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Synthesis of Unsymmetrical Substituted 1,4-Dihydropyridines through Thermal and Microwave Assisted [4+2] Cycloadditions of 1-Azadienes and Allenic Esters

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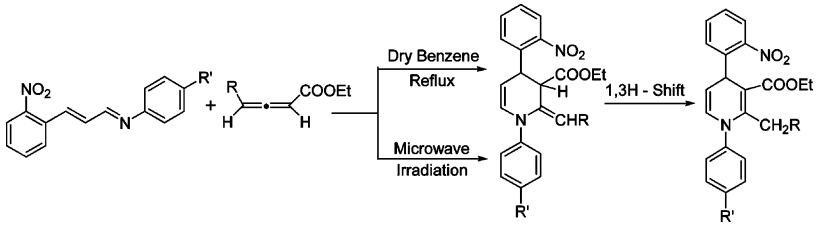

Thermal and microwave assisted [4+2] cycloadditions of 1,4-diaryl-1-aza-1,3-butadienes with allenic esters lead to cycloadducts, which after a 1,3-H shift afford variedly substituted unsymmetrical 2-alkyl-1,4-diaryl-3-ethoxycarbonyl-1,4-dihydropyridines in high yields. Reactions carried out under microwave irradiation are cleaner and give higher yields with much shortened reaction times. Density functional theory (DFT) at the B3LYP/6-31G* level has been used to calculate geometric features of the reactants, barrier for s-trans to s-cis and reverse isomerization of azadienes (**5a**−**d**, **10a**−**e**), dihedral angles between N_1, C_2, C_3, and C_4 atoms of azadienes along with various indices such as chemical hardness (η), chemical potential (μ), global electrophilicity (ω), and the difference in global electrophilicity ($\Delta\omega$) between the reacting pairs and Fukui functions (f^+ and f^-). The results revealed that s-trans is the predominant conformation of azadienes at ambient temperature and the barrier for conversion of the s-trans rotamer of 1-azadienes to s-cis may be the major factor influencing the chemoselectivity, i.e., [4+2] verses [2+2] cycloaddition. The regiochemistry of the observed cycloadditions is collated with the obtained local electrophilicity indices (Fukui functions). Transition states for the formation of both [4+2] and [2+2] cycloadducts as located at the PM3 level indicate that the transition state for the formation of [4+2] cycloadducts has lower energy, again supporting the earlier conclusion that preferred formation of [4+2] cycloaaducts at higher temperature may be a consequence of barrier for s-trans to s-cis transformation of 1-azadienes.

Introduction

A vast number of pharmacologically active heterocyclic compounds are known which are in regular clinical use.[1] 1,4-Dihydropyridines (1,4-DHPs) such as Nifedipine (**1**) make up the most potent and largest series of heterocyclic compounds available experimentally and clinically; the series embraces both potent calcium channel antagonist (**1**, **2**) and potent calcium channel agonist (**3**, **4**).[2] Besides their overwhelming utilization in the cardiovascular pharmacology as Ca^{2+} channel blockers (CCBs),[3] other activities attributed to these molecules include selective adenosine-A_3 receptor antagonism[4] and NMDA-receptor antagonism (anticonvulsant).[5]

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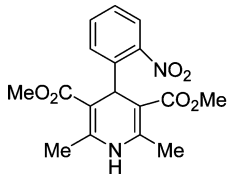
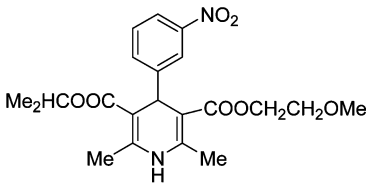


1
Nifedipine



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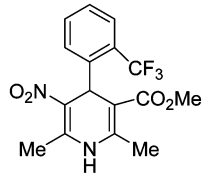
Nimodipine



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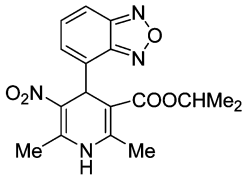

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Some recently discovered biological activities of 1,4-dihydropyridines include HIV-I protease inhibition,[6] neuromodulatory (anticonvulsant),[7] and nitric oxide-like activities.[8] Dihydropyridines have also been found to be potent α_{1a}-adrenoreceptor antagonists acting as inhibitors of human prostate contraction and hence are useful for treatment of benign prostate hyperplasia;[9] they are also useful NADH models.[10] Recently, these molecules have also been investigated for other pharmacological activities such as antidiabetic, antiviral, antibacterial, membrane protecting, anticancer,[11] antitubercular,[12] and antimicrobial.[13]

Though the chemistry and biomedical applications of 1,4-dihydropyridines have been comprehensively reviewed,[3a,b] the details of subtle stereoelectronic requirements for interactions at various receptors are still being investigated. However, as with many other drugs, the symmetrical substitution pattern in medicinally active 1,4-dihydropyridines such as Nifedipine (**1**) has proven to be more of a consequence of synthetic methodology rather than a receptor requirement, and recently the unsymmetrically substituted variants have been shown to display better pharmacological properties.[14] It now has been recognized that the absolute configuration at the C_4 position of the 1,4-DHP nucleus is indispensable for activity modulation. Indeed enantiomers of an unsymmetrically 4-substituted 1,4-DHP usually differ in their biological properties, and sometimes they could have exactly the opposite action profile (e.g., calcium channel antagonist vs calcium channel agonist).[15] Also, the presence of different substituents or heteroatoms has allowed an expansion of the structure−activity relationship thus providing a better insight into the molecular interaction at the receptor level. The knowledge of stereochemical/conformational requirements for any biological activity requires the study of other related analogues of the DHP ring.[16] Consequently, with attribution of many other types of biological activities to 1,4-DHPs, the design, synthesis, and evaluation of novel 1,4-DHPs with a varied pattern of substitution assumes a lot of significance.

Since the first report of the Hantzsch synthesis of 1,4-dihydropyridines, a number of strategies involving different catalysts and conditions have been developed but all suffer from one or more drawbacks including low yields, use of costly reagents, and drastic reaction conditions.[3b,12] Hetero-Diels−Alder methodology is of tremendous synthetic utility in organic synthesis, and recently, besides definite advancements in theoretical understanding, a number of novel catalytic conditions have been developed for easy realization of hetero-Diels−Alder reactions.[17] However, there are very few reports available on cycloadditions involving allenes and heterodienes.[18] Contrary to the earlier reported[18c] cycloaddition reactions of 1-azadienes with allenes leading to the formation of cyclohexanones through rearrangement of [2+2] cycloadducts, it was observed[19] that reaction of 1-aza-1-aryl-4-phenyl-1,3-butadienes (**5**) with allenic esters (**6**), in refluxing benzene led to [4+2] cycloadducts, which after a 1,3-H shift, furnish valuable substituted-1,4-dihydropy-

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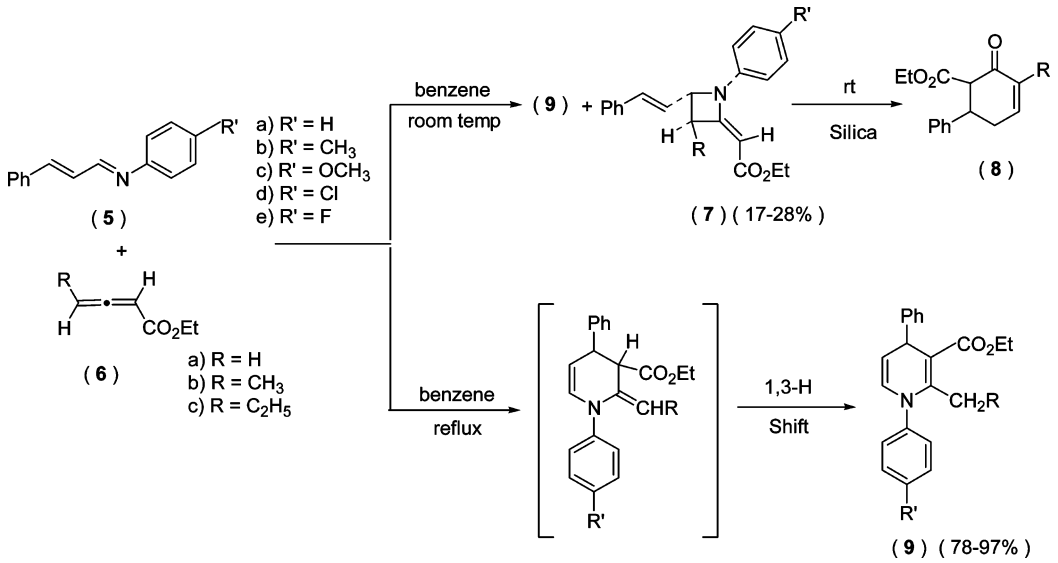
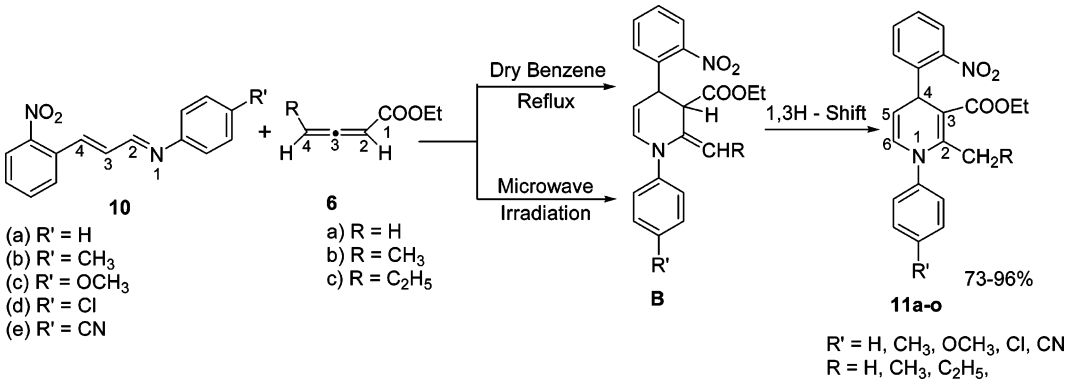
SCHEME 1. Formation of [2+2] and [4+2] Cycloadducts at Different Reaction Conditions



SCHEME 2. Thermal and Microwave Assisted Reactions of 1-Azadienes and Allenic Esters



ridines (**9**) in high yields and the earlier reported cyclohexanones (**8**) were formed in low yields (Scheme 1).

In view of the above recorded observations that the symmetrical structure of Nifedipine is a consequence of the synthetic methodology, i.e., Hantzsch synthesis, rather than any receptor requirement and the fact that in the case of unsymmetrical 1,4-dihydropyridines differential selectivity is displayed by receptors for configuration (R/S) at C_4,[14] it was decided to synthesize unsymmetrical substituted 1,4-dihydropyridines with varied patterns of substitution utilizing thermal cycloadditions of 1,4-diaryl-1-aza-1,3-butadiens with allenic esters. However, as extended reaction times are a major problem with thermal methodology under reflux conditions and yields are low, employment of microwave irradiation, a nonconventional technique that has made a mark in organic synthesis,[20] was also investigated. Though the exact mechanism is still to be investigated, it seems, however, to be accepted that the different temperature range caused by the microwave dielectric heating is the main contributing factor to any observed acceleration of reaction.[13,20] Furthermore, to have a better insight into the mechanism of cycloaddition, density functional theoretical (DFT) calculations were also carried out.

Results and Discussion

Initially, thermal cycloadditions of 1,4-diaryl-1-azadienes (**10a**−**e**) were carried out with a number of allenic esters (**6a**−**c**) by refluxing the solutions of addends (1:1.2 molar, respectively) in dry benzene under N_2 atmosphere. The obtained unsymmetrical 1,4-dihydropyrpyridines (**11a**−**o**, 73−87%, Scheme 2) were isolated by column chromatography over silica gel and characterized spectroscopically.

Alternatively, solutions of 1-azadienes (**10a**−**e**) and allenic esters (**6a**−**c**) (1:1.2 molar, respectively) in 2 mL of dry benzene as a solvent were exposed to microwave irradiation using a focused monomode microwave reactor (CEM-Discover), and the formed unsymmetrical 1,4-dihydropyridines (**11a**−**o**, 83−96%, Scheme 2) were purified by column chromatography and characterized spectroscopically; the results of thermal as well as microwave assisted reactions are summarized in Table 1.

All 1,4-DHPs were obtained as yellow crystalline compounds and were characterized by spectroscopic techniques (^{1}H NMR, ^{13}C NMR, IR, mass spectroscopy) and microanalytical data. The ^{1}H NMR spectrum of compound **11a** displayed, besides resonances in the aromatic region, a 1H doublet at δ 6.10 (J = 6.3 Hz) assigned to C_6-H. Overlapping C_4-H and C_5-H

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TABLE 1. Reaction Times and Product Yields for Reactions of Various 1-Azadienes with Allenic Esters

entry	R′	R	1,4-DHP	thermal reflux time, h (yield,[a] %)	microwave irradiation time, min (yield,[a] %)
1	−H	−H	**11a**	76 (74)	5 (85)
2	$-CH_3$	−H	**11b**	69 (80)	7 (90)
3	$-OCH_3$	−H	**11c**	56 (84)	8 (92)
4	−Cl	−H	**11d**	72 (87)	9 (96)
5	−CN	−H	**11e**	64 (73)	5 (84)
6	−H	$-CH_3$	**11f**	40 (81)	12 (89)
7	$-CH_3$	$-CH_3$	**11g**	44 (77)	10 (86)
8	$-OCH_3$	$-CH_3$	**11h**	48 (75)	15 (83)
9	−Cl	$-CH_3$	**11i**	40 (79)	17 (89)
10	−CN	$-CH_3$	**11j**	42 (78)	07 (91)
11	−H	$-CH_2CH_3$	**11k**	36 (73)	08 (86)
12	$-CH_3$	$-CH_2CH_3$	**11*l***	33 (82)	09 (94)
13	$-OCH_3$	$-CH_2CH_3$	**11m**	34 (78)	10 (85)
14	−Cl	$-CH_2CH_3$	**11n**	38 (76)	13 (87)
15	−CN	$-CH_2CH_3$	**11o**	35 (80)	08 (92)

[a] Yield refers to isolated pure product.

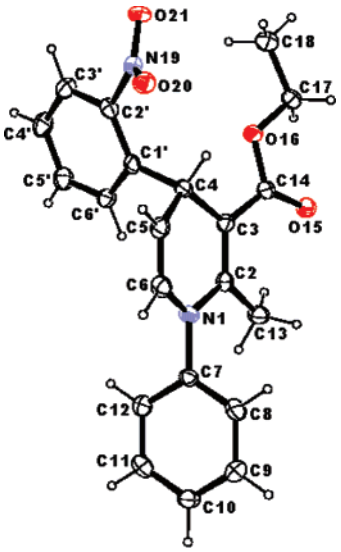

FIGURE 1. ORTEP view of **11a**.

resonances led to a multiplet (2H) at δ 5.19−5.16. Protons of ester function showed up as a quartet at δ 3.87 (2H, J = 7.0 Hz) and a triplet at δ 0.94 (3H, J = 7.0 Hz). A 3H singlet at δ 2.20 was due to C_2-CH_3. The assigned structure was also corroborated by ^{13}C NMR, IR, and mass spectroscopy data. Subsequently, the structure of **11a** was confirmed by X-ray crystallography (Figure 1).[21]

The investigations were further extended by reacting 1-azadienes (**10a**−**e**) with allenic esters (**12a**,**b**) both by the conventional benzene reflux method and microwave assisted irradiation. However, none of the reactions led to the formation of any [4+2] cycloadduct (Scheme 3).

Mechanistically, it has been postulated[19] that reaction of electron neutral 1-aza-1,3-dienes with allenic esters is initiated by interaction of azadiene nitrogen with central allenic carbon (Scheme 4) leading to formation of the common intermediate **B**. The intermediate **B** can collapse to either a [2+2] cycloadduct **13** or a [4+2] cycloadduct **11**. It also has been suggested that the [4+2] cycloaddition, favored at high temperature, may be proceeding via a concerted process,[19] which is thermodynamically controlled, and formation of the [2+2] cycloadduct at ambient temperature proceeds via a stepwise mechanism through intermediate **B**. In the case of 1-aryl-4-(*o*-nitrophenyl)-1-azadiene (**10a**−**e**) cycloadditions, which are presently investigated, only [4+2] cycloadducts (**11a**−**o**) were isolated under both thermal and microwave irradiation conditions; [2+2] cycloadducts were detected in trace amounts in some cases on NMR analysis of column chromatography fractions. Therefore, to gain an insight into the mechanistic details of the cycloadditions involving 1-azadienes and allenic esters, a recourse was made to density functional theory (DFT)[22] due to its recent resounding success in affording an alternative paradigm for explaining both reactivities and selectivities for a variety of cycloaddition processes.[22c,23] Though a number of reports on theoretical investigations involving reactions of 1-azadienes/imines and ketenes[17B, 24] exist, there is no available report of similar investigations involving 1-azadienes and allenic esters.

According to the DFT formalism, components involved in a cycloaddition process are characterized by their global electrophilicity index[25] (ω) as electrophilic and nucleophilic (less electrophilic) leading to the classification of a cycloaddtion reactions as normal or inverse electron demand. Thus the mechanism of a cycloaddition changes progressively from nonpolar-concerted-synchronous to polar-asynchronous and ultimately to polar-stepwise as the electrophilicity difference between addends ($\Delta\omega = \omega_A - \omega_B$) increases. The regioselectivity is predicted in terms of local descriptors of electrophilicity and nucleophilicity (less electrophilicity) by Fukui functions f_k^+ and f_k^-; the site with maximum f_k^+ is the site that has high propensity to favor a nucleophilic attack, whereas the site with

(21) The crystal data of **11a** has already been submitted to The Cambridge Crystallographic Data Centre (CCDC No. 283396). The X-ray analysis reveals the possible H-bonding involving hydrogens of the ester function and nitro group.

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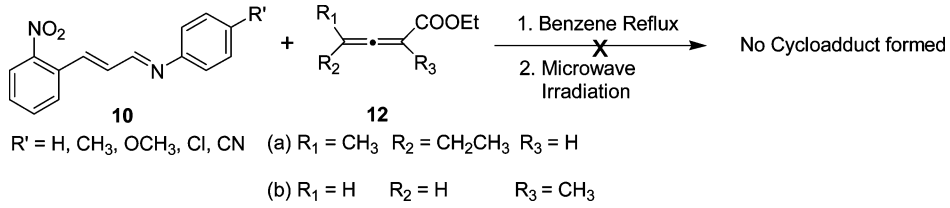
SCHEME 3



SCHEME 4

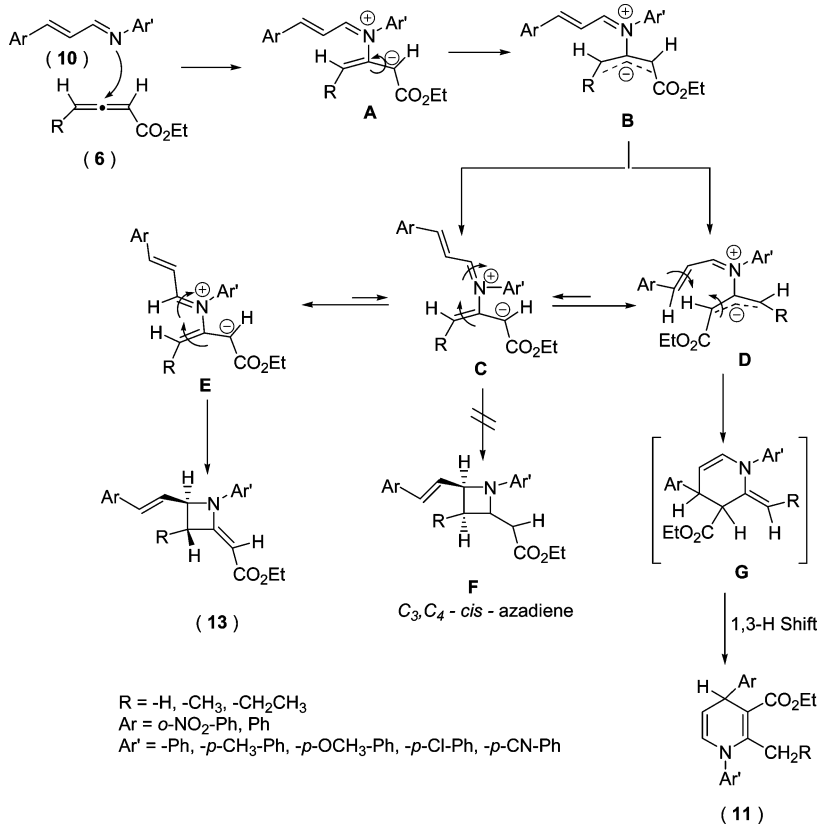


TABLE 2. Activation Barrier for s-Trans Rotamer to s-Cis ($E^{\ddagger}_{TC}$) and Vice Versa ($E^{\ddagger}_{CT}$) and Energy Difference (ΔE, kcal/mol) between Both Rotamers Calculated at the B3LYP/6-31G* Level

azadiene	R′	$E^{\ddagger}_{TC}$	$E^{\ddagger}_{CT}$	$\Delta E = E_T - E_C$
5a	H	11.0	8.7	2.3
5b	Me	11.0	8.7	2.3
5c	OMe	11.2	8.8	2.4
5d	Cl	11.2	8.9	2.3
10a	H	10.1	7.2	2.9
10b	Me	10.2	7.2	2.9
10c	OMe	10.5	7.5	2.9
10d	Cl	10.2	7.3	2.9
10e	CN	11.1	8.3	2.8

maximum f_k^- is considered as the site most amenable to an electrophilic attack.[22c,23a,c,26]

Initially, geometric features of the reactants and barrier for s-trans to s-cis and reverse isomerization of azadienes **5a**−**d** and **10a**−**e** were calculated at the B3LYP/6-31G* level. The results (Table 2, Figure 2) indicate that s-trans is the predominant conformation at embient temperature: it is energetically more stable and the barrier for s-trans to s-cis transformation (10.1−11.2 kcal/mol) is higher than for the reverse, i.e., s-cis to s-trans conversion (7.2−8.9 kcal/mol). Figure 2 shows both rotamers and transition state separating them for azadienes **5a** and **10a**.

Dihedral angles (D) between N_1, C_2, C_3, and C_4 atoms of the diene part for various azadienes **5a**−**d** and **10a**−**e** for both rotamers and for transition states between them were also determined (Table 3). Apparently one of the plausible reasons for obtaining the [2+2] adduct at low reaction temperature could be the higher energy barrier of s-trans to s-cis isomerization; only the latter geometric isomer can ensure the formation of the [4+2] cycloadduct.

In the next step chemical hardness (η), chemical potential (μ), global electrophilicity (ω, Table 4, all values in eV), and difference in global electrophilicity ($\Delta\omega$, Table 5, all values in eV) between the reacting pairs were computed at the B3LYP/6-31G* level.

The difference in the electrophilicity values of the reacting species ($\Delta\omega$) is used to predict the polarity of the transition state and to characterize the reactants as donor or acceptor in a cycloaddition process. The results indicate that azadienes have a higher value of ω, therefore, they shall be acting as acceptors in these cycloadditions. It has been shown that the higher the

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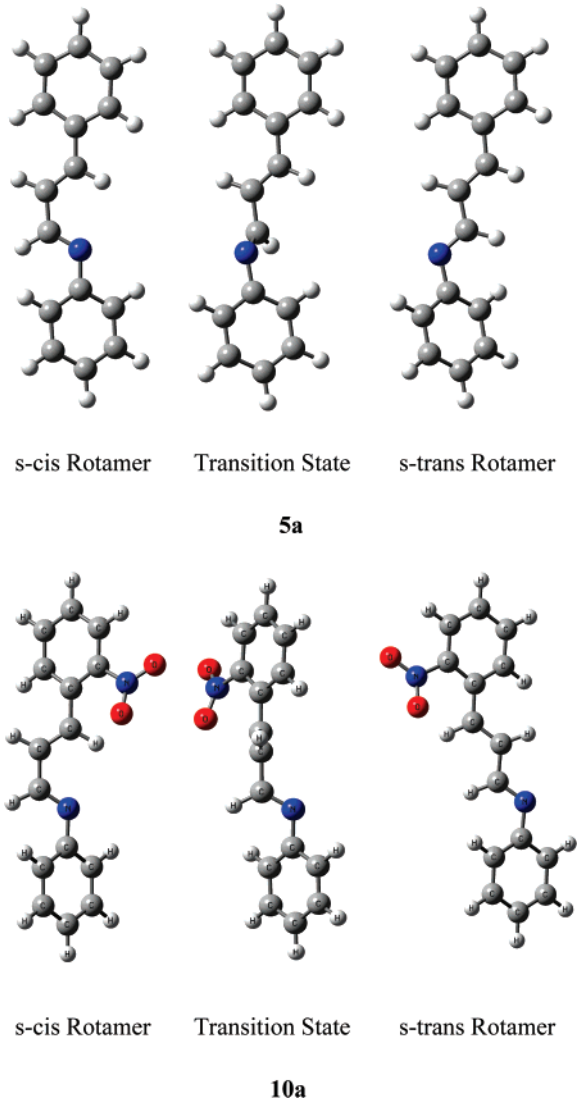


FIGURE 2. Optimized geometrical structures of s-trans, s-cis rotamers and the corresponding transition state between two forms of azdienes **5a** and **10a** calculated at the B3LYP/6-31G* level.

TABLE 3. The Dihedral Angle (*D*) of the Diene Part in Various Azadienes

		D, deg		
azadiene	R′	s-cis rotamer	transition state	s-trans rotamer
5a	H	2.2	95.1	179.9
5b	Me	2.3	95.0	180.0
5c	OMe	2.9	95.0	180.0
5d	Cl	2.4	95.1	179.7
10a	H	7.1	94.9	179.8
10b	Me	7.1	94.7	179.7
10c	OMe	6.8	94.8	179.4
10d	Cl	7.1	95.0	179.8
10e	CN	6.5	93.2	179.8

value of $\Delta\omega$, the more polar the transition state is.[23d,e,24a,25c] The above results show that the $\Delta\omega$ values are in the range 1.0−3.0 eV indicating highly polarized transition states. It is pertinent to mention here that $\Delta\omega$ values are higher for reacting pairs involving azadienes **10a**−**e** and allenic esters **6a**−**c**, and these reactions predominently afford [4+2] cycloadditions.

TABLE 4. Chemical Hardness (η), Chemical Potential (μ), and Global Electrophilicity (ω) Calculated at the B3LYP/6-31G* Level

azadiene	species	η, eV	μ, eV	ω, eV
5a	s-cis	1.85	−3.78	3.87
	s-trans	1.90	−3.79	3.77
5b	s-cis	1.81	−3.70	3.78
	s-trans	1.86	−3.70	3.68
5c	s-cis	1.71	−3.53	3.64
	s-trans	1.76	−3.53	3.53
5d	s-cis	1.82	−3.93	4.24
	s-trans	1.87	−3.93	4.12
10a	s-cis	1.69	−4.25	5.33
	s-trans	1.67	−4.31	5.56
10b	s-cis	1.63	−4.15	5.28
	s-trans	1.61	−4.21	5.52
10c	s-cis	1.51	−3.97	5.22
	s-trans	1.49	−4.03	5.46
10d	s-cis	1.68	−4.35	5.62
	s-trans	1.67	−4.41	5.85
10e	s-cis	1.77	−4.63	6.05
	s-trans	1.76	−4.68	6.24
6a	R = H	3.10	−4.10	2.71
6b	R= Me	3.05	−3.93	2.53
6c	R = Et	3.05	−3.91	2.51
12a	R_1= Me	3.00	−3.73	2.31
	R_2 = Et			
12b	R_3= Me	2.66	−3.97	2.96

TABLE 5. Global Electrophilicity Difference ($\Delta\omega$) between the Reactant Pairs Calculated at the B3LYP/6-31G* Level

		$\Delta\omega$, eV ($\omega_{azadiene} - \omega_{allene}$)				
azadiene	species	**6a** R = H	**6b** R = Me	**6c** R = Et	**12a** R_1 = Me R_2 = Et	**12b** R_3 = Me
5a	s-cis	1.16	1.34	1.38	1.56	0.91
	s-trans	1.08	1.24	1.26	1.46	0.81
5b	s-cis	1.07	1.25	1.29	1.47	0.82
	s-trans	0.97	1.15	1.27	1.37	0.72
5c	s-cis	0.93	1.11	1.13	1.33	0.68
	s-trans	0.82	1.00	1.02	1.22	0.67
5d	s-cis	1.53	1.71	1.73	1.93	1.28
	s-trans	1.41	1.59	1.61	1.81	1.16
10a	s-cis	2.62	2.80	2.82	3.01	2.36
	s-trans	2.86	3.04	3.05	3.25	2.60
10b	s-cis	2.57	2.75	2.77	2.96	2.31
	s-trans	2.81	2.99	3.01	3.21	2.56
10c	s-cis	2.51	2.69	2.71	2.91	2.26
	s-trans	2.76	2.94	2.95	3.14	2.49
10d	s-cis	2.92	3.10	3.11	3.31	2.66
	s-trans	3.14	3.32	3.34	3.53	2.88
10e	s-cis	3.34	3.52	3.54	3.74	3.09
	s-trans	3.53	3.71	3.73	3.93	3.28

TABLE 6. Site with Higher f^+ Value in Azadienes (10a−e)

entry	species	N_1	C_2	C_3	C_4
10a	R′ = H	0.076	0.053	0.017	0.063
10b	R′ = Me	0.067	0.052	0.015	0.060
10c	R′ = OMe	0.047	0.051	0.015	0.057
10d	R′ = Cl	0.062	0.049	0.015	0.057
10e	R′ = CN	0.073	0.045	0.020	0.058

Fukui functions (f^+ and f^-) have also been calculated for understanding the regiochemical outcome of these cycloadditions. The results reveal the most reactive sites in 1-azadienes (**10a**−**e**) and allenic esters (**6a**−**c** and **12a**,**b**). It was observed that the site with the higher f^+ value is the N-atom of azadienes (**10a**−**e**, Table 6) and the site with the higher f^- value is the C_3-carbon atom of allenes (**6a**−**c** and **12a**,**b**, Table 7).

TABLE 7. Site with Higher f^- Value in Allenes (6a−c, 12a,b)

entry	species	C_2	C_3	C_4
6a	R = H	0.110	0.141	0.110
6b	R = Me	0.103	0.133	0.085
6c	R = Et	0.100	0.130	0.081
12a	R_1 = Me, R_2 = Et	0.094	0.123	0.062
12b	R_3= Me	0.085	0.127	0.101

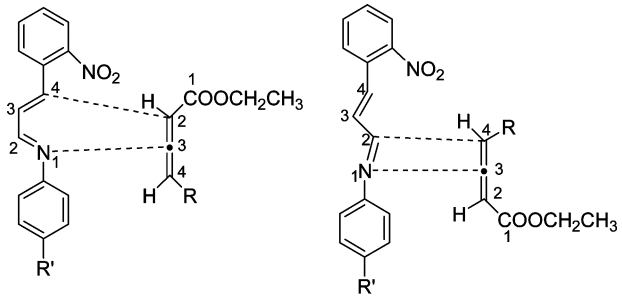
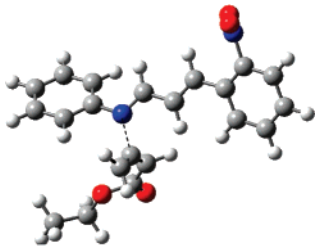


FIGURE 3.



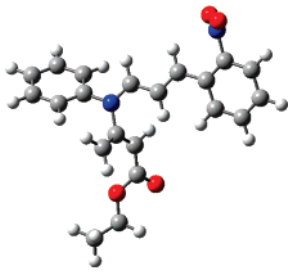
TS I

FIGURE 4. Common transition state leading to intermediate.

The results are in agreement with the obtained regiochemistry for [2+2] cycloadditions;[19] however, the f^- values for C_2 and C_4 of allenic ester are close and a different regiochemistry, i.e., involvement of $C_2-C_3\pi$, is obtained for [4+2] cycloadditions (Figure 3).

Although the most reactive atom (in the diene part) of the azadienes is the nitrogen atom and the present calculations predict the azadienes to be acceptors, earlier theoretical attempts at rationalization[17b,24] of cycloadditions of azadienes and imines with ketenes and other heterocumulenes have invoked the interaction of the nonbonding lone pair of azadiene nitrogen with the central heterocumulenic carbon leading to a dipolar intermediate as the first step in a stepwise reaction process. It is pertinent to mention here that the nonbonding lone pair represents the HOMO of the azadienes.[24l]

An attempt was made to locate the transition states for a stepwise cycloaddition process involving the intraction of the nitrogen lone pair of azadiene **10a** and the central allenic carbon of allenic ester **6a** at the PM3 level for [4+2] and [2+2] cycloadditions. Figure 4 shows the common transition state TS I resulting from intraction of the N-atom of azadiene **10a** and the allenic ester **6a** and leading to the common intermediate **B** (Figure 5) for both modes of addition, wherein the diene and dienophile orientation is perpendicular to each other due to steric encumbrance.



B

FIGURE 5. Common reaction intermediate.

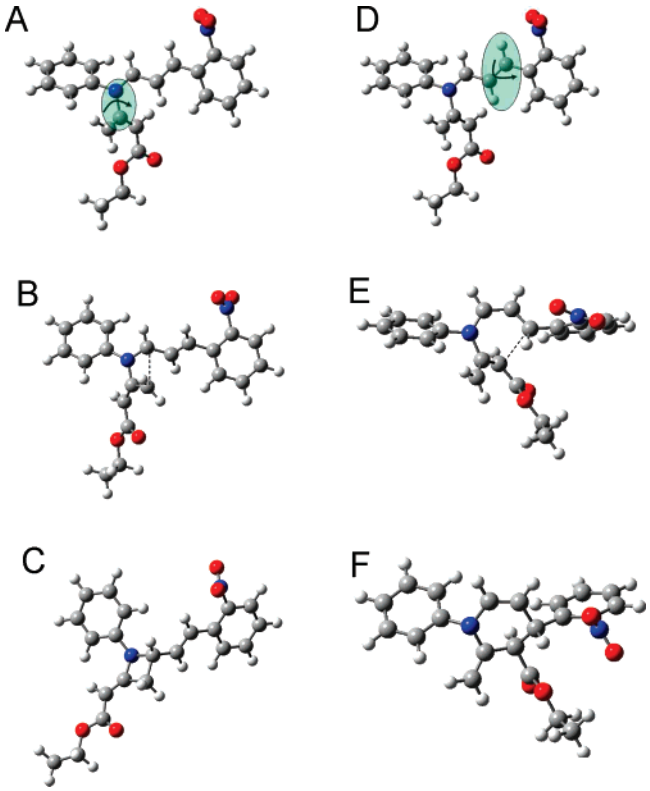


FIGURE 6. (A) Rotation leading to [2+2] cycloadduct; (B) transition state TS-IIA for [2+2] addition; (C) [2+2] cycloadduct; (D) rotation for conversion of s-trans rotamer into s-cis facilitating [4+2] cycloaddition; (E) transition state TS-IIB for [4+2] addition; and (F) [4+2] cycloadduct.

Rotation of a specific bond as shown in Figure 6A transforms the intermediate **B** to transition state TS IIA (Figure 6B), leading to the [2+2] cycloadduct (Figure 6C). Alternatively, a rotation converting s-trans azadiene into s-cis as shown in Figure 6D propells this intermediate **B** to transition state TS IIB (Figure 6E) leading to formation of the [4+2] cycloadduct (Figure 6F), which undergo 1,3-H shift to afford valuable unsymmetrical substituted 1,4-dihydropyridines (**11a**−**o**). It is important to note that conversion of the s-trans rotamer into the s-cis rotamer is favored at high temperature.

Activation energy barriers for both types of addition using azadiene **10a** and various allenic esters (**6a**−**c**) were also calculated (Figure 7). The difference in the activation energy for both types of additions is shown in Table 8.

It is clear from the investigations that the activation energy for [4+2] addition is less than that for [2+2] addition, hence, the limiting factor for the reaction between 1-azadienes and

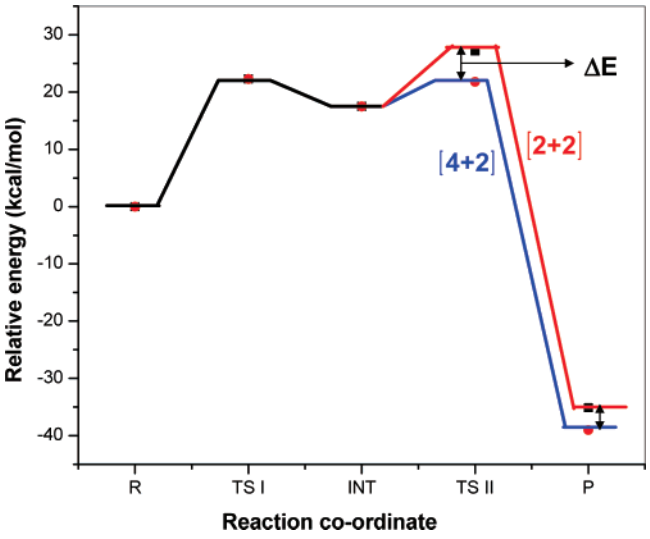


FIGURE 7. Activation energy barrier for [2+2] and [4+2] addition.

TABLE 8. Δ*E* for Both Types of Addition

azadiene	allenic ester	Δ*E*,[a] kcal/mol
10a	**6a**	5.5
10a	**6b**	3.0
10a	**6c**	3.7

[a] Difference in activation energy for [2+2] and [4+2] cycloadditions.

allenic esters to yield either a [2+2] cycloadduct or a [4+2] cycloadduct is not the overall activation energy of the reaction, rather it is the energy required to convert s-trans azadienes into their s-cis forms. We were not able to get transition states and difference in activation energy of both types of cycloadditions for allenic esters **12a**,**b** with 1-azadienes **10a**−**e** (Scheme 3); reactions of these allenic esters did not lead to the formation of any cycloadduct. Possibly an increase in the number of electron releasing alkyl groups on the allenic moiety, making the central carbon atom of allenic esters **12a**,**b** less electron deficient, along with the steric hindrance caused by these bulky groups may be the reason for the failure of these allenes to undergo cycloaddition reactions with 1-azadienes.

Conclusion

The investigations have established the general applicability of thermal cycloadditions of 1-azadienes with allenic esters as a facile route to novel variedly substituted unsymmetrical 1,4-dihydropyridines. The reactions carried out under microwave irridiation are cleaner, attended with higher yields, and require much shorter reaction times. Theoretical calculations for the optimized geometry of reactants, energy barriers between the two rotamers of azadienes, and the electrophilicity index of diene/dienophile pairs were carried out at the B3LYP/6-31G* level. Results indicate that s-trans is the preferred low-energy conformation of azadienes. The high-energy barrier for conversion of s-trans azadienes to s-cis may be the reason for formation of the [2+2] cycloadduct at low temperature. The $\Delta\omega$ values (1.0−3.0 eV) indicate that the transition states for these cycloadditions are highly polar. The Fukui function results clearly support the observed regiochemistry in the case of [2+2] cycloadducts; however, altered regiochemistry of addition for [4+2] cycloadducts is not unequivocally supported by these calculations. Location of the transition states at the PM3 level for [2+2] and [4+2] cycloadditions showed that the activation energy required for [4+2] cycloaddition is less than that for [2+2] cycloaddition. Apparently, the preferred formation of [4+2] cycloadducts at higher reaction temperature may be attributed to the facile conversion of the s-trans rotamer of azadienes into the s-cis rotamer. Alternatively, as postulated earlier, the [2+2] cycloaddition may be proceeding through a concerted ($\pi^2_s + \pi^2_s + \pi^2_s$) process and, hence, preferred at low temperature. Though higher level theoretical calculations are required to gain a deeper insight into the mechanistic details, the present investigations have provided an efficient route to unsymmetrical substituted 1,4-dihydropyridines.

Experimental Section

Starting materials and reagents were purchased from commercial suppliers and purified/distilled/crystallized before use. Hexane, petroleum ether, and ethyl acetate used in column chromatography were distilled before use; the petroleum ether employed was the fraction boiling in the range of 40−60 °C. Allenic esters were prepared by the method of Lang and Hansen and characterized spectroscopically.[27] 1,4-Diaryl-1-azadienes were also prepared according to the literature method and characterized spectroscopically.[28]

Bruker AC-200 FT (200 MHz) and JEOL AL-300FT (300 MHz) spectrometers were used to record ^{1}H NMR and ^{13}C NMR (50 and 75 MHz) spectra. Chemical shifts (δ) are reported as downfield displacements from TMS used as internal standard and coupling constants (J) are reported in Hz. IR spectra were recorded with a Shimadzu FT-IR-8400S spectrophotometer on KBr pellets. Mass spectra, EI and ESI methods, were recorded on Shimadzu GCMS-QP-2000A and Bruker Daltonics Esquire 300 mass spectrometers, respectively. Elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer and are reported in percent atomic abundance. The CEM-Discover Focused Monomode Microwave apparatus (2450 MHz, 300w) was used for microwave irradiation. All melting points are uncorrected and measured in open glass capillaries on a Veego (make) MP-D digital melting point apparatus. All the calculations were performed with the Gaussian 98 package. The molecules have been optimized at the B3LYP/6-31G* level. All of them were found to be minimum on the potential energy surface with zero imaginary frequency. Global reactivity indexes were calculated by using the working equations available in the literature. Local reactivity indices, Fukui functions, have been calculated by using the DMOL program implemented in the Cerius2 package employing the Hershfeld populations scheme.

Procedure for the Thermal Reaction of 1,4-Diaryl-1-aza-1,3-butadienes (10) with Allenic Esters (6). A solution of 1,4-diaryl-1-azadiene (**10a**−**e**, 200 mg) and allenic ester (**6a**−**c**) (1.2 molar equiv) in dry benzene (20 mL) was refluxed under an atmosphere of nitrogen until the 1-azadiene was completely consumed. After the completion of the reaction (TLC basis), solvent was removed under vacuum and the formed 1,4-DHPs (**11a**−**o**) were purified by column chromatography (silica gel 60−120 mesh, eluent hexane: EtOAc 9:1).

Procedure for Microwave Assisted Reaction of 1,4-Diaryl-1-aza-1,3-butadienes (10) with Allenic Esters (6). In a 50 mL round-bottomed flask, the solutions of 1,4-diaryl-1-azadiene (**10a**−**e**, 200 mg) and allenic ester (**6a**−**c**) (1.2 molar equiv) in dry benzene (2 mL) were exposed to microwave radiation (150 W, 100 °C) for the time as given in Table 1. After the completion of the reaction (TLC basis), solvent was removed under vacuum and the formed

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1,4-DHPs (**11a**−**o**) were purified by column chromatography (silica gel 60−120 mesh, eluent hexane:EtOAc 9:1).

All the 1,4-DHPs were obtained as yellow crystalline compounds, recrystallized from dichloromethane−hexane (1:1), in good yields (Table 1). The physical and spectroscopic data for various 1-aza-dienes (**10a**−**e**) and 1,4-dihydropyridines (**11a**−**o**) are as follows:

1-Aza-4-(*o*-nitrophenyl)-1-phenyl-1,3-butadiene (10a): R_f 0.54 ($CHCl_3$/hexane 9:1); mp 121−122 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.30 (d, J = 8.87 Hz, 1H), 8.04 (dd, J = 8.11, 1.28 Hz, 1H), 7.76−7.52 (m, 4H), 7.37−7.32 (m, 3H), 7.15−6.98 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.49, 149.54, 148.02, 138.22, 133.13, 132.97, 132.21, 131.09, 129.52, 129.22, 128.30, 124.92, 122.16; IR (KBr) ν 1608.52, 1583.45, 1568.02, 1517.87, 1483.16, 1473.51, 1448.44, 1342.36, 1317.29, 1303.79, 1249.79, 1157.21, 1135.99, 1072.35; MS (70 eV, EI) *m*/*z* (%) 252 (15) [M^+], 251 (30) [M^+ − H], 205 (45), 169 (100). Anal. Calcd (%) for $C_{15}H_{12}N_2O_2$ (252.09): C 71.42, H 4.79, N 11.10. Found: C 71.16, H 4.60, N 11.03.

1-Aza-4-(*o*-nitrophenyl)-1-*p*-tolyl-1,3-butadiene (10b): R_f 0.56 ($CHCl_3$/hexane 9:1); mp 81−82 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.34 (d, J = 8.87 Hz, 1H), 8.02 (dd, J = 8.02, 1.24 Hz, 1H), 7.77−7.61 (m, 3H), 7.54−7.50 (m, 1H), 7.20−7.01 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.29, 148.50, 147.97, 137.07, 136.34, 133.39, 133.10, 131.25, 129.70, 129.27, 128.24, 124.84, 120.89, 21.03; IR (KBr) ν 1608.52, 1585.38, 1569.95, 1525.59, 1502.44, 1473.51, 1342.36, 1313.43, 1299.93, 1253.64, 1155.28, 1135.99, 1108.99; MS (70 eV, EI) *m*/*z* (%) 266 (20) [M^+], 265 (25) [M^+ − H], 219 (65), 169 (100). Anal. Calcd (%) for $C_{16}H_{14}N_2O_2$ (266.29): C 72.16, H 5.30, N 10.52. Found: C 72.02, H 5.26, N 10.42.

1-*p*-Anisyl-1-aza-4-(*o*-nitrophenyl)-1,3-butadiene (10c): R_f 0.68 ($CHCl_3$/hexane 9:1); mp 113−114 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.35 (d, J = 8.84 Hz, 1H), 8.00 (d, J = 8.04 Hz, 1H), 7.77−7.58 (m, 3H), 7.51−7.44 (m, 1H), 7.22 (d, J = 8.7 Hz, 2H), 7.06 (dd, J = 15.7, 8.8 Hz, 1H), 6.92 (d, J = 8.6 Hz, 2H), 5.82 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.79, 157.88, 148.00, 143.89, 136.45, 133.56, 133.05, 131.38, 129.14, 128.17, 124.85, 122.33, 114.30, 55.16 ppm; IR (KBr) ν 1623.95, 1608.52, 1569.95, 1525.59, 1502.44, 1467.73, 1344.29, 1294.15, 1247.86, 1211.21, 1159.14, 1107.06, 1033.77; MS (70 eV, EI) *m*/*z* (%) 283 (60) [M^+ + 1], 282 (27) [M^+], 281 (20), 236 (10), 170 (10), 169 (100). Anal. Calcd (%) for $C_{16}H_{14}N_2O_3$ (282.10): C 68.07, H 5.00, N 9.92. Found: C 67.81, H 4.95, N 9.85.

1-Aza-1-*p*-chloro-4-(*o*-nitrophenyl)-1,3-butadiene (10d): R_f 0.76 ($CHCl_3$/hexane 9:1); mp 109−110 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.29 (d, J = 8.85 Hz, 1H), 7.99 (dd, J = 8.08, 1.09 Hz, 1H), 7.73−7.60 (m, 3H), 7.50−6.99 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.91, 149.57, 147.91, 138.50, 133.39, 132.81, 132.11, 130.99, 129.71, 129.25, 128.38, 124.90, 122.21 ppm; IR (KBr) ν 1606.59, 1596.95, 1569.95, 1517.87, 1485.09, 1446.51, 1353.01, 1342.36, 1153.35, 1089.71, 1010.63; MS (70 eV, EI) *m*/*z* (%) 287 (17) [M^+ + 1], 286 (25) [M^+], 285 (35), 284 (60), 283 (60), 240 (30), 169 (100). Anal. Calcd (%) for $C_{15}H_{11}ClN_2O_2$ (286.05): C 62.84, H 3.87, N 9.77. Found: C 62.61, H 3.83, N 9.71.

1-Aza-1-*p*-cyano-4-(*o*-nitrophenyl)-1,3-butadiene (10e): R_f 0.53 ($CHCl_3$/hexane 9:1); mp 135−136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 9.0, 1H), 8.12−8.02 (m, 1H), 7.79−7.53 (m, 6H), 7.22 (d, J = 7.4, 2H), 7.09−7.0 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.92, 155.14, 147.21, 140.30, 133.34, 132.59, 132.35, 130.14, 129.02, 128.57, 125.04, 121.53, 118.78, 109.59, IR (KBr) ν 2223.77, 1629.74, 1614.31, 1589.23, 1569.95, 1521.73, 1494.73, 1440.73, 1346.22, 1307.65, 1257.50, 1159.14, 1137.92, 1112.85; MS (ESI) *m*/*z* (%) 277.9 [M^+]. Anal. Calcd (%) for $C_{16}H_{11}N_3O_2$ (277.09): C 69.31, H 4.00, N 15.15. Found: C 69.26, H 3.93, N 15.10.

3-Ethoxycarbonyl-2-methyl-4-(*o*-nitrophenyl)-1-phenyl-1,4-dihydropyridine (11a): R_f 0.62 ($CHCl_3$/hexane 8:2); mp 105−106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73−7.20 (m, 9H), 6.10 (d, J = 6.3 Hz, 1H), 5.19−5.16 (m, 2H), 3.87 (q, J = 7.0 Hz, 2H), 2.20 (s, 3H), 0.94 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.48, 149.60, 148.01, 143.48, 143.41, 132.95, 131.17, 129.86, 129.68, 127.67, 126.50, 123.11, 106.35, 100.50, 59.33, 36.27, 18.51, 13.91 ppm; IR (KBr) ν 1691.46, 1670.24, 1560.30, 1523.66, 1490.87, 1380.94, 1355.86, 1332.72, 1220.86, 1209.28, 1107.06, 1074.28; MS (ESI) *m*/*z* (%) 387.1 [M^+ + Na]. Anal. Calcd (%) for $C_{21}H_{20}N_2O_4$ (364.14): C 69.22, H 5.53, N 7.69. Found: C 69.18, H 5.49, N 7.60.

3-Ethoxycarbonyl-2-methyl-4-(*o*-nitrophenyl)-1-*p*-tolyl-1,4-dihydropyridine (11b): R_f 0.57 ($CHCl_3$/hexane 8:2); mp 125−126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74−7.07 (m, 8H), 6.08 (d, J = 6.9 Hz, 1H), 5.18−5.16 (m, 2H), 3.87 (q, J = 6.7 Hz, 2H), 2.38 (s, 3H), 2.20 (s, 3H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.87, 150.12, 147.84, 143.51, 140.80, 137.65, 133.09, 131.13, 130.23, 130.06, 127.42, 126.52, 123.12, 106.05, 99.92, 59.34, 36.66, 21.02, 18.35, 13.82 ppm; IR (KBr) ν 1681.81, 1660.60, 1560.30, 1517.87, 1510.16, 1380.94, 1352.01, 1340.43, 1222.79, 1205.43, 1114.78, 1070.42; MS (ESI) *m*/*z* (%) 378.0 [M^+]. Anal. Calcd (%) for $C_{22}H_{22}N_2O_4$ (378.16): C 69.83, H 5.86, N 7.40. Found: C 69.76, H 5.81, N 7.37.

1-*p*-Anisyl-3-ethoxycarbonyl-2-methyl-4-(*o*-nitrophenyl)-1,4-dihydropyridine (11c): R_f 0.67 ($CHCl_3$/hexane 8:2); mp 111−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74−6.92 (m, 8H), 6.06 (d, J = 6.9 Hz,1H), 5.19−5.14 (m, 2H), 3.87 (q, J = 6.9 Hz, 2H), 3.84 (s, 3H), 2.19 (s, 3H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.77, 158.77, 150.31, 147.69, 143.47, 136.06, 133.05, 131.05, 130.12, 128.74, 126.45, 123.02, 114.65, 105.83, 99.54, 59.23, 55.41, 36.13, 18.18, 13.73 ppm; IR (KBr) ν 1685.67, 1670.24, 1550.66, 1521.73, 1508.23, 1490.87, 1346.22, 1249.79, 1220.86, 1203.50, 1103.21, 1076.21; MS (ESI) *m*/*z* (%) 417.1 [M^+ + Na]. Anal. Calcd (%) for $C_{22}H_{22}N_2O_5$ (394.15): C 66.99, H 5.62, N 7.10. Found: C 66.90, H 5.54, N 7.02.

1-*p*-Chlorophenyl-3-ethoxycarbonyl-2-methyl-4-(*o*-nitrophenyl)-1,4-dihydropyridine (11d): R_f 0.70 ($CHCl_3$/hexane 8:2); mp 130−131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73−7.13 (m, 8H), 6.04 (d, J = 7.5 Hz, 1H), 5.20−5.14 (m, 2H), 3.87 (q, J = 7.0 Hz, 2H), 2.19 (s, 3H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.30, 148.99, 148.05, 143.08, 141.95, 133.51, 132.95, 131.04, 129.87, 129.49, 128.96, 126.60, 123.18, 106.70, 101.16, 59.43, 36.26, 18.47, 13.86 ppm; IR (KBr) ν 1685.67, 1665.46, 1560.30, 1527.52, 1487.01, 1357.79, 1220.86, 1209.28, 1107.06, 1095.49, 1068.49; MS (ESI) *m*/*z* (%) 421.0 [M^+ + Na]. Anal. Calcd (%) for $C_{21}H_{19}ClN_2O_4$ (398.10): C 63.24, H 4.80, N 7.02. Found: C 63.22, H 4.77, N 7.01.

1-*p*-Cyanophenyl-3-ethoxycarbonyl-2-methyl-4-(*o*-nitrophenyl)-1,4-dihydropyridine (11e): R_f 0.45 ($CHCl_3$/hexane 8:2); mp 162−163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.52 (m, 8H), 6.17 (d, J = 7.8 Hz, 1H), 5.28 (dd, J = 7.8, 4.9 Hz, 1H), 5.20 (d, J = 4.2 Hz, 1H), 3.90 (q, J = 6.9 Hz, 2H), 2.17 (s, 3H), 0.94 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.33, 155.65, 148.04, 147.94, 142.26, 133.58, 133.16, 130.81, 128.91, 127.78, 126.89, 123.38, 116.30, 110.91, 107.33, 103.16, 59.75, 36.27, 18.85, 13.72 ppm; IR (KBr) ν 2229.56, 1685.67, 1666.38, 1566.09, 1521.73, 1504.37, 1444.58, 1386.72, 1353.94, 1218.93, 1112.85, 1105.14, 1093.56, 1066.56, 1016.42; MS (ESI) *m*/*z* (%): 412.1 [M^+ + Na]. Anal. Calcd (%) for $C_{22}H_{19}N_3O_4$ (389.14): C 67.86, H 4.92, N 10.79. Found: C 67.79, H 4.84, N 10.71.

3-Ethoxycarbonyl-2-ethyl-4-(*o*-nitrophenyl)-1-phenyl-1,4-dihydropyridine (11f): R_f 0.64 ($CHCl_3$/hexane 8:2); mp 106−107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74−7.25 (m, 9H), 6.06 (d, J = 6.3 Hz, 1H), 5.20−5.14 (m, 2H), 3.88 (q, J = 6.9 Hz, 2H), 2.72−2.68 (m, 2H), 1.01 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.91, 155.80, 147.80, 143.47, 143.11, 133.03, 130.83, 130.28, 129.51, 128.11, 127.87, 126.47, 123.11, 106.15, 98.83, 59.02, 36.02, 22.84, 13.80, 13.38 ppm; IR (KBr) ν 1691.46, 1674.10, 1556.45, 1519.80, 1492.80, 1373.22, 1350.08, 1263.29, 1215.07, 1197.71, 1110.92, 1083.92, 1033.71; MS (ESI) *m*/*z* (%) 401.1 [M^+ + Na]. Anal. Calcd (%) for

$C_{22}H_{22}N_2O_4$ (378.16): C 69.83, H 5.86, N 7.40. Found: C 69.74, H 5.78, N 7.37.

3-Ethoxycarbonyl-2-ethyl-4-(*o*-nitrophenyl)-1-*p*-tolyl-1,4-dihydropyridine (11g): R_f 0.59 ($CHCl_3$/hexane 8:2); mp 153−154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74−7.12 (m, 8H), 6.02 (d, J = 5.2 Hz, 1H), 5.18−5.13 (m, 2H), 3.87 (q, J = 7.0 Hz, 2H), 2.71−2.67 (m, 2H), 2.40 (s, 3H), 1.01 (t, J = 7.3 Hz, 3H), 0.94 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.04, 156.14, 147.82, 143.66, 140.58, 137.84, 133.06, 130.91, 130.45, 130.20, 127.93, 126.46, 123.14, 106.07, 98.54, 59.28, 36.08, 22.88, 21.10, 13.84, 13.45 ppm; IR (KBr) ν 1685.67, 1668.31, 1556.45, 1517.87, 1512.09, 1440.73, 1371.29, 1355.86, 1211.21, 1114.78, 1108.99, 1078.13, 1026.06; MS (ESI) *m*/*z* (%) 392.0 [M^+]. Anal. Calcd (%) for $C_{23}H_{24}N_2O_4$ (392.17): C 70.39, H 6.16, N 7.14. Found: C 70.34, H 6.12, N 7.11.

1-*p*-Anisyl-3-ethoxycarbonyl-2-ethyl-4-(*o*-nitrophenyl)-1,4-dihydropyridine (11h): R_f 0.69 ($CHCl_3$/hexane 8:2); mp 138−139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−6.93 (m, 8H), 6.01 (d, J = 6.9 Hz, 1H), 5.18−5.14 (m, 2H), 3.89 (q, J = 6.3 Hz, 2H), 3.84 (s, 3H), 2.73−2.65 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.13, 158.93, 156.39, 147.73, 143.67, 135.84, 133.11, 130.87, 130.59, 129.28, 126.48, 123.14, 114.64, 105.92, 98.30, 59.27, 55.48, 36.05, 22.87, 13.79, 13.38 ppm; IR (KBr) ν 1689.53, 1674.10, 1560.30, 1510.16, 1458.08, 1440.73, 1352.01, 1247.86, 1213.14, 1199.64, 1184.21, 1114.781107.06, 1080.06; MS (ESI) *m*/*z* (%) 431.2 [M^+ + Na]. Anal. Calcd (%) for $C_{23}H_{24}N_2O_5$ (408.17): C 67.63, H 5.92, N 6.86. Found: C 67.57, H 5.87, N 6.82.

1-*p*-Chlorophenyl-3-ethoxycarbonyl-2-ethyl-4-(*o*-nitrophenyl)-1,4-dihydropyridine (11i): R_f 0.72 ($CHCl_3$/hexane 8:2); mp 127−128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.19 (m, 8H), 6.02 (d, J = 7.2 Hz, 1H), 5.22−5.15 (m, 2H), 3.88 (q, J = 6.9 Hz, 2H), 2.72−2.67 (m, 2H), 1.01 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.80, 155.23, 147.75, 143.07, 141.56, 130.65, 133.58, 133.02, 129.73, 129.68, 129.40, 126.53, 123.12, 106.35, 99.37, 59.30, 36.03, 22.70, 13.66, 13.24 ppm; IR (KBr) ν 1691.46, 1679.88, 1562.23, 1517.87, 1488.94, 1460.01, 1352.01, 1213.14, 1197.71, 1112.85, 1083.92; MS (ESI) *m*/*z* (%) 435.2 [M^+ + Na]. Anal. Calcd (%) for $C_{22}H_{21}ClN_2O_5$ (412.12): C 64.00, H 5.13, N 6.79. Found: C 63.97, H 5.07, N 6.72.

1-*p*-Cyanophenyl-3-ethoxycarbonyl-2-ethyl-4-(*o*-nitrophenyl)-1,4-dihydropyridine (11j): R_f 0.47 ($CHCl_3$/hexane 8:2); mp 112−113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77−7.26 (m, 8H), 6.10 (d, J = 7.8 Hz, 1H), 5.26 (dd, J = 7.5, 5.1 Hz, 1H), 5.17 (d, J = 4.8 Hz, 1H), 3.90 (q, J = 7.2 Hz, 2H), 2.85−2.81 (m, 1H), 2.65−2.58 (m, 1H), 0.99 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.69, 154.27, 147.94, 147.10, 142.40, 133.59, 133.15, 130.52, 129.42, 128.53, 126.82, 123.40, 117.88, 111.35, 107.33, 101.46, 59.67, 36.04, 22.75, 13.69, 13.29 ppm; IR (KBr) ν 2225.70, 1674.10, 1566.09, 1521.73, 1504.37, 1469.66, 1371.29, 1336.58, 1257.50, 1236.29, 1190.00, 1118.64, 1095.49, 1024.13; MS (ESI) *m*/*z* (%) 426.1 [M^+ + Na]. Anal. Calcd (%) for $C_{23}H_{21}N_3O_4$ (403.15): C 68.47, H 5.25, N 10.42. Found: C 68.41, H 5.19, N 10.37.

3-Ethoxycarbonyl-4-(*o*-nitrophenyl)-1-phenyl-2-propyl-1,4-dihydropyridine (11k): R_f 0.66 ($CHCl_3$/hexane 8:2); mp 78−79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−7.24 (m, 9H), 6.07 (d, J = 7.2 Hz, 1H), 5.20−5.17 (m, 2H), 3.88 (q, J = 7.0 Hz, 2H), 2.70−2.55 (m, 2H), 1.52−1.40 (m, 2H), 0.95 (t, J = 7.0 Hz, 3H), 0.72 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.22, 154.61, 147.80, 143.51, 143.20, 133.10, 130.87, 130.30, 129.57, 128.09, 127.85, 126.52, 123.19, 106.11, 99.25, 59.33, 36.14, 31.47, 22.51, 14.11, 13.82 ppm; IR (KBr) ν 1687.60, 1670.24, 1556.45, 1521.73, 1492.80, 1353.94, 1211.21, 1116.71, 1076.21; MS (ESI) *m*/*z* (%) 415.2 [M^+ + Na]. Anal. Calcd (%) for $C_{23}H_{24}N_2O_4$ (392.17): C 70.39, H 6.16, N 7.14. Found: C 70.33, H 6.13, N 7.08.

3-Ethoxycarbonyl-4-(*o*-nitrophenyl)-2-propyl-1-*p*-tolyl-1,4-dihydropyridine (11l): R_f 0.59 ($CHCl_3$/hexane 8:2); mp 84−85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74−7.11 (m, 8H), 6.03 (d, J = 6.9 Hz, 1H), 5.19−5.14 (m, 2H), 3.88 (q, J = 7.0 Hz, 2H), 2.64−2.59 (m, 2H), 2.40 (s, 3H), 1.53−1.41 (m, 2H), 0.94 (t, J = 7.0 Hz, 3H), 0.74 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.26, 154.92, 147.75, 143.65, 140.61, 137.79, 133.10, 130.90, 130.45, 130.15, 127.82, 126.48, 123.14, 105.97, 98.86, 59.28, 36.13, 31.47, 22.54, 21.08, 14.16, 13.82 ppm; IR (KBr) ν 1685.67, 1670.24, 1552.59, 1525.59, 1510.16, 1444.58, 1353.94, 1209.28, 1114.78, 1078.13, 1033.77; MS (ESI) *m*/*z* (%) 429.2 [M^+ + Na]. Anal. Calcd (%) for $C_{24}H_{26}N_2O_4$ (406.19): C 70.92, H 6.45, N 6.89. Found: C 70.87, H 6.40, N 6.85.

1-*p*-Anisyl-3-ethoxycarbonyl-4-(*o*-nitrophenyl)-2-propyl-1,4-dihydropyridine (11m): R_f 0.71 ($CHCl_3$/hexane 8:2); mp 81−82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73−6.90 (m, 8H), 5.98 (d, J = 6.6 Hz, 1H), 5.15−5.11 (m, 2H), 3.87 (q, J = 6.7 Hz, 2H), 3.84 (s, 3H), 2.62−2.57 (m, 2H), 1.49−1.42 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H), 0.75 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.07, 158.96, 154.99, 147.92, 143.76, 136.09, 132.97, 130.97, 130.55, 129.29, 126.43, 123.14, 114.64, 106.06, 98.89, 59.23, 55.40, 36.20, 31.52, 22.61, 14.31, 13.91 ppm; IR (KBr) ν 1689.53, 1672.17, 1562.23, 1517.87, 1508.23, 1350.08, 1245.93, 1211.21, 1182.28, 1078.13, 1039.56; MS (ESI) *m*/*z* (%) 445.2 [M^+ + Na]. Anal. Calcd (%) for $C_{24}H_{26}N_2O_5$ (422.18): C 68.23, H 6.20, N 6.63. Found: C 68.15, H 6.13, N 6.55.

1-*p*-Chlorophenyl-3-ethoxycarbonyl-4-(*o*-nitrophenyl)-2-propyl-1,4-dihydropyridine (11n): R_f 0.78 ($CHCl_3$/hexane 8:2); mp 108−109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−7.19 (m, 8H), 6.01 (d, J = 6.6 Hz, 1H), 5.21−5.15 (m, 2H), 3.88 (q, J = 7.0 Hz, 2H), 2.66−2.58 (m, 2H), 1.49−1.41 (m, 2H), 0.94 (t, J = 7.0 Hz, 3H), 0.76 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.09, 154.05, 147.88, 143.20, 141.81, 133.66, 133.10, 130.77, 129.96, 129.81, 129.45, 126.63, 123.28, 106.49, 99.96, 59.45, 36.17, 31.39, 22.53, 14.10, 13.79 ppm; IR (KBr) ν 1685.67, 1674.10, 1556.45, 1523.66, 1490.87, 1350.08, 1340.43, 1211.21, 1114.78, 1080.06; MS (ESI) *m*/*z* (%) 449.2 [M^+ + Na]. Anal. Calcd (%) for $C_{23}H_{23}ClN_2O_4$ (426.13): C 64.71, H 5.43, N 6.56. Found: C 64.67, H 5.37, N 6.52.

1-*p*-Cyanophenyl-3-ethoxycarbonyl-4-(*o*-nitrophenyl)-2-propyl-1,4-dihydropyridine (11o): R_f 0.58 ($CHCl_3$/hexane 8:2); mp 178−179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.26 (m, 8H), 6.11 (d, J = 7.5 Hz, 1H), 5.27 (dd, J = 5.1, 4.8 Hz, 1H), 5.18 (d, J = 5.1 Hz, 1H), 3.91 (q, J = 7.2 Hz, 2H), 2.81−2.74 (m, 1H), 2.58−2.49 (m, 1H), 1.46−1.39 (m, 2H), 0.95 (t, J = 7.0 Hz, 3H), 0.75 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.81, 152.89, 147.23, 142.37, 138.46, 133.56, 133.13, 131.22, 130.53, 128.42, 126.82, 123.41, 117.89, 111.23, 107.37, 102.12, 59.69, 36.17, 31.25, 22.61, 13.91, 13.71 ppm; IR (KBr) ν 2231.49, 1697.24, 1602.74, 1564.16, 1514.02, 1440.73, 1371.29, 1350.08, 1265.22, 1215.07, 1112.85, 1083.92, 1022.20; MS (ESI) *m*/*z* (%) 440.2 [M^+ + Na]. Anal. Calcd (%) for $C_{24}H_{23}N_3O_4$ (417.17): C 69.05, H 5.55, N 10.07. Found: C 69.00, H 5.50, N 10.03.

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Supporting Information Available: ^{1}H NMR spectras of compounds **10a**−**e** and **11a**−**o**, geometrical structures of both rotamers and transition states between them for various azadienes (**5a**−**e** and **10a**−**e**), activation energy barriers for [2+2] and [4+2] cycloaddtions of azadiene **10a** and allenic esters **6a**−**c**, and a crystallographic information file. This material is available free of charge via the Internet at http://pubs.acs.org.

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