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Research Article

Synthesis of 1,2-Dihydro-Substituted Aniline Analogues Involving *N*-Phenyl-3-aza-Cope Rearrangement Using a Metal-Free Catalytic Approach

Osamah Alduhaish,[1] Ravi Varala,[2] Syed Farooq Adil,[1] Mujeeb Khan,[1] Mohammed Rafiq H. Siddiqui,[1] Abdulrhman AlWarthan,[1] and M. Mujahid Alam[3]

[1]*Department of Chemistry, King Saud University, Riyadh 11451, Saudi Arabia*
[2]*Scrips Pharma, Mallapur, Hyderabad 500 076, Telangana, India*
[3]*Department of Chemistry, College of Science, King Khalid University, P.O. Box 9004, Abha 61413, Saudi Arabia*

Correspondence should be addressed to Ravi Varala; varalaravirnd@gmail.com and Syed Farooq Adil; sfadil@ksu.edu.sa

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An efficient metal-free domino reaction leading to structural/electronically divergent 1,2-dihydropyridines from easily accessible propargyl vinyl anilines via *N*-phenyl 3-aza-Cope sigmatropic rearrangement is reported with good to excellent yields using 1,2-dichlorobenzene as solvent under thermal conditions. Spirocyclic substitution is also tolerated under the present optimized conditions.

1. Introduction

Dihydropyridine (DHP) is amongst the most attractive molecules that have gained the attention of pharmaceutical researchers due to its promising biological efficiency mainly against hypertension and angina [1]. A variety of DHPs such as amlodipine and nifedipine are presently in the market as potent antihypertensive drugs. Literature reports on the synthesis of easily accessible 1,2- and 1,4-dihydropyridine intermediates, which have led to a copious library of biological active drug molecules and natural product compounds including alkaloids [2].

The search for new feasible synthetic approaches for the preparation of the derivatives of azaheterocycles, particularly, 1,2-dihydropyridines (1,2-DHPs), is an important study as these compounds can exhibit diverse biological activities such as follows [3, 4]: 1,2-DHPs act as starting materials for the synthesis of the 2-azabicyclo[2.2.2]octanes (isoquinuclidines) ring system present in various alkaloids such as ibogaine, dioscorine, and catharanthine (vinca alkaloids) (Figure 1). The anti-influenza drug, oseltamivir phosphate (Tamiflu), is also synthesized from 1,2-DHP *via* an isoquinuclidine intermediate [5] (Figure 2).

Considerable efforts have been directed toward the development of new and efficient methodologies for the synthesis of 1,2-dihydropyridines since the first synthesis started by Fowler [6]. 1,2-DHPs are prepared by hydrogenation involving the redox cycloisomerization approach [7] and via 6π-azaelectrocyclization [8]. More pioneering work particularly in this field is carried out by Tejedor et al. using microwave-assisted domino reaction of a propargyl vinyl ether (secondary or tertiary) and a primary amine (aliphatic or aromatic) in toluene or methanol [9–11].

Harschneck and Kirsch have exploited transition metal catalysts such as $AuCl_3$ for preparation of 1,2-DHPs, wherein propargyl vinyl ethers and amines were used as starting materials [12, 13]. In another study, a four-component synthetic approach was employed to prepare derivatives of 1,2-DHPs [14] through a one-pot multicomponent reaction of acetophenone, aldehyde, and ammonium acetate with ethyl cyanoacetate or malononitrile, respectively. Besides these several other transition

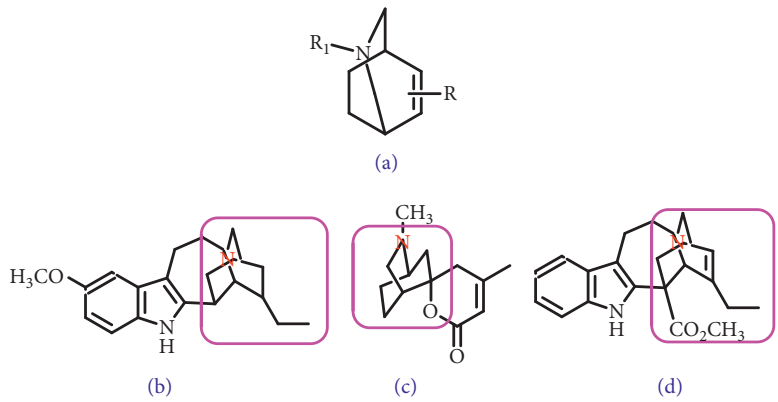


Figure 1: Natural product alkaloids isoquinuclidines (a), ibogaine (b), dioscorine (c), and catharanthine (vinca alkaloids) (d).

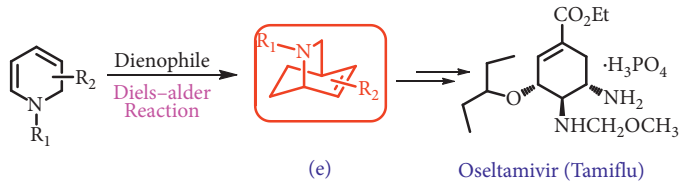


Figure 2: Structures of some medicinally important compounds/cores accessible from 1,2-DHPs.

metals have also been utilized as catalysts, for example, Rh [15], Cu/Mo [16], and low-valent Co complexes [17] for the synthesis of 1,2-DHPs *via* C-H activation/6π-electrocyclization pathways. Furthermore, various other metal complexes have also been evaluated, including Pt (II)-catalyzed cycloisomerization of aziridinyl propargylic esters [18], $Sc(OTf)_3$-catalyzed imino-Aldol reactions using vinyloxiranes as masked dienolates [19], $BF_3.Et_2O$-catalyzed 6π-electrocyclization of enaminonitriles with α,β-unsaturated aldehydes [20], and *N*-amino-3-aza-Cope rearrangements [21, 22]. Additionally, various other examples of the synthesis of 1,2-dihydropyridines have been comprehensively compiled by Silva et al. in a recent review [4]. Notably, most of the preparation methods of 1,2-dihydropyridines are based on nucleophilic addition to *N*-alkyl or *N*-acylpyridinium salts which often yield undesirable side products [23]; hence, to overcome these limitations, various alternative reaction strategies have been designed [24]. In most of the already reported methodologies, use of expensive metal catalysts or harsh reaction condition stimulates the need for further improvement in the synthesis of 1,2-DHPs.

In this regard, sigmatropic rearrangement reactions can be an advantageous alternative approach for the synthesis of 1,2-dihydropyridines. These types of reactions constitute fascinating chemical bond reorganizations reactions, which have been extensively used in organic synthesis [25]. Herein, we present our preliminary results pertaining to an efficient domino reaction, which led to the formation of electronically divergent 1,2-DHPs from easily accessible propargyl vinyl anilines involving a metal-free *N*-phenyl 3-aza-Cope sigmatropic rearrangement with good to excellent yields using 1,2-dichlorobenzene as solvent.

2. Materials and Methods

General melting points were determined on a Reichert Thermovar apparatus and are uncorrected. Thin-layer chromatography was performed on Merck silica gel 60 F254 0.2 mm thick plates and visualized under UV light or by exposing to iodine vapour. For preparative separation, the plates were 0.51 mm thick. For flash chromatography silica Merck Kieselgel, 60 and 70–230 mesh were used. Infrared (IR) spectra were recorded on a Perkin–Elmer 1000X FT-IR spectrometer. Proton and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker ARX 400 spectrometer (400 MHz for ^1H, 100.63 MHz for ^{13}C). Chemical shifts are reported relative to tetramethylsilane as the internal reference. Mass spectra were recorded on Fisons TRIO 2000 or AEI MS-9 spectrometer. High-resolution MS spectra (HRMS) were obtained on a FT-ICR/MS Finnigan FT/MS 2001-DT spectrometer at 70 eV by electron impact or on a Finnigan MAT 900 ST spectrometer by ESI. Elemental analysis was performed in Hewlett-Packard, model 185 (United States) (HP). Microwave reactions were conducted in sealed glass vessels (capacity 10 mL) using a CEM Discover microwave reactor equipped with a surface sensor to measure the temperature of the reaction mixture.

Usual workup implies drying the water- or brine-washed organic extracts over anhydrous sodium sulfate or magnesium sulfate, followed by filtration and solvent removal

under reduced pressure. Anhydrous solvents were dried and freshly distilled by standard methods [26].

2.1. Synthesis of Starting Materials (Typical Model Reaction-Schemes 1 and 2)

2.1.1. 1,1-Dimethylpropargyl Acetate (B). To a stirred solution of compound a (5 ml, 51.28 mmol, 1 equiv.) in dry DCM (40 ml), triethyl amine (7.67 ml, 1.08 equiv.), acetic anhydride (6.0 ml, 1.15 equiv.), and DMAP (325 mg, 5 mol%) are added sequentially at room temperature and stirred overnight (Scheme 1). After being monitored by TLC, the reaction mixture is diluted with saturated NH_4Cl solution. Aqueous phase of the reaction mixture is extracted with DCM (2×25 ml). Organic phase obtained is washed with 1 ml HCl twice and concentrated using vacuum, which gives the crude compound, which is further purified by flash column chromatography using diethyl ether: *n*-hexane (1 : 3) to afford b in 91% isolated yield (5.87 g).

2.1.2. Spectral Data for Compound B. Light yellow oil. IR (NaCl): ν 3288 (C≡C-H); 2991, 2165 (C≡C), 1746 (C=O), 1367, 1247, 1136, 1016, 966, 844 Cm^{-1}. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.61 (6H, s, $C(C\underline{H}_3)_2C{\equiv}CH$), 1.97 (3H, s, $CO_2C\underline{H}_3$), 2.49 (1H, s, $C(CH_3)_2C{\equiv}C\underline{H}$). ^{13}C NMR ($CDCl_3$; 100 MHz): δ 21.7 ($CO_2\underline{C}H_3$), 28.7 ($C(\underline{C}H_3)_2C{\equiv}CH$), 71.4 ($\underline{C}(CH_3)_2C{\equiv}CH$), 72.1 ($C(CH_3)_2C{\equiv}\underline{C}H$), 84.6 ($\underline{C}(CH_3)_2\underline{C}{\equiv}CH$), 169.2 ($\underline{C}O_2CH_3$)

2.1.3. N-(1,1-Dimethylpropargyl)-aniline (C). Aniline (0.657 ml, 7.21 mmol, 1 equiv.) is slowly added to a stirred solution of b (1 g, 7.93 mmol, 1.1 equiv.), CuCl (70 mg, 0.1 equiv.), and triethyl amine (1.12 ml, 1.1 equiv.) dissolved in THF (10 ml) at room temperature (Scheme 1). Then, the reaction mixture is refluxed for 90 min, while monitoring the reaction mixture for the complete consumption of starting material, and the reaction mixture is then concentrated and then dissolved in EtOAc (10 ml). Then, the reaction mixture is treated with saturated NH_4Cl solution (10 mL) twice followed by brine solution (10 ml). The organic layer is then concentrated under reduced pressure to give crude residue, which is then subjected to flash column chromatography using gradient elution system starting from *n*-hexane to 1 : 5 of ethyl acetate: *n*-hexane, to afford desired product c in 71% isolated yield (0.83 g).

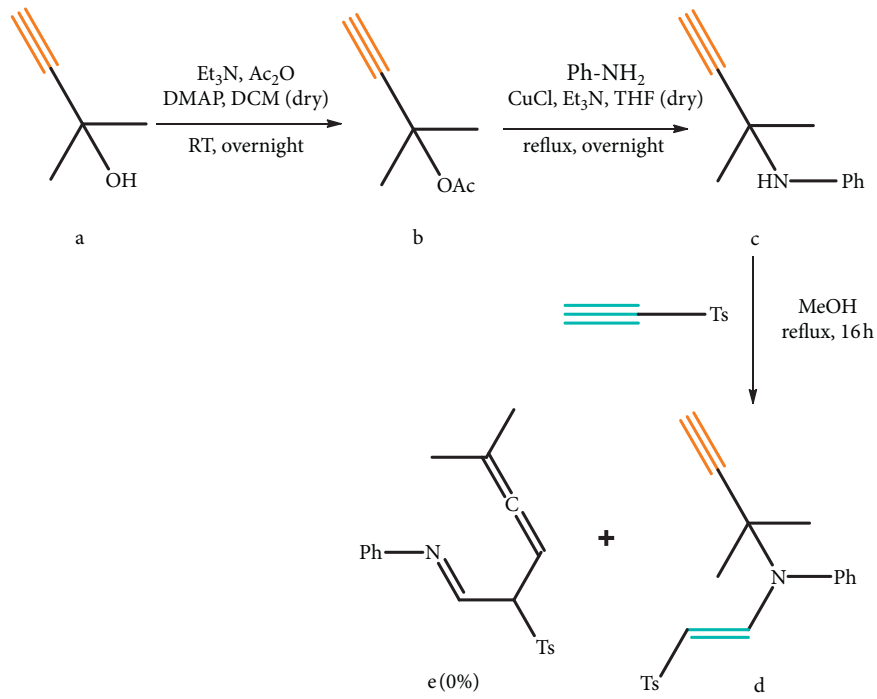
2.1.4. Spectral Data for Compound C. Mp 35-36 °C (ethyl acetate). IR (NaCl; cm^{-1}): 3402 (N-H); 3290 (C≡C-H), 3052, 2979, 2933, 2156 (C≡C), 1601, 1503, 1382, 1316, 1258, 1212, 1181, 843, 750, 694. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.64 (6H, s, $NC(C\underline{H}_3)_2C{\equiv}CH$), 2.40 (1H, s, $NC(CH_3)_2C{\equiv}C\underline{H}$), 3.59 (1H, sl, NH), 6.83 (1H, t, J = 7.4 Hz, Ar-H), 6.97 (2H, d, J = 7.4 Hz, Ar-H), 7.23 (2H, t, J = 7.4 Hz, Ar-H).

2.1.5. (E)-N-(1,1-Dimethylpropargyl)-N-(enamino)-aniline (D). To a stirred solution of compound **C** (45 mg, 1 equiv.) in methanol (3 mL) is added ethynyl *p*-tolyl sulfone, 50 mg, 1.0 equiv., and refluxed for 16 h (Scheme 1). The crude reaction mixture is purified by neutral alumina employing 1 : 1 ether: *n*-hexane as eluent and separated the desired fraction **D** in 85% yield (81 mg) as a white solid.

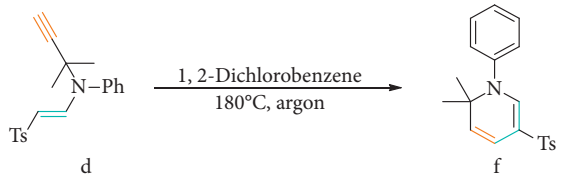
2.1.6. Spectral Data for Compound D. Mp 109-110°C (Et_2O). IR (NaCl; cm^{-1}): 3252 (C≡C-H), 3064, 2988, 2939, 2114 (C≡C), 1607 (C=C), 1586, 1493, 1369, 1296 (SO_2), 1158 (SO_2), 1135 (SO_2), 1082, 854, 814, 695, 659. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.52 (6H, s, $NC(C\underline{H}_3)_2C{\equiv}CH$), 2.37 (3H, s, Ar-$CH_3$), 2.60 (1H, s, $NC(CH_3)_2C{\equiv}C\underline{H}$), 4.51 (1H, d, J = 12.6 Hz, NCH=CHTs), 7.11 (2H, d, J = 6.8 Hz, Ar-H), 7.21 (2H, d, J = 8.1 Hz, Ar-H), 7.34–7.40 (3H, m, Ar-H); 7.65 (2H, d, J = 8.2 Hz, Ar-H); 8.17 (1H, d, J = 12.6 Hz, NCH=CHTs). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4 (Ar-CH_3), 30.1 ($NC(\underline{C}H_3)_2C{\equiv}CH$), 56.3 ($N\underline{C}(CH_3)_2C{\equiv}CH$), 73.5 ($NC(CH_3)_2C{\equiv}\underline{C}H$), 85.9 ($NC(CH_3)_2\underline{C}{\equiv}CH$), 98.5 (NCH=CHTs), 126.3 (Ar-C), 128.6 (Ar-C), 129.3 (Ar-C), 129.6 (Ar-C), 129.7 (Ar-C), 139.3 (Ar-C), 141.5 (Ar-C), 142.2 (Ar-C), 147.8 ($N\underline{C}H$=CHTs). *m/z* (EI): 324 ($C_{19}H_{18}NO_2S$+, 5); 260 (45); 184 ($C_{13}H_{14}N$, 30); 110 (70); 77 (C_6H_5+, 100). Elemental analysis for $C_{20}H_{21}NO_2S$: Calcd. *C*, 70.77; *H*, 6.24; *N*, 4.13; *S*, 9.45; found *C*, 70.44; *H*, 6.40; *N*, 4.04; *S*, 9.28.

2.1.7. N-Phenyl-2,2-dimethyl-5-tosyl-1,2-dihydropyridine (F). Compound D (100 mg) is dissolved in 1,2-dichorobenzene (2 mL) and heated at 180°C, for 20 min, while monitoring the reaction progress by TLC (Scheme 2). After the starting material is almost completely consumed, the crude reaction mixture is subjected to direct flash chromatography using *n* -hexane as the first eluent to remove the solvent; i.e., 1,2-DCB and then 10% ethyl acetate : *n*-hexane solution is utilized as eluent to obtain the desired compound F as colourless oil in 95% isolated yield (95 mg).

2.1.8. Spectral Data for Compound F. IR (NaCl; cm^{-1}) 3060, 2972, 2924, 1630 (C=C), 1564, 1492, 1366, 1295 (SO_2), 1150 (SO_2), 1132 (SO_2), 1104, 1071, 805, 706, 676. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.26 (6H, s, $C(C\underline{H}_3)_2CH=CH$), 2.40 (3H, s, Ar-$CH_3$), 4.95 (1H, d, J = 9,8 Hz, $C(CH_3)_2C\underline{H}=CH$), 6.09 (1H, dd, J = 9.8 Hz + J = 1, 4 Hz, $C(CH_3)_2CH=C\underline{H}$), 7.22–7.24 (2H + 1H, m, Ar-H + NCH=CTs), 7.27 (2H, d, J = 8.1 Hz, Ar-H), 7.33–7.41 (3H, m, Ar-H), 7.73 (2H, d, J = 8.1 Hz, Ar-H). ^{13}C NMR ($CDCl_3$; 100 MHz): δ 21.5 (Ar-CH_3), 29.0 ($C(\underline{C}H_3)_2CH=CH$), 58.8 ($\underline{C}(CH_3)_2CH=CH$), 107.6 (NCH=$\underline{C}$Ts), 117.6 ($C(CH_3)_2CH=\underline{C}H$), 122.1 ($C(CH_3)_2\underline{C}H=CH$), 126.5 (Ar-C), 128.1 (Ar-C), 129.0 (Ar-C), 129.1 (Ar-C), 129.5 (Ar-C), 140.7 (Ar-C), 142.5 (Ar-C), 142.5 (Ar-C), 144.0 ($N\underline{C}H$=CTs). *m/z* (EI): 339 (M+, 25); 323 ($C_{19}H_{19}NO_2S$+, 100); 168 (25); 154 (38); 91 (C_7H_7+, 14); 77 (C_6H_5+, 25). HRMS : Calcd. for $C_{20}H_{21}NO_2S$ (M+): 339.129301; found: 339.129909.



Scheme 1: Synthesis of easily accessible *N*-propargyl vinyl anilines: (E)-*N*-(1,1-dimethylpropargyl)-*N*-vinyl-aniline as model reaction.



Scheme 2: Metal-free propargyl aza-Cope rearrangement.

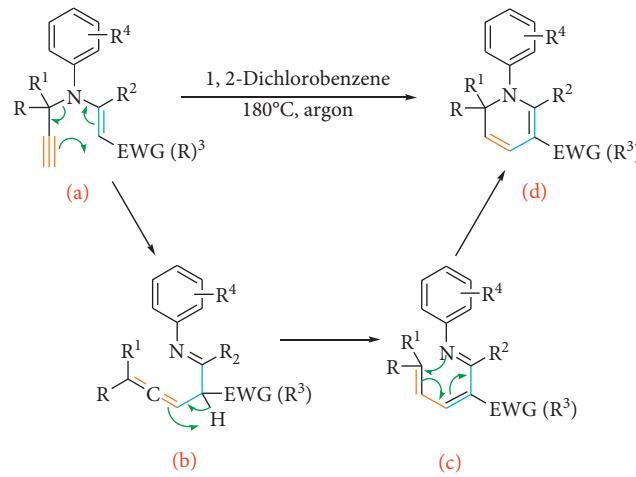
3. Results and Discussion

2-Methyl-3-butyn-2-ol (a) (dimethyl ethynyl carbinol) is acylated using 1.1 equiv, of acetic anhydride, 1.1 equiv. of triethyl amine, and 0.05 equiv. of DMAP in dry DCM at ambient temperature for overnight, as shown in Scheme 1, followed by routine workup to give 1,1-dimethylpropargyl acetate (b) in almost quantitative yield (91%) [18, 27].

Further compound B is made to react with aniline to yield *N*-(1,1-dimethylpropargyl)-aniline (c) in 71% isolated yield using Imada's protocol [28]. The alkylation product (c) is then made to react with one of the Michael acceptors, ethynyl *p*-tolyl sulfone in methanol under reflux conditions to yield corresponding (*e*)-*N*-(1,1-dimethylpropargyl)-*N*-(enamino)-aniline (d) in 85% yield. Interestingly, the addition reaction selectively produces *trans*-enamine (d). No formation of allene (e) is observed.

All the compounds obtained were subjected to spectroscopic analysis. The FT-IR of compound D showed an absorption band of approximately 1607 cm^{-1}, indicating that the product has a double bond conjugated to a heteroatom (enamine) [29]. Furthermore, bands at 1296 cm^{-1}, 1158 cm^{-1}, and 1135 cm^{-1} corresponding to the SO_2 bonds of the tosyl group were also observed. In the ^1H NMR spectra of compound D, doublets were displayed at δ 8.17 (d, $J = 12.6$ Hz, 1H) and 4.51 (d, $J = 12.6$ Hz, 1H), confirming the enamine in conjugation with *trans*-configuration. Both signals are characteristic of the tosyl group. ^{13}C NMR spectrum of D shows characteristic peaks at δ 98.5 and 147.8, respectively, corresponding to the double bond of enamine. Elemental analysis of this compound further supported the proposed structure D.

(E)-*N*-(1,1-Dimethylpropargyl)-*N*-(enamino)-aniline (d) is refluxed in 0.1 M 1,2-dichlorobenzene (1,2-DCB) under argon atmosphere at 180°C, and the progress of the reaction was monitored by TLC, IR, and NMR at regular intervals. Surprisingly, the expected rearranged product (f) is obtained in 30 min, with an excellent yield of 95%. Spectroscopic analysis confirmed the formation of final product F, which is established by the disappearance of alkynic group at 3252 cm^{-1} in FT-IR spectrum. Furthermore, the ^1H NMR spectra of compound **F** yields a



Scheme 3: Proposed mechanism for the formation of 1,2-DHPs.

Table 1: Effect of various solvents for the synthesis of 1,2-DHP (f).

Solvent	Condition	Time (m)	Isolated yield (%)	Inference
Toluene	111°C	180 min	32	—
1, 2-Dichlorobenzene (1,2-DCB)	180°C	30 min	95	Optimized*
Benzene	80°C	10 min	0	No reaction
Diphenyl ether	265°C	180 min	42	—
Chlorobenzene	140°C	30 min	54	—
Xylene	140°C	2 days	0	No reaction
Microwave (1,2-DCB)	150 W, 120°C	30 min	78	Yield is less than conventional reflux
DMF	155°C	120 min	—	Complex mixture

*Optimized as best suitable solvent under conventional conditions.

doublet at δ 6.09 (dd, $J = 9.8$ and 1.4 Hz, 1H) and 4.95 (d, $J = 9.8$ Hz, 1H), which confirms the complete electrocyclization. ^{13}C NMR further confirms the formation of the product, as propargylic peaks at δ 85.9 and δ 73.5 disappeared and new peaks at δ 117.6 and δ 122.1 appeared, representing the formation of double bond. HRMS data further confirmed the formation of the desired product F.

We propose a mechanism pathway for the above aza-Cope rearrangement, as shown in Scheme 3, which is quiet similar to the one reported previously [30]. In brief, when compound (a) is heated to 180°C, it undergoes a [3, 3]-sigmatropic rearrangement yielding the allene (b). This is followed by proton migration, which isomerizes to triene (c) which through intramolecular electrocyclization gives the final reaction product 1,2-dihydropyridine (d). However, further studies along with experimental and spectroscopic studies must be carried out to authenticate the claim.

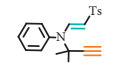
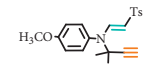
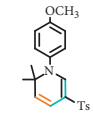
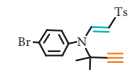
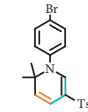
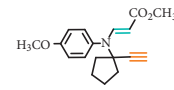
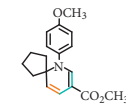
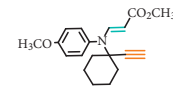
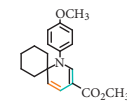
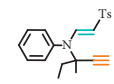
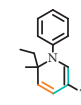
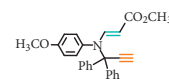
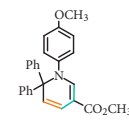
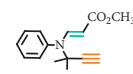
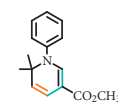
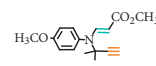
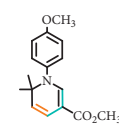
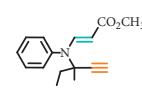
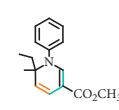
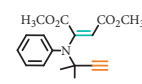
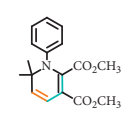
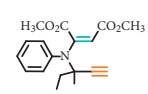
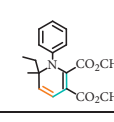
Different solvents were tested for optimization, and it was found that, among the various solvents investigated, 1,2-DCB is the best solvent (see Table 1).

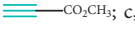
From the studies carried out, it is concluded that conventional heating yields better results compared to the same reaction performed employing microwave irradiation under the mentioned parameters (entries 2 and 7, Table 1).

Inspired by the successful formation of F (Scheme 2), the study is extended with electronically divergent anilines, substituted propargyl acetates, and other Michael acceptors such as ethynyl *p*-tolyl sulfone (a), methyl propargylate (b), and dimethyl acetylene dicarboxylate (c) to synthesize corresponding 1,2-DHPs (Table 2). The study is extended by utilizing five types of propargyl acetates and reacted with electronically divergent anilines to form corresponding propargyl vinyl amines, which in turn were subjected to the aza-Cope sigmatropic rearrangement, yielding the corresponding 1,2-DHPs.

Among the three Michael acceptors utilized in this methodology, the addition reaction employing dimethyl acetylene dicarboxylate (entries 11 and 12, see Table 2) yields the lowest product. This can be attributed to the deactivation of the acceptor due to the presence of two electron withdrawing groups in opposite positions, causing a reduction in the electrophilicity of triple bond as compared to the triple bond of the remaining acceptors employed. Furthermore, under the optimized conditions, cyclopentyl propargyl vinyl aniline or cyclohexyl propargyl vinyl aniline also undergo aza-Cope sigmatropic rearrangement; however, the yield is less compared to the open chain propargyl vinyl anilines (entries 4 and 5, Table 2). This protocol is unsuccessful with an aniline having electron-withdrawing group, such as NO_2. However, when propargyl acetate or 1-methyl propargyl

Table 2: Scope of the annulation reaction of *N*-propargyl vinyl anilines.

Entry	Propargyl acetate	Aniline	Michael acceptors[a]	Propargyl vinyl amine	1,2-Dihydropyridine	Yield (%)[b]
1		Aniline	a			95
2		*p*-Anisidine	a			88
3		4-Bromo aniline	a			76
4		*p*-Anisidine	b			48
5		*p*-Anisidine	b			56
6		Aniline	a			81
7		*p*-Anisidine	b			85
8		Aniline	b			70
9		*p*-Anisidine	b			84
10		Aniline	b			92
11		Aniline	c			68
12		Aniline	c			61

a, ; b,  ; c, ; isolated yields by column chromatography.

acetate are used as precursors, the rearranged product obtained is pyridines instead of desired 1,2-dihydropyridines.

Observation of ^{13}C NMR spectra shows the proximity of all these signals presents very similar chemical deviations. In the case of the proposed structures, it is possible

to draw a plane of symmetry passing along the dihydropyridine ring, and that due to the planarity of all the different functional groups, all obtained molecules extend beyond this ring [30].

4. Conclusions

In this study, we have successfully demonstrated the synthesis of various substituted 1,2-dihydropyridines from electronically divergent *N*-propargyl vinyl anilines, using metal-free aza-Cope rearrangement. This improved version delivers these important heterocyclic scaffolds with a wider diversity at the ring, along with mono- and disubstitution at the sp^3 position. Spiro-substituted 1,2-DHPs are also obtained under this reaction conditions albeit in lesser yields. The protocol can be extended to secondary and tertiary propargyl vinyl ethers bearing internal or terminal alkyne moieties and primary aromatic amines. Extension of this protocol to aliphatic amines and other Michael acceptors is also currently underway.

Data Availability

The data of the research work carried out are presented in the manuscript and supplementary materials itself, and all the readers of this article shall be able to get the desired information. Further data will be available on request to the corresponding author.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

R. V. and S. F. A. conceptualized the study and proposed methodology. M. M. A. analyzed using software. R. V. did formal analysis. R. V. and S. F. A. were responsible for gathering resources. M. K. and M. R. H. S. performed data curation. R. V., M. K., and S. F. A. wrote the original draft. O. A. and M. R. H. S helped in obtaining funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Supplementary Materials

General melting points were determined on a Reichert Thermovar apparatus and are uncorrected. Thin-layer chromatography was performed on Merck silica gel 60 F254 0.2 mm thick plates, visualized under UV light or by exposing to iodine vapour. For preparative separations, the plates were 0.51 mm thick. For flash chromatography silica Merck Kieselgel, 60 and 70–230 mesh were used. Infrared (IR) spectra were recorded on a Perkin–Elmer 1000X FT-IR spectrometer. Proton and 13 C NMR spectra were recorded in CDCl3 on a Bruker ARX 400 spectrometer (400 MHz for 1H, 100.63 MHz for 13C). Chemical shifts are reported relative to tetramethylsilane as the internal reference (δ H 0.00) for 1H NMR spectra and to $CDCl_3$ (δ C 77.00) for 13C NMR spectra. Ordinary mass spectra were recorded on Fisons TRIO 2000 or AEI MS-9 spectrometer. High-resolution MS spectra (HRMS) were obtained on a FT-ICR/MS Finnigan FT/MS 2001-DT spectrometer at 70 eV by electron impact or on a Finnigan MAT 900 ST spectrometer by ESI. Elemental analysis was performed in Hewlett-Packard, model 185 (United States) (HP). Microwave reactions were conducted in sealed glass vessels (capacity 10 mL) using a CEM Discover microwave reactor equipped with a surface sensor to measure the temperature of the reaction mixture. (*Supplementary Materials*)

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