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Facile, Regioselective [4 + 2] Cycloaddition Involving 1-Aryl-4-phenyl-1-azadienes and Allenic Esters: An Efficient Route to Novel Substituted 1-Aryl-4-phenyl-1,4-dihydropyridines

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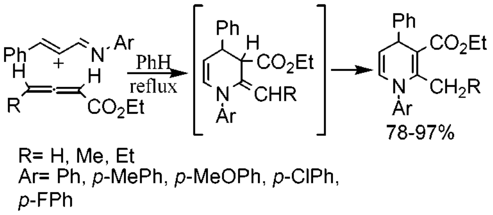
ABSTRACT



1-Aryl-4-phenyl-1-azadienes undergo facile, regioselective [4 + 2] cycloaddition to the C2,C3 π-bond of allenic esters in refluxing benzene, and the formed adducts undergo a 1,3-H shift to afford novel 2-alkyl-1-aryl-3-ethoxycarbonyl-4-phenyl-1,4-dihydropyridines (78–97%). However, when the reaction is carried at room temperature, besides the [4 + 2] addition, the [2 + 2] mode of addition involving C═N of azadiene and C3,C4 π-bond of allenic esters also intervenes. The resulting *N*-aryl-2-ethoxy-carbonyl-methylidene-4-styrylazetidines (17–28%) undergo reorganization on silica gel to afford 2-cyclohexen-1-ones.

As compared to extensive preparative, mechanistic and theoretical investigations on Diels−Alder reaction, the hetero-Diels−Alder processes have attracted relatively less attention despite comparable synthetic utility. However, in the past couple of decades, a considerable amount of work has been reported in the field of hetero-Diels−Alder methodology, with definite advancements in theoretical understanding and synthetic utilization.[1] Among the heterodienes, the 1-azadienes have been reported to be sluggish as dienes in hetero-Diels−Alder reactions, and their 4π participation is marred by, inter alia, competing [2 + 2]

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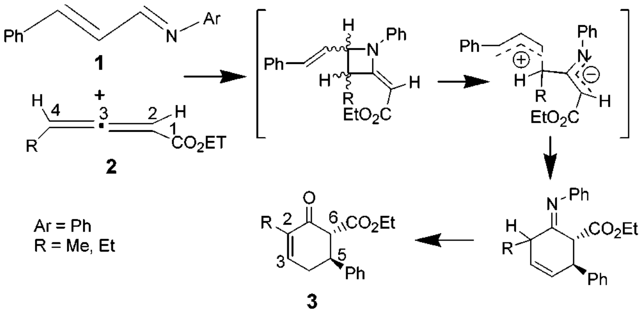
additions.[1a,b] Various strategies that have been devised[1a−h,2] to ensure their 4π participation include the introduction of electron-withdrawing substituent(s) on azadienes so as to improve their frontier orbital complementarity for inverse electron demand Diels−Alder reaction. It has been reported[3] that reaction of 1-aza-1,4-diphenyl-1,3-butadiene (**1**, Ar = Ph) and allenic esters (**2**) leads to formation of cyclohexenones (**3**) in low yield (25−30%); the latter are postulated to be derived from (2 + 2) cycloadducts (Scheme 1), though no such proposed intermediate had been isolated and/or characterized, and no other reaction product has been reported.

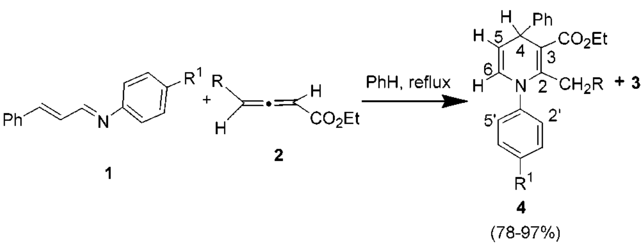
Scheme 1



Taking cognizance of a recent report on cycloadditions of cyclic and acyclic dienes with ketenes, wherein interconvertibility of initially formed (4 + 2), and (2 + 2) cycloadducts has been described,[4] we decided to reinvestigate the above azadiene−allenic ester cycloadditions with the aim of establishing the mechanism of the reported[3] cyclohexenone formation and to develop a protocol for 4π participation of azadienes in reactions with allenic esters. The latter was of particular interest for development of a simple route to novel substituted 1,4-dihydropyridines, which are highly sought on account of both their diverse biological activities and synthetic applications.[1g,p,2,5]

Initially, the reactions were carried out by heating equivalent amounts of azadiene (**1**) and allenic ester (**2**) in dry refluxing benzene, with strict exclusion of moisture. Contrary to the earlier report,[3] this led to almost exclusive formation of 2-alkyl-1-aryl-3-ethoxycarbonyl-4-phenyl-1,4-dihydropyridines (**4**). Apparently, these dihydropyridines are derived from an initial (4 + 2) cycloaddition followed by a 1,3-hydrogen shift. The earlier reported[3] cyclohexenones (**3**) were detected in trace amount only in some cases, and it was observed that the rate of the reaction decreased with increasing size of the 4-alkyl substituent on the allenic esters (Scheme 2, Table 1).

Scheme 2



The dihydropyridines have been characterized by detailed spectroscopic analysis, microanalytical data, and comparison of the spectroscopic data with the reported data for related system.[6] In their IR spectra these molecules displayed a band due to ester carbonyl at $\sim$1690 cm^{-1}, indicating an extensively conjugated ester carbonyl, which was reminiscent of the IR band of ester carbonyl in Hantzsch esters. In its proton NMR spectrum compound **4f** displayed, besides resonances in the aromatic region, a doublet at δ 5.99, which was coupled to a double doublet at δ 4.88; the latter was coupled to a doublet at δ 4.58. These resonances have been assigned, respectively, to C6−H, C5−H, and C4−H (compare ref 6). The assigned structures (**4a−h**) are also corroborated by the ^{13}C NMR spectral data.

Table 1. Reactions of Azadiene (**1**) and Allenic Esters (**2**) in Refluxing Benzene

no.	R	R^1	reaction time (h)	**4** (% yield)[a]
1	H	H	58	**4a** (96)
2	Me	H	70	**4b** (85)
3	Et	H	80	**4c** (79)
4	H	Me	57	**4d** (95)
5	Me	Me	65	**4e** (88)
6	H	OMe	55	**4f** (97)
7	Me	OMe	68	**4g** (92)
8	Et	OMe	80	**4h** (85)
9	H	Cl	55	**4i** (94)
10	Me	Cl	65	**4j** (89)
11	Et	Cl	85	**4k** (78)
12	H	F	55	**4l** (97)
13	Me	F	65	**4m** (90)
14	Et	F	85	**4n** (85)

[a] Yield refers to isolated pure product.

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As almost exclusively the (4 + 2) mode of cycloaddition was obtained under these conditions, and in the light of recent report on formation of (2 + 2) adducts on reacting ketenes with cyclic/acyclic dienes at room temperature,[4] we attempted the reactions of azadienes with allenic esters by stirring at ambient temperature. Our goal was the isolation of the (2 + 2) adduct and investigation of its transformation to cyclohexenones (**3**). Equimolar solutions of azadiene (**1**) and allenic esters (**2**) in dry benzene were stirred at room temperature for 45−65 days. The ^{1}H NMR spectrum of the crude sample obtained after evaporation of the solvent showed the presence of considerable amounts of (2 + 2) cycloadducts (**5**, Scheme 3) in addition to the dihydropyridines (**4**); the relative ratios of **4** and **5** determined from ^{1}H NMR of crude reaction products are given in Table 2 along with reaction times.

Scheme 3

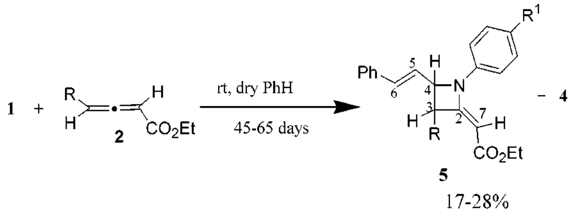


Table 2. Reactions of Azadiene (**1**) and Allenic Ester (**2**) at Room Temperature

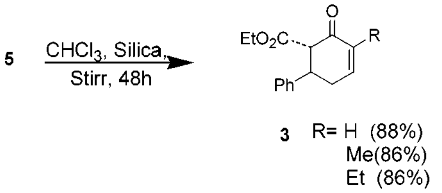
no.	R^1	R	reaction time (days)	**4**/**5** product ratio^a	**5** (% yield)^b
1	Me	Me	62	2.5/1.0	**5a** (27)
2	Cl	Me	52	2.3/1.0	**5b** (28)
3	Cl	Et	45	1.9/1.0	**5c** (28)
4	Cl	H	49	4.0/1.0	**5d** (17)
5	H	Me	60	2.2/1.0	**5e** (26)
6	OMe	Me	65	2.8/1.0	**5f** (25)

^{a} Ratio measured from the ^{1}H NMR spectra of crude reaction products. ^{b} Yield refers to the isolated pure adducts (**5**) and amount of cyclohexenones (**3**) formed.

The (2 + 2) cycloadducts were isolated by flash column chromatography and characterized spectroscopically. In its ^{1}H NMR, **5a** (R = Me) revealed a 1H double doublet at δ 6.35 (C5−H), a 1H split singlet at δ 5.34 (C7−H), a double doublet at δ 4.56 (1H, $J = 7.56, 2.44$ Hz, C4−H), a quartet at δ 4.15 (2H, $-CO_2CH_2$), another split quartet at δ 3.41 (C3−H), and a doublet at δ 1.59 (3H, C3−CH_3); some of these ^{1}H NMR spectral assignments were aided by comparison of the spectral data reported for (2 + 2) cycloadducts of 1-azadienes with ketenes.[1g,7] The *trans*-arrangement around the C3−C4 bond is based on the low value of $^3J_{3,4}$ ($\sim$2.5 Hz),[7c] and the obtained spectral data indicates single geometry at the exocyclic double bond. However, the assigned geometry is tentative, based mainly on nonobservance of NOE for C1′−H on irradiating C3−Me resonance in **5a**.

To confirm the formation of cyclohexenones through (2 + 2) adduct, the isolated (2 + 2) adducts (**5**) were stirred with silica gel, in chloroform, for 2 days at which time most of the (2 + 2) adduct were converted to cyclohexenones (**3**, Scheme 4); the latter were separated by column chromatography and identified spectroscopically.[3]

Scheme 4



Mechanistic aspects of the reported observations are far from clear. In keeping with the mechanistic proposals for reactions of 1-azadienes/imines with ketenes[1g,h,7a,b,8] and reported detection of zwitterionic intermediates in additions to allenes[9] and in view of the fact that allenic esters are related to ketenes, it is often tempting[3] to consider the formation of both (2 + 2) and (2 + 4) adducts through a common zwitterionic intermediate, **B** (Scheme 5). However, the involvement of a common zwitterionic intermediate (**B**),[10] though in consonance with the obtained single geometric arrangement around the exocyclic double bond in **5** as well orientation of the azadiene moiety in adducts, fails to explain the differential π-bond selectivity of the two modes of addition and the complete stereoselectivity of (2 + 2) mode of addition, i.e., *trans*-arrangement around the C3−C4 bond in azetidines (**5**). Heating **5** in refluxing benzene for extended

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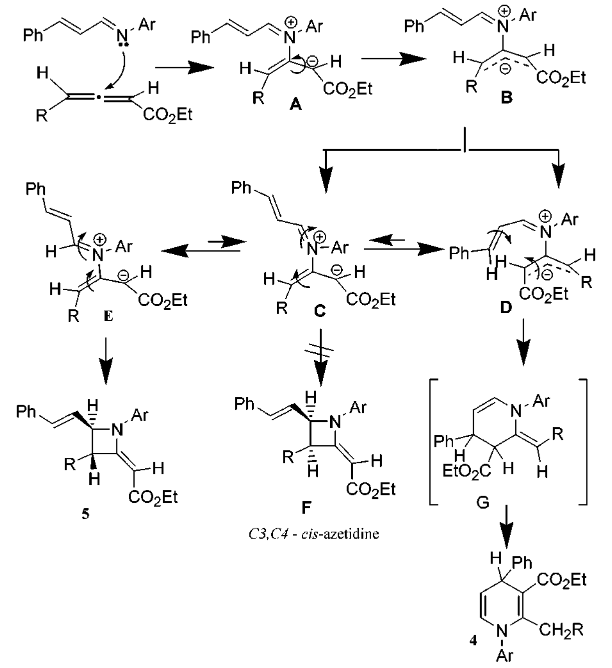
(10) The formation of zwitterionic intermediate **B** shall involve the interaction of a nitrogen lone pair of electrons with the LUMO of the C2−C3-π bond at the central allenic carbon; the azadiene shall approach from the side opposite to substituent R on the allenic moiety. In the intermediate **B**, substituents on the allenic moiety are kept away from the azadiene component, and reported low-energy *anti*-arrangement around C═N (Anteuis, N.; Bruyn, A. De.; Sandhu, J. S. *J. Magn. Reson.* **1972**, *8*, 7) has been maintained.

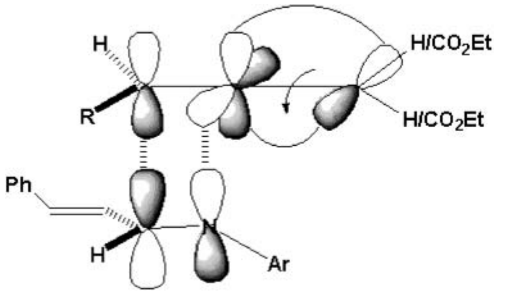
Scheme 5



periods led to their slow deterioration, and not a trace of dihydropyridine (**4**) was detected at any stage, thereby indicating the complete irreversibility of azetidine formation or at least that of **5**, under the reaction conditions. Therefore, the major mode of transformation has to be the cyclization in **D** leading to **G**, followed by 1,3-H shift in **G** to afford **4**; such facile 1,3-H shifts are precedented in allene chemistry.[11]

Alternatively, the obtained C2−C3 π-bond selectivity for the (4 + 2) mode of addition is consistent with a concerted cycloaddition through a HOMO-diene−LUMO-dienophile interaction; therefore, only the electron-deficient C2−C3 π bond of allenic esters is involved. Involvement of such electron-neutral 1-azadienes in HOMO-diene controlled hetero-Diels−Alder reactions with electron-deficient dienophiles is anticipated.[1a−h,2,12] It may be mentioned here that geometric outcome at the exocyclic double bond and the stereochemistry of addition (at C3) in (4 + 2) adducts, which could have provided useful information, is lost due to H-shift leading to **4**.

The formation of azetidines can also be rationalized as a concerted ($\pi^2{}_\mathrm{s}$ + $\pi^2{}_\mathrm{s}$ + $\pi^2{}_\mathrm{s}$) process; though such a mechanism for observed facile (2 + 2) additions of allene was proposed[13a] and latter discarded in favor of a diradical mechanism,[13b] many of the recently obtained results have been rationalized in terms of such a concerted mechanism.[14,15] The involved orbital interactions are depicted in **H** (Figure 1). A HOMO−C3−C4 π bond and LUMOs of C=N, and C2−C3 π bond interaction may be the reason for the observed involvement of only the relatively electron-rich π bond of allenic esters in this mode of cycloaddition. The obtaining of relatively higher yields of (2 + 2) adducts from allenic esters bearing electron-donating alkyl substituents at C4 supports such a contention. It may be mentioned here that similar divergent π-bond selectivities for formation of (4 + 2) and (2 + 2) addition products from reaction of electron-rich siloxy-dienes with allenic esters have been recently reported.[16]



H

Figure 1.

Though the mechanistic details of the reported transformations need further probing, the facile 4 π participation of 1-azadienes, leading to valuable 1,4-diaryl-1,4-dihydropyridines, in very high yields is of significant synthetic value.[17] The investigations have also led to the isolation of azetidines (**5**), and their reorganization to cyclohexenones (**3**) has been established.

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Supporting Information Available: Experimental procedures and full characterization of compound **4a−n**, **5a−f** and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] Regiochemistry for both modes of addition, when considered as concerted processes, is in consonance with atomic orbital coefficients in the frontier molecular orbitals of both reactants.[1g,13b]

[16] Jung, M. E.; Nishimura, N. *J. Am. Chem. Soc.* **1999**, *121*, 3529.

[17] This approach is all the more important in the light of reported low reactivity of 1-azadienes towards acetylenic dienophiles.[1a,b]