Tetrahedron Letters 52 (2011) 3455–3459

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Sequential three-component reactions: synthesis, regioselectivity and application of functionalized dihydropyridines (DHPs) for the creation of fused naphthyridines

Abu T. Khan *, Md. Musawwer Khan

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781 039, India

ARTICLE INFO

Article history:
Received 3 February 2011
Revised 25 April 2011
Accepted 26 April 2011
Available online 1 May 2011

Keywords:
Sequential multicomponent reactions
Dihydropyridines
Imino-Diels–Alder reactions
Substituted naphthyridines

ABSTRACT

Facile and efficient synthesis of tetrasubstituted 1,4- and 1,6-dihydropyridines (DHPs) has been achieved by employing three-component domino reaction using dimethyl acetylenedicarboxylate (DMAD), aliphatic amines, and α,β-unsaturated aldehyde in the presence of 30 mol % trifluoroacetic acid. Interestingly, regioselectivity for the synthesis of 1,4-dihydropyridines can be increased by using 30 mol % triflic acid. In addition, the synthesis of fused-naphthyridine derivatives has been accomplished involving imino-Diels–Alder reaction by employing 1,4-dihydropyridines, aromatic aldehydes, and aromatic amines.

Multi-component reactions (MCRs) have been proven to be an elegant and sophisticated approach to access complex structures in a single step from readily available synthetic precursors.[1] Superior atom economy, simpler procedures, lower costs, high variability, and high bond forming efficiency (BFE) are some important features of MCRs.[2]

Nitrogen containing heterocycles are widely distributed in natural products and pharmaceutically important small molecules. Among them, dihydropyridines (DHPs) represent an important class of the nitrogen-heterocycle. They exhibit a diverse range of biological activities[3] such as those for the treatment of cardiovascular disease and hypertension,[4] potent calcium channel antagonist, and agonist.[5] They also have potential application in other pharmacological activities.[6–10] In addition, they have been used as a hydride source for reductive amination[11] and used as synthetic intermediates.[12,13] After the first synthesis of dihydropyridines reported by Hantzsch,[14] many synthetic efforts have been made from all over the world to access these compounds due to their medicinal and synthetic usefulness.[15,16] In this Letter, we wish to report a three-component domino reaction for the synthesis of unsymmetrically substituted 1,4- and 1,6-DHPs, an improved method for regioselective synthesis of 1,4-DHPs and its application for the synthesis of naphthyridine derivatives using imino-Diels–Alder reaction.

With this objective, the reaction of dimethyl acetylenedicarboxylate (DMAD, **1**, 1 mmol), benzylamine (**2a**, 1 mmol), and crotonaldehyde (**3a**, 1 mmol) was carried out with 20 mol % of trifluoroacetic acid (TFA) in dicholoromethane and afforded two products **4a** and **5a** with overall 62% yield with the ratio of 56:44. The structures of compounds **4a** and **5a** were determined by IR, ^{1}H NMR, ^{13}C NMR spectra and from their elemental analysis. After obtaining the desired products, a suitable reaction condition was tried to find out both in terms of yield and selectivity of products. A series of experiments were performed with various catalysts such as TFA, acetic acid, pTSA, and triflic acid (TfOH) by varying the amounts of catalysts. Different solvents, such as DCM, DCE, MeOH, MeCN, THF, and toluene were also screened. The results and observations are summarized in Table SI-1, (Supplementary data). From these experiments, two optimized reaction conditions were obtained. Method A in which both the products **4a** and **5a** were obtained nearly in equal amounts with 82% overall yield from the reaction of **1**, **2a**, and **3a** using 30 mol % of TFA in THF. In method B a regioselective 1,2,3,4-tetrasubstituted dihydropyridine (**4a**) was obtained in 76% yield using TfOH acid (30 mol %) in THF.

After optimizing the reaction conditions, the reaction was performed with DMAD (**1**, 1 mmol), *n*-butylamine (**2b**, 1 mmol), and crotonaldehyde (**3a**, 1.2 mmol) by the following method A. Both the products **4b** and **5b** were obtained in the ratio of 55:45, respectively with 83% being the total yield. The scope of this protocol was further examined with various aliphatic amines, such as *iso*-butylamine, *iso*-propylamine, *n*-hexylamine, cyclohexylamine, and furfurylamine. The corresponding dihydropyridine derivatives **4c–g**

* Corresponding author. Tel.: +91 361 2582305; fax: +91 361 2582349.
E-mail address: atk@iitg.ernet.in (A.T. Khan).

0040-4039/$ - see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2011.04.098

and **5c**–**g** were obtained in good yields and the ratio of the products is shown in Table 1 (entries 3–7).

We turned our attention toward synthesis of regioselective 1,4-DHPs by the following method B. The mixture of DMAD (**1**, 1 mmol), *n*-butylamine (**2b**, 1 mmol) and crotonaldehyde (**3a**, 1.2 mmol) was stirred using method B and the major product **4b** was obtained in 72% yield.

Encouraged by this result, the reaction of various other amines, such as *iso*-butylamine, *iso*-propylamine, *n*-hexylamine, cyclohexylamine, furfurylamine, and ethylamine was also studied with DMAD and crotonaldehyde under identical reaction conditions. The reaction time and percentage yield of the products **4c**–**h** are summarized in Table 1.

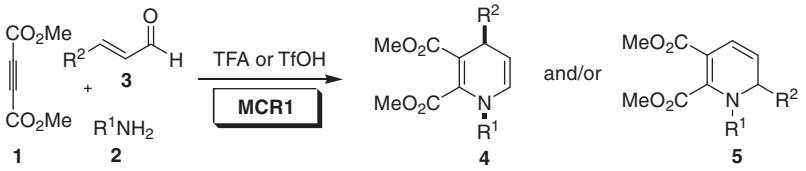
Cinnamaldehyde exhibits similar regioselectivity pattern in both protocols as mentioned in Table 1, however method B furnished good yields of products **4i** and **j**. All these products were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectra as well as elemental analysis. The structure of compound **4i** was confirmed by X-ray crystallographic analysis (Fig. SI1). The present methods were unsuccessful for the synthesis of substituted *N*-aryl dihydropyridines using aniline by following both the methods; this may be due to less nucleophilicity of aniline as compared to aliphatic amines.

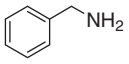
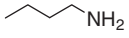
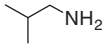
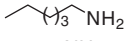
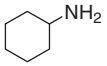
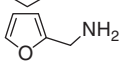
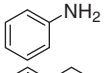
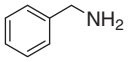
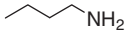
We propose a plausible mechanism for the formation of 1,4 and 1,6-DHPs. Initially, the amine reacts with DMAD to form hydroamination product **A**. The intermediate **A** reacts with α,β-unsaturated aldehyde in two ways either *path a* or *path b*. In *path a*, the intermediate **A** on reaction with α,β-unsaturated aldehyde leads to the formation of intermediate imine **B** which on electrocyclic cyclization gives the 1,4-dihydropyridine derivative **4**. In *path b*, the intermediate **C** is formed from the intermediate **A** on reaction with α,β-unsaturated aldehyde via Michael addition reaction. Finally, 1,6-dihydropyridine derivative **5** is obtained through cyclization from **C** followed by dehydration as shown in Scheme 1. We believe that *path a* is preferred to *path b* in the case of TfOH ($pK_a = -15$) which is highly acidic as compared to TFA ($pK_a = 0.5$), which favors imine formation by protonation of the carbonyl group as compared to Michael addition reaction.

The synthetic utility of 1,4-DHPs as a dienophile in imino-Diels–Alder reaction (Povarov reaction),[17] has been demonstrated for the synthesis of substituted naphthyridine derivatives for the creation of molecular diversity. The applications of 1,4-dihydropyridine as a dienophile have been described for Povarov reaction by others.[13] However, the newly designed 1,2,3,4-tetrasubstituted dihydropyridines having α and β amino acid functionality have remained unexplored, which may offer a new platform for the synthesis of different substituted naphthyridine derivatives.

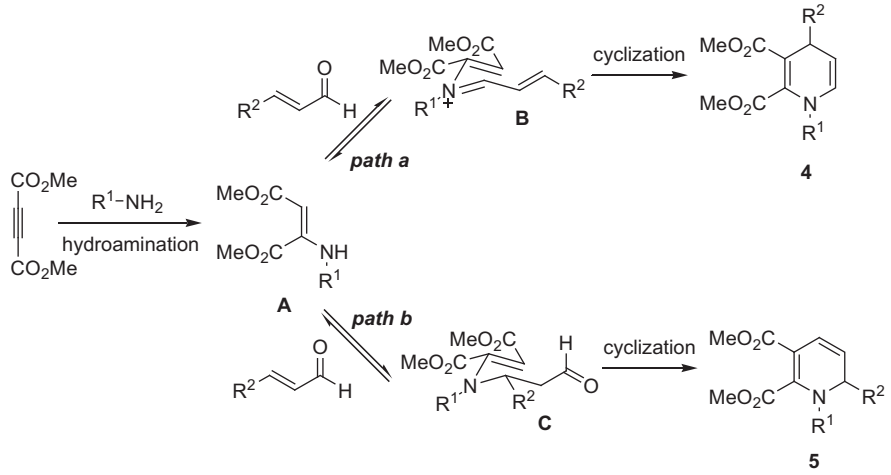
With this idea in mind, a three component one-pot reaction was conducted with 1,4-DHP (**4a**), benzaldehyde, and aniline catalyzed by 20 mol % of $BF_3{\cdot}OEt_2$ in acetonitrile. The cycloaddition reaction

Table 1
Synthesis of various 1,2,3,4- and/or 1,2,3,6-tetrasubstituted dihydropyridines **4** and **5**[19]



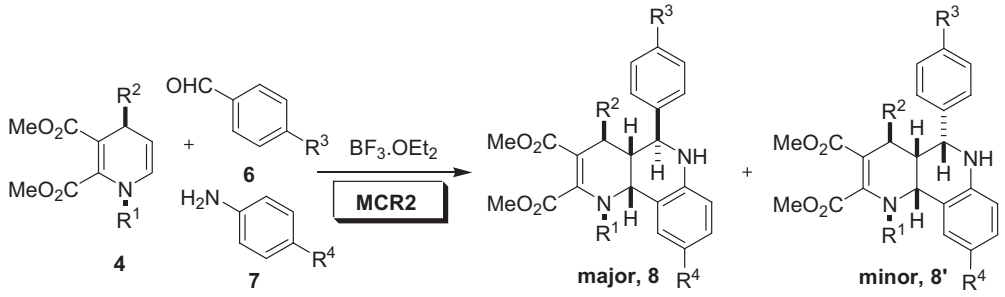
Entry	R^1NH_2	R^2	Method A		Method B	
			Ratio[a] (**4**:**5**)	Yield[b](%)	Ratio[a] (**4**:**5**)	Yield[c] (%)
1		Me	51:49	82	88:12	**4a**, 76
2		Me	55:45	83	86:14	**4b**, 72
3		Me	58:42	83	87:13	**4c**, 75
4		Me	60:40	82	83:17	**4d**, 69
5		Me	55:45	82	86:14	**4e**, 72
6		Me	54:46	81	88:12	**4f**, 73
7		Me	48:52	83	86:14	**4g**, 72
8		Me			78:22	**4h**, 57
9		Me	No reaction	—	—	No reaction
10		Ph	80:20	59	82:18	**4i**, 62
11		Ph	75:25	56	80:20	**4j**, 58

Method A: DMAD (1 mmol), Amines (1 mmol), enals (1.2 mmol) and TFAA (0.3 mmol) in THF at rt.
Method B: DMAD (1 mmol), Amines (1 mmol), enals (1.2 mmol) and TfOH (0.3 mmol) in THF at rt.
[a] Product ratio determined by crude ^{1}H NMR.
[b] Combined yields of **4** and **5**.
[c] Isolated yields.



Scheme 1. Proposed mechanism for amination reaction of DMAD promoting for cascade reaction.

Table 2
Synthesis of substituted naphthyridine derivatives **8**[20]



Entry	R^1	R^3	R^4	Time (h)	Ratio[a]	Yield[b] (%)
1	Bn	H	H	6	4:1	**8a**, 65
2	Bn	Me	H	6	3:1	**8b**, 61
3	Bn	MeO	H	6	4:1	**8c**, 63
4	Bn	Cl	H	8	4:1	**8d**, 54
5	Bn	Br	H	8	4:1	**8e**, 62
6	Bn	NO_2	H	10	3:1	**8f**, 51
7	Bn	Cl	MeO	6	2:1	**8g**, 52 **8g′**, 21
8	Bn	Cl	Me	6	2:1	**8h**–**h′**, 76
9	*n*-C_4H_9	H	H	10	3:1	**8i**, 59

[a] Ratio determined by crude ^{1}H NMR.
[b] Isolated yield.

afforded two diastereomers **8a** and **8a′** with a ratio of 4:1. The major isomer **8a** was isolated in 65% yield. Likewise, the reaction of **4a** with aniline and other aromatic aldehydes substituted with Me, MeO, Cl, Br, and NO_2 at position 4 was also investigated. The reactions proceeded smoothly and various substituted naphthyridine derivatives **8b**–**f** were obtained in good yields. The reaction of aniline derivatives such as 4-methylaniline and 4-methoxyaniline was also studied under similar conditions and the results are summarized in Table 2. Similar diastereoselectivity was observed by others[18] for imino-Diels–Alder reaction with an electron rich dienophile. However, we have obtained relatively lower diastereoselectivity in the case of 4-methyl aniline and 4-methoxyaniline due to steric repulsion between the benzyl group and a methyl or methoxy group present at the 4th-position. Finally, the reaction of 1,4-DHP **4b** with benzaldehyde and aniline was performed and gave major isomer **8i** in 59% yield.

The functionalized naphthyridine derivatives have four contiguous stereocenters, and gave only two diastereoisomers. A fairly good diastereoselectivity was observed in the above study. The structures of all the compounds were ascertained by usual spectroscopic studies as well as the literature precedent.[13] For example, the structure of compound **8i** was established by NMR (^{1}H, ^{13}C, COSY, NOESY). This isomer shows ^{1}H NMR peaks with δ values 4.42, 1.93, and 4.16 for H_1, H_2, and H_4, all having doublets with coupling constants $J_{1,2}$ = 2.0 Hz and $J_{2,4}$ = 10.8 Hz, representing *cis* arrangement of hydrogen between two ring fusions. The proton H_4 is *trans* with ring junction proton H_2. In addition, H_1, H_2, and Me are all in same plane, however, H_3 and H_4 are in other planes depicted by NOE as shown in Figure 1. Finally, the observed structure and stereochemistry were fully supported by single crystal X-ray structure determination of compound **8b** (major isomer) and **8g′** (minor isomer) as shown in Figure 2.[21]

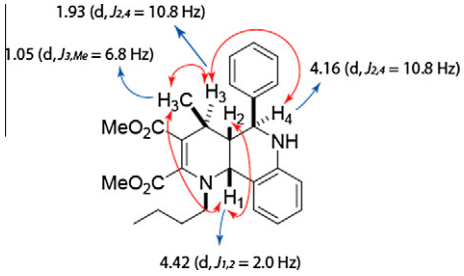
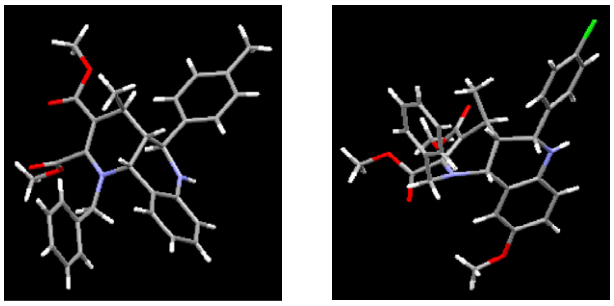


Figure 1. Diagnostic ^{1}H NMR and NOE of **8i**.



8b (CCDC no. 810814) **8g'** (CCDC no. 810813)

Figure 2. X-ray crystal structures of **8b** and **8g′**.

In conclusion, the Brønsted acid catalyzed synthesis of unsymmetrical tetrasubstituted 1,4- and 1,6-DHPs using one-pot three-component reactions of DMAD, aliphatic amines, and α,β-unsaturated aldehydes have been accomplished. The regioselective synthesis of tetrasubstituted 1,4-DHPs were also achieved in good yields. These 1,4-DHPs can be used for a new class of dienophiles for imino-Diels–Alder reaction for the construction of highly substituted naphthyridine derivatives. The significant advantages of present protocol are simple experimental procedure, nontoxic byproduct, high atom economy, good regioselectivity, and diastereoselectivity. The new heterocyclic entities containing β-amino acid skeleton might exhibit interesting pharmacological activities. Further studies on regioselectivity and applications of these DHPs are going on in our laboratory which will be reported in due course of time.

Acknowledgment

M.M.K. is grateful to the UGC, New Delhi, India for research fellowship. We are also thankful to Dr. S. Ranganathan, Assistant Professor, IIT Patna for necessary correction of the manuscript. The authors are greatful to the referees for their valuable comments and suggestions.

Supplementary data

Supplementary data (optimization table, X-ray crystallographic data (CIF file) of **4i**, **8b** and **8g′**, spectral data of all compounds and copies of ^{1}H and ^{13}C NMR spectra of products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.098.

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19. *General procedure for 1,4- and 1,6-dihydropyridines **4** and **5***: Method A: To a stirred solution of dimethyl acetylenedicarboxylate **1** (DMAD, 1.0 mmol) in THF (2 mL) was added amine **2** (1.0 mmol) at room temperature. After 10 min of stirring, α,β-unsaturated aldehyde **3** (1.2 mmol) and trifluoroacetic acid (0.3 mmol) were added successively and kept for further stirring. After completion of reaction (monitored by TLC), the reaction mixture was neutralized with $NaHCO_3$ solution and it was extracted with DCM (20 mL × 2). The organic phase was washed with water, brine solution, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude mixture was purified through silica gel chromatography using hexane/ethyl acetate/NEt_3 (92:7:1) and it afforded the products **4a–j** and **5a–j**, respectively in good yields. For Method B, the same procedure was followed except that the catalyst triflic acid (30 mol %) is used in place of TFA. *Compound* **4a**: yellow liquid (126 mg, 42%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.24 (m, 5 H), 5.75 (d, 1H, J = 7.2 Hz), 4.87 (dd, 1H, J = 7.2 Hz, J = 5.6 Hz), 4.36 (d, 1H, J = 16.4 Hz), 4.28 (d, 1H, J = 16.4 Hz), 3.78 (s, 3H), 3.68 (s, 3H), 3.39–3.32 (m, 1H), 1.08 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 166.1, 144.3, 137.0, 128.9, 128.0, 127.6, 127.3, 110.6, 101.2, 54.6, 52.9, 51.6, 27.1, 25.3; IR ν_{max} (KBr): cm^{-1} 2951, 1739, 1695, 1575, 1434, 1269, 1216, 1187, 734. Anal Calcd for $C_{17}H_{19}NO_4$ (301.34): C, 67.76; H, 6.36; N, 4.65; found: C, 67.71; H, 6.32; N, 4.58. *Compound* **5a**: yellow liquid (121 mg, 40%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.29 (m, 5H), 6.41 (d, 1H, J = 9.6 Hz), 5.02 (dd, 1H, J = 9.6 Hz, J = 5.2 Hz), 4.37 (d, 1H, J = 15.6 Hz), 4.30 (d, 1H, J = 15.6 Hz), 3.98–3.93 (m, 1H), 3.87 (s, 3H), 3.71 (s, 3H), 1.14 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 166.0, 147.9, 136.4, 128.9, 128.2, 127.7, 121.3, 114.9, 97.8, 54.4, 53.1, 52.7, 51.3, 19.2; IR ν_{max} (KBr): cm^{-1} 2950, 1739, 1693, 1542, 1434, 1297, 1230, 1125, 728. Anal Calcd for $C_{17}H_{19}NO_4$ (301.34): C, 67.76; H, 6.36; N, 4.65; found: C, 67.70; H, 6.31; N, 4.60.
20. *General procedure for synthesis of substituted tetrahydroquinoline derivatives* **8**: 1,4-DHP **4a** (0.3 mmol) was added to a stirring solution of aromatic aldehyde (0.3 mmol) and aromatic amine (0.3 mmol) in acetonitrile (2 mL). Finally, catalyst $BF_3{\cdot}OEt_2$ (20 mol %) was added to the reaction mixture and stirring was continued. After completion of the reaction (monitored by TLC), the mixture was extracted with DCM (20 mL × 2). The organic phase was washed with saturated solution of $NaHCO_3$, brine solution, and dried over Na_2SO_4. The

crude products were purified by silica gel chromatography (hexane/ethyl acetate, 85:15) to afford the products **8a–i** in good yields. *Compound* **8a**: White solid (94 mg, 65%); mp 242–245 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.28 (m, 5H), 7.28–7.23 (m, 2H), 7.18–7.12 (m, 2H), 7.10 (t, 2H, J = 7.2 Hz), 6.63 (d, 1H, J = 7.6 Hz), 6.51–6.47 (m, 2H), 4.42 (d, 1H, J = 2.8 Hz), 4.29 (d, 1H, J = 16.8 Hz), 4.25 (d, 1H, J = 10.8 Hz), 4.17 (s, 1H), 4.14 (d, 1H, J = 16.8 Hz), 3.78 (s, 3H), 3.65 (s, 3H), 2.43–2.36 (m, 1H), 1.92 (d, 1H, J = 10.8 Hz), 1.09 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 166.9, 147.9, 144.3, 143.0, 137.6, 131.9, 130.2, 128.7, 128.6, 128.2, 128.0, 127.2, 127.1, 115.7, 115.6, 113.8, 98.3, 56.0, 52.8, 52.1, 51.2, 41.8, 26.9, 23.1; IR ν_{max} (KBr): cm^{-1} 3413, 2955, 1744, 1683, 1573, 1498, 1224, 1142, 1088, 735. Anal Calcd for $C_{30}H_{30}N_2O_4$ (482.57): C, 74.67; H, 6.27; N, 5.81; found: C, 74.61; H, 6.14; N, 5.71.

21. Complete crystallographic data of **4i**, **8b,** and **8g**′ for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 810812, 810814 and 810813, respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).