demonstrated with various aromatic, heteroaromatic, unsaturated aldehydes, and anilines, benzylic amines in impressive yields.

The chemistry of dihydropyridines (DHPs) dates back to more than a century when Hantzsch published their synthesis in 1882.[1] Since then, DHPs have been given a prominent place in organic synthesis due their prevalence as intermediates in the synthesis of a broad variety of pyridine derivatives.[2] Among the DHPs, 1,4-dihydropyridines (1,4-DHPs) are well studied scaffolds in pharmaceuticals as calcium channel modulating agents viz. Nifedipine, Amlodipine, Lacidipine, Diludine, etc.[3] However, 1,2-DHPs are relatively unexplored for their biological potential which makes them a prospective candidate structure for the design of heterocyclic drug libraries. 1,2-DHPs are regarded as important synthetic intermediates for conversion to pyridine, piperidine and pyridone derivatives,[4] as a diene component in Diels–Alder reaction,[5] and as a key intermediate in the synthesis of marine natural product oroidin.[6] Some of the key synthetic approaches towards 1,2-DHPs include [4+2] cycloaddition of azadienes and phosphazenes,[7] cascade synthesis using starting materials such as acetylenic esters, propargyl vinyl ethers, enaminones[8] and nucleophilic addition onto *N*-acyl or alkylpyridinium salts.[9] Recently, transition metal catalysts were engaged in the synthesis of 1,2-DHPs in a sequential manner utilizing substrates such as propargyl vinyl ethers, α,β-unsaturated *N*-benzyl aldimines, aziridinyl propargylic esters, furans, vinyloxiranes and pyridines.[10] By and large, some of the disadvantages associated with the reports, vide supra, for the synthesis of 1,2-DHPs include harsh conditions, metal-catalyst, long reaction time, moisture sensitive and multi-step sequence with moderate to low yields. Recently, several reports (see references) towards the synthesis of 1,2-DHPs have been published which accentuate its importance by synthetic community. Herein, we report the use of a less explored substrate *sec*-(allylamino)-dienaminodioate **2** (Fig. 1) in a one-pot cascade reaction with in situ generated imine to afford 1,2-DHP, under mild conditions, possessing two diversity elements and two reactive ester groups which can be employed in building diversity oriented synthetic library of 1,2-DHPs.

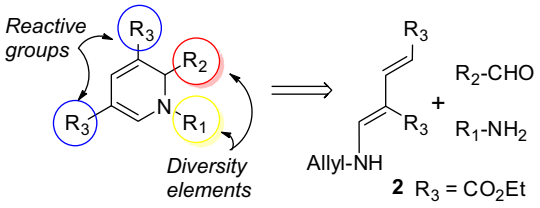

Figure 1. Proposed one-pot synthesis of 1,2-DHP from dienaminodioate **2**.

We serendipitously discovered the formation of dienaminodioate **2** during our attempts to epoxidize enaminoate **1** (Scheme 1) in the presence of mCPBA.[11] Dienaminodioate **2** formation was initially realized by Bottomley et al. by conjugate addition of amines to methyl propiolate.[12] Utilization of **2** as a substrate towards its derivatives was restricted to the synthesis of pyrroles, and pyridinones by bromocyclization.[13] While dienaminodioate was never utilized in the synthesis of DHPs, enaminoate was used as a substrate in Lewis acid induced cyclization for the synthesis of 1,4-DHP.[14] To expand the scope of utilization of **2** and inspired by a variant of Povarov reaction which utilizes imine and enamine,[15] we envisioned synthetic utility of **2** as a suitable enamine component for the synthesis of functionalized DHPs and other pyridine

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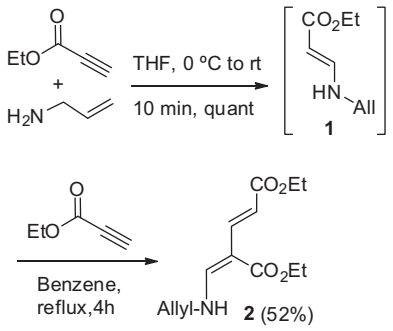
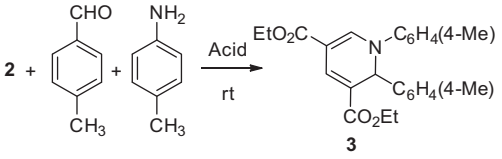


Scheme 1. One-pot synthesis of dienaminodioate **2**.

derivatives. Thus, to unveil the synthetic potential of dienamino diesters in the construction of heterocyclic compounds we set forth to synthesize **2** using ethyl propiolate as the starting material (Scheme 1). A one-pot sequential reaction with ethyl propiolate and allyl amine generated enaminoate **1** in a quantitative yield. As our initial attempt using mCPBA offered **2** in a very low yield, we adopted an alternative method[16] of treating **1** after evaporation in the same pot with one more equivalent of ethyl propiolate in benzene which under reflux afforded **2** in a good yield.[17]

Initial investigation with an aromatic imine derived in situ from 4-methylbenzaldehyde and *p*-toluidine as model substrates in a one-pot cascade reaction with **2** in the presence of catalytic amount of trifluoroacetic acid (TFA) afforded a yellow coloured spot on TLC in a trace amount which after isolation was characterized as 1,2-DHP **3** (Table 1), as expected. The ^{1}H NMR analysis of **3** shows two discernible singlets for olefinic protons at δ 7.70 and 8.05 ppm. A characteristic splitting pattern of the ethyl group of both the esters akin to 1,2- and 1,4-DHPs, presence of both the phenyl groups which was evident from the integration, established the structure of **3**. The mechanistic rationale behind the primary event during the cascade sequence could be realized as a hetero Diels–Alder cycloaddition as proposed by Palacios et al. in their

Table 1
Optimization of reaction conditions for the synthesis of 1,2-DHP **3**



3

Entry[a]	Acid	Solvent[b]	Time	Yield[c] (%)
1	TFA	CH_3CN	45 min	95
2	TMSOTf	CH_3CN	8 h	12
3	*p*-TsOH	CH_3CN	8 h	27
4	4 M HCl in Dioxane	CH_3CN	7 h	30
5	$BF_3{\cdot}Et_2O$	CH_3CN	1.5 h	68
6	$FeCl_3$	CH_3CN	11 h	38
7	AcOH	CH_3CN	24 h	61
8	TCA	CH_3CN	1.4 h	82
9	TFA	CH_2Cl_2	45 min	84
10	TFA	EtOH	4 h	61
11	TFA	THF	4 h	93
12	TFA	CH_3CN	4 h	92
13	TFA	CH_3CN	45 min	95
14	TFA	CH_3CN	45 min	94

Abbreviations: TFA = trifluoroacetic acid, TMSOTf = trimethylsilyl triflate, *p*-TsOH = *p*-toluenesulfonic acid.

[a] All reactions were carried out with 1.2 equiv of both aldehyde and amine, and 1 equiv of acid except for entries 12–14 where 0.25, 1.5, and 2.5 equiv were used, respectively.

[b] Solvents were used without distillation.

[c] Isolated yields.

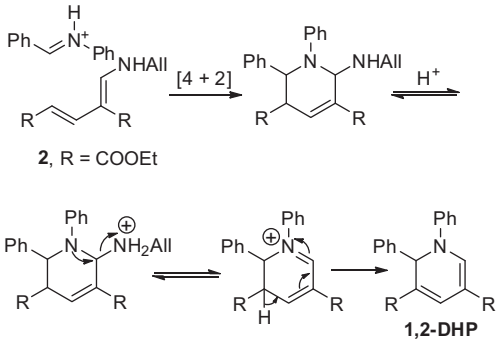
1,2-DHP synthesis,[7] followed by elimination of allyl amine in the presence of an acid and rearrangement to afford 1,2-DHP (Scheme 2).

Encouraged by this result we proceeded to optimize the reaction conditions for affording 1,2-DHP using different acids (Table 1). Initial attempt with TFA (25 mol %) using CH_3CN as the solvent provided 1,2-DHP **3** in an impressive 92% yield (entry 12) at room temperature. To avoid longer reaction time we increased TFA concentration to stoichiometric amount (1 equiv) which led to complete formation of the product in just 45 min with 95% yield (entry 1). Increase in the number of equivalents to 1.5 or 2.5 led to no considerable change in time or yield of the product (entries 13–14). Change of solvent to CH_2Cl_2, EtOH or THF (entries 9–11) led to longer reaction time with 1 equiv of TFA. To ascertain the generality of the acid, investigation of other common acids in stoichiometric amounts (entries 2–6) led to a decrease in yield of 1,2-DHP with longer reaction time. Interestingly, usage of 1 equiv of acetic acid and trichloroacetic acid (entries 7–8) showed the influence of pK_a over the outcome of the reaction with respect to yield and time. Therefore, usage of 1 equiv of TFA and CH_3CN as the solvent was chosen as the optimized conditions for one-pot cascade synthesis of 1,2-DHP. To determine the mildness of our approach, all reactions were conducted without distillation of solvents and in the absence of inert atmosphere.

The scope of this transformation by variation of different aldehydes was studied using *p*-toluidine as the amine component under optimized conditions (Table 2).[18] Aromatic aldehydes, in general, gave good yields of 1,2-DHP **4** in less than 2 h (entries 1–6). Heteroaromatic aldehydes, however, took longer reaction time with the desired 1,2-DHPs as major products along with other impurities (entries 7–8). Polycyclic aromatic hydrocarbons showed similar behaviour towards reactivity as simple aromatic hydrocarbons without offering any steric hindrance in the formation of 1,2-DHPs (entries 9–10).

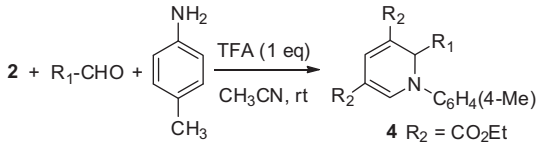
The substrate scope was further investigated by variation of amines along with a few representative aldehydes for the formation of 1,2-DHP **5** (Table 3). The results were as expected with impressive yields showing tolerance towards both electron releasing and withdrawing substituents in the para position (entries 1–12). Even benzylic amines (entries 13–16) offered decent yields for this transformation which prompted us to try butylamine but we observed the product formation **5q** (entry 17) in a lower yield under the reaction conditions. Interestingly, attempts with α,β-unsaturated aldehydes also yielded 1,2-DHPs in a moderate to good yield (entries 18–21).

In summary, we have developed a one-pot cascade reaction of in situ generated imine with dienaminodioate **2** for the formation of 1,2-dihydropyridines. A broad aromatic substrate scope with various aromatic, heteroaromatic, unsaturated aldehydes, and anilines, benzylic amines in impressive yields, demonstrates synthetic utility in diversification of 1,2-DHPs to produce pharmaceutically



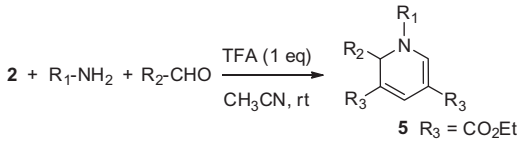
Scheme 2. Proposed formation of 1,2-DHP.

Table 2
Substrate scope: cascade synthesis of 1,2-DHP **4** by variation of aldehydes



Entry	R_1	Product	Yield (%)
1	Ph	**4a**	87
2	4-Cl-C_6H_4	**4b**	75
3	4-Br-C_6H_4	**4c**	74
4	4-CN-C_6H_4	**4d**	91
5	4-NO_2-C_6H_4	**4e**	96
6	4-MeO-C_6H_4	**4f**	77
7	5-Methyl-thiophene-2-	**4g**	75
8	Furan-2-	**4h**	75
9	Naphthalene-2-	**4i**	84
10	Pyrene-1-	**4j**	79

Table 3
Substrate scope: cascade synthesis of 1,2-DHP **5** by variation of aldehydes and amines



Entry	R_1	R_2	Product	Yield (%)
1	Ph	Ph	**5a**	98
2	4-MeO-C_6H_4	4-MeO-C_6H_4	**5b**	97
3	4-MeO-C_6H_4	4-NO_2-C_6H_4	**5c**	93
4	4-MeO-C_6H_4	4-CN-C_6H_4	**5d**	80
5	4-MeO-C_6H_4	4-Cl-C_6H_4	**5e**	95
6	4-Cl-C_6H_4	4-MeO-C_6H_4	**5f**	97
7	4-Cl-C_6H_4	4-NO_2-C_6H_4	**5g**	98
8	4-Cl-C_6H_4	4-CN-C_6H_4	**5h**	75
9	4-I-C_6H_4	4-MeO-C_6H_4	**5i**	65
10	4-I-C_6H_4	4-CN-C_6H_4	**5j**	71
11	4-I-C_6H_4	4-Cl-C_6H_4	**5k**	70
12	4-F-C_6H_4	4-NO_2-C_6H_4	**5l**	91
13	Benzyl	4-Me-C_6H_4	**5m**	94
14	4-F-Benzyl	4-Me-C_6H_4	**5n**	42
15	Benzyl	4-NO_2-C_6H_4	**5o**	69
16	4-F-Benzyl	4-NO_2-C_6H_4	**5p**	89
17	4-MeO-C_6H_4	Propyl	**5q**	22
18	4-Me-C_6H_4	Prop-1-enyl	**5r**	66
19	4-Me-C_6H_4	Styryl	**5s**	69
20	4-Me-C_6H_4	4-NO_2-Styryl	**5t**	37
21	4-Me-C_6H_4	4-MeO-Styryl	**5u**	30

important libraries. The advantages associated with this transformation over the current methods of 1,2-DHP synthesis include conditions that are metal-free, one-pot, room temperature, usage of undistilled solvent and expeditious in excellent yields. Our further endeavours involve utilization of bifunctional aldehydes/amines to expand the substrate scope of this transformation, and derivatization of 1,2-DHPs.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.037.

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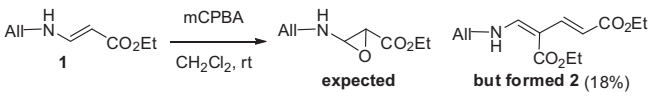
11. 

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17. To a solution of allyl amine (382 μL, 5.09 mmol) in THF was added ethyl propiolate (520 μL, 5.09 mmol) slowly at 0 °C and warmed to room temperature. After 10 min, the reaction mixture was concentrated and the resulting enaminoate **1** was dissolved in benzene (5 mL). To the reaction mixture ethyl propiolate (520 μL, 5.09 mmol) was added and stirred under reflux for 4 h at 100 °C. The reaction mixture was then concentrated and purified by flash column chromatography (10:1 hexane/EtOAc) affording dienaminodioate **2** (669 mg, 52%) as a light yellow oily product. R_f 0.3 (hexane/EtOAc 4:1); ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7 Hz, –$CO_2CH_2CH_3$), 1.35 (t, 3H, J = 7 Hz, –$CO_2CH_2CH_3$), 3.89 (app t, 2H, J = 5.5 Hz, –CH_2–CH), 4.18 (q, 2H, J = 7 Hz, –$CO_2CH_2CH_3$), 4.25 (q, 2H, J = 7 Hz, –$CO_2CH_2CH_3$), 5.24 (m, 2H, –CH=CH_2), 5.86 (ddt, 1H, J = 5.5, 10.5, 16 Hz, –CH=CH_2), 6.03 (d, 1H, J = 15.5 Hz, CH=$CHCO_2$Et), 7.19 (d, 1H, J = 13.5 Hz, C=CH), 7.39 (d, 1H, J = 15.5 Hz, CH=$CHCO_2$Et), 8.94 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.4, 14.4, 51.1, 59.6, 59.8, 95.3, 108.2, 117.9, 133.4, 143.2, 156.9, 168.8,169.1; ESI-HRMS [M+Na]$^+$ $C_{13}H_{19}NO_4Na$ calcd for m/z 276.12118, found 276.12000.
18. *General procedure for 1,2-DHP synthesis.* To a solution of **2** in CH_3CN was added pertinent aldehyde (1.2 equiv), amine (1.2 equiv), and TFA (1.0 equiv) in a sequence at room temperature. The reaction mixture usually develops a bright yellow color within 15 min which is an indication of the formation of 1,2-DHP. After complete consumption of **2**, as observed on TLC, the reaction mixture was quenched with saturated $NaHCO_3$, extracted with ethyl acetate, dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash column chromatography to afford 1,2-DHP derivative.