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Stereoselective Synthesis, NMR Conformational Study and Diels-Alder Reaction of β-Functionalized 1-Acetylvinyl arenecarboxylates

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Abstract: A stereoselective synthesis of novel β -substituted 1-acetylvinyl arenecarboxylates 2a-2h, via the bromo derivative 4a, is described. Isomer Z was the only product formed. Low temperature NMR experiments showed an *s-cis/s-trans* (20:80) conformeric equilibrium, and also a restricted rotational C-N barrier in 2a. X-ray diffraction of the latter revealed a planar *s-trans* conformation. Alkene 4a proved to be more reactive than 2a-2b towards cyclopentadiene (6) and isoprene (11) in Diels-Alder additions, giving the corresponding adducts 10 and 14 in high stereo- and regioselectivity.

The stereoselective synthesis of α,β -difunctionalized enones, acrylic esters and acroleins has attracted significant attention since they have proved to be interesting synthetic targets,¹ efficient dienophiles² and heterodienes³ in Diels-Alder cycloadditions. Recently, we reported that captodative 1-acetylvinyl arenecarboxylates, 1, showed highly selective Diels-Alder⁴ and 1,3-dipolar⁵ cycloadditions. Besides, they were useful synthesis in natural terpenoid synthesis.⁶

As a part of our efforts to prepare α , β -disubstituted enones from 1, in order to evaluate their reactivity and selectivity as dienophiles and dienes in Diels-Alder reactions and as versatile intermediates in organic synthesis, we now report a stereoselective synthesis of novel β -functionalized 1-acetylvinyl arenecarboxylates 2. Furthermore, we describe a low temperature NMR analysis of *s*-*cis/s*-*trans* conformations of vinilogous dimethylamide 2a, as well as, the determination of the activation energies of their C-C and C-N rotation barriers.

RESULTS AND DISCUSSION

Olefins 2 were prepared by a three-step synthetic route from compound $1a^{6a,7}$ as starting material (Scheme 1). When 1a was brominated, the dibromo compound 3 was afforded in 92% yield. This was treated with triethylamine under smooth conditions to give bromo derivative 4a in 72% yield. The ¹H NMR spectrum of the crude showed only one series of signals, confirming the presence of a single stereoisomer. The assignment of the Z configuration of the double bond was established by single crystal X-ray diffraction (Figure

1). This exhibits two molecules in the asymmetric unit, both of them maintaining the planar s-trans conformation and the Z configuration. Hence, the dehydrobromination reaction was highly stereoselective.



Scheme 1. Preparation of olefins 2a-2h.

This selectivity could be explained by comparison of the stability of **4a** with respect to *E* isomer **4b**. Considering a similar *s*-trans or *s*-cis planar conformation of the enone system of **4b**, as shown in the structure of **4a** (Figure 1), it appears that repulsive interactions present in **4b** between the π -planar acetyl group and the bromine atom would destabilize the elimination process.⁸



Figure 1. Perspective view of the X-ray crystal structure of 4a.

The addition of nucleophiles (YH) such as amines, anilines and thiols to 4a provided the desired β -substituted olefins 2a-h in fair yields (Table 1). Secondary amines were added rapidly under gentle conditions giving derivatives 2a-d. Anilines activated by electron-releasing groups were also added, but they required the presence of triethylamine as catalyst and longer reaction times. The increase of temperature led to lower yields. In the case of anilines, in contrast with secondary amines, it was necessary to use a more polar solvent.

Inactivated anilines, e.g. nitroanilines, even aniline itself, were not reactive enough to undergo addition toward 4a.

Methoda	Y	Product	mp (°C)	Yield (%) ^b
A	NMe ₂	2a	153-154	84
А	NEt ₂	2 b	155-156	84
А	Ni-Pr2	2 c	159-160	51
А	N(CH ₂) ₄	2d	163-164	16
в	NHC ₆ H ₄ p-Me	2 e	172-173	56
В	NHC6H4p-OMe	2 f	168-169	41
С	Sn-Pr	2 g	119-120	93
С	SPh	2 h	63-64	85

Table 1. Reaction Conditions for the Preparation of Olefins 2 by Addition of Nucleophiles (YH) to 4a.

^a A: CH₂Cl₂, rt, 1 h; B: Et₃N, DMF, rt, 24 h; C: Et₃N, DMF, rt, 1 h. ^b After recrystallization.

Similar conditions were used with the thiols: *n*-propyl mercaptan and thiophenol, to yield olefins 2g and 2h, respectively. The reactivity of these nucleophiles was higher, because the conversion of starting materials was completed in only 1 h, and the yields were better. On the other hand, the introduction of an oxygenated functionality, by addition of alcohols and phenols to the brominated compound 4a, was unsuccessful. Transesterification of the *p*-nitrobenzoyl (PNB) group took place rapidly.

The new compounds **2a-2h** were thoroughly characterized by spectroscopy and elemental analysis. The configuration of the double bond was established by ¹H NMR using NOE experiments. A correlation between vinyl proton H-4 and the acetyl group was observed, proving to be a Z configuration as for **4a**.

The proton spectra for the amino derivatives **2a-2d** appear as broad signals in both CDCl₃ and C₆D₆. An equilibrium between the *s*-*cis* and *s*-*trans* rotamers I and II (Scheme 2) has been previously proposed for analogous enamino carbonyl compounds.⁹ Indeed, when we determined low temperature ¹H NMR spectra for **2a** in CDCl₃, the ensemble of the broad singlets for the *N*,*N*-dimethyl, acetyl and PNB groups and the olefinic proton became narrow and a second series of signals was distinguished in *ca*. 80 : 20 ratio (Figures 2a and b) with a coalescence temperature of *ca*. 18°C. The smaller vinylic proton signal was shifted to low field (7.23 ppm), which suggests a *s*-*cis* conformer attribution.¹⁰ Moreover, when the solution was cooled to -32.5°C (Figure 2c) a second coalescence temperature was reached for the *N*,*N*-dimethyl groups (2.87 ppm) and at -61°C (Figure 2d) four signals were completely separated. This is interpreted in terms of the existence of two pairs of rotamers I/III and II/IV, respectively, owing to restricted rotation around the C₄-N bond and leading to differentiation of the two methyl groups.



Scheme 2. Equilibria between pairs of rotamers s-cis I/III and s-trans II/IV of olefin 2a.

In contrast with enamino aldehydes and ketones $1^{10a,11}$ these results showed: (a) the preponderance of the s-trans rotamer II (ca. 80%) over the s-cis isomer I (ca. 20%), which agrees with polarized enamides; ^{10b} (b) the rotation around the C_2 - C_3 bond was slower than the C₄-N rotation. These equilibria and the higher thermodynamic stability of the involved rotamers depend on several factors. The steric interactions between the olefin substituents located in a cis or geminal positions would tend to diminish the mesomerism of the nitrogen lone-pair with the π -enone system, and consequently, the rotational barriers of the single bonds would then be reduced. While the mesomerism increases the stability of the planar conformers, the steric hindrance could destabilize them. Activation energies (ΔG_c^{\star}) for rotation around C4-NMe₂ in unsubstituted enaminones have been calculated at the coalescence temperature (T_c) to be ca. 13.5 Kcal/mol.^{10a,12} Using equation 1^{13} and considering the T_c for each equilibrium for olefin 2a, the ΔG_c^{\neq} were estimated. For the C₄-N restricted rotation, barriers of 11.8 Kcal/mol and 11.6 Kcal/mol were calculated for the isomers s-trans and s-cis, respectively. These are approximate values, because no distinction was possible between the coalescence temperatures (-32.5°C) of the two isomers, since their signals overlapped. These energies are similar to those calculated (ca. 11.0 Kcal/mol) for 4-methyl-4-dimethylamino substituted butenone^{10a} and α -cyanoacrylates;¹⁴ but they are higher than the barrier energy for 4-dimethylamino-3-methyl-3-buten-2-one, structurally closely related to 2a, in which case the NMe₂ group signal was not split, even decreasing the temperature down to -120°C.^{10a} This suggests that the PNB group on C3 does not have a strong effect in inhibiting the enaminone mesomerism in **2a**, but it could play a role in favoring the s-trans form.¹⁵ We calculated an activation energy for the s-cis/strans equilibrium and the value for 2a amounts to $\Delta G_c^{\neq} = 14.0$ Kcal/mol, which is somewhat higher than the value obtained (ca. 11.0 Kcal/mol) for the unsubstituted enaminone 4-dimethylamino-3-buten-2-one,9 and less than the polarized enamines (ca. 17.0 Kcal/mol).¹⁶

$$\Delta G_c^{\neq} = 2.3 \text{ RT}_c (10.32 + \log T_c/k_c)$$
[1]

$$k_c = 2.22 \Delta v \text{ and } \Delta v = \delta_{\text{rot I}} - \delta_{\text{rot II}} (Hz)$$

where



Figure 2. Low temperature ¹H NMR spectra of 2a in CDCl₃.

Dabrowski and Kozerski¹⁷ estimated that the C₄-N barrier of compound **5a** was too low to be observed and there was free rotation around the C₂-C₃ bond. Therefore, they attributed the experimentally determined value of $\Delta G_c^{\neq} = 13.8$ Kcal/mol to the C₃=C₄ barrier. They argued a less effective conjugation of the nitrogen lone electron pair due to steric interactions between N(CH₃)₂ and the acetoxy group on C₃. A similar explanation was followed for compound **5b**, with values amounting to $\Delta G_c^{\neq} = 11.0$ and 11.2 Kcal/mol, corresponding to C₄-N and C₃=C₄ barriers, respectively.



Considering the structural analogy between **5a** and **2a**, and that the $C_3=C_4$ barrier of **5a** was comparable to *s-cis/s-trans* equilibrium of **2a**, we assessed the possibility that the latter was rather an E/Z isomerization (Scheme 3). Low temperature (-18.4°C) NOE experiments with selected irradiation on both isomeric N(CH₃)₂ signals [3.05 ppm (major isomer) and 2.98 ppm (minor isomer) (Figure 2b)], exhibited enhancements in both singlets of the PNB protons, attributed to the split signals of the two isomers [8.36 ppm (minor isomer) and 8.31 ppm (major isomer) (Figure 2b)]. This agrees with a Z geometric configuration in both isomers, since no NOE effect should be expected for the (*E*)-isomer. Therefore, the first equilibrium detected at $T_c = 18$ °C (Figure 2) corresponded to the C_2 - C_3 rotation: (*Z*)-*s-trans*/(*Z*)-*s-cis*.

Likewise, the $C_3=C_4$ barrier was estimated to be relatively high, since only a normal slight enlargement of the signals was observed by ¹H NMR (300 MHz), and the shape of the original spectrum was recovered after cooling to room temperature, when a sample of **2a** in DMSO-d₆ was gradually heated up to 150°C. No additional signals were formed, which would provide an evidence of the isomer *E* formation. Attemps to isomerize **2f** by acidic treatment (*p*-TsOH, CDCl₃) were unsuccesful. Only side-product signals were gradually detected by ¹H NMR up to 60°C. This appears to support the higher stability of the *Z* isomer with respect to the *E* isomer.^{1h,1m,18}



Scheme 3. Low temperature (-18.4°C) NOE experiments of **2a** showed only the presence of isomers (Z)-s-trans and (Z)-s-cis.

In fact, a strong electronic delocalization through the coplanar π -orbitals of the vinylogous amide should be reflected in a shortness of C₄-N and C₂-C₃ bonds. Indeed, the single crystal X-ray structure of **2a** (Figure 3) shows these bond distances (Table 2) to be shorter than those expected for non-delocalized enone and enamine groups.¹⁹ Moreover, the bond distance for N-CH₃ is rather close to an N_{sp}2 hybridation. The dihedral angles (Table 3) revealed that the enone was planar with a sp^2 hybridation of the nitrogen atom, allowing an extensive conjugation of all the enamino carbonyl π -orbitals. As regards the conformation of 2a, the *s*-trans was the preferred one, at least in the crystalline form, as well as for that of compound 4a (Figure 1).



Figure 3. Perspective view of the X-ray crystal structure of 2a.

Table 2. Comparison of X-ray Selected Bond Distances (Å) (estimated standard deviations) of Crystal Structure of **2a** with the Average Lenghts of Bonds of Enone and Enamine Systems.¹⁹

Bond	X-ray	Average Length ¹⁹
C(1)-C(2)	1.501 (9)	1.511
C(2)-O(8)	1.231 (7)	1.222
C(2)-C(3)	1.41 (1)	1.462
C(3)-C(4)	1.366 (9)	1.340
C(4)-N(5)	1.32 (1)	$1.358 (Nsp^2); 1.418 (Nsp^3)$
N(5)-C(6)	1.447 (8)	1.451(Nsp ²)
N(5)-C(7)	1.45 (1)	$1.468 (Nsp^3)$
C(3)-O(9)	1.423 (7)	1.353
O(9)-C(10)	1.354 (6)	1.359

Table 3. Selected Bond Angles (deg) and Torsion Angles (deg) (estimated standard deviations) of Crystal Structure of 2a.

Bond	Angles (deg)	Torsion A	Torsion Angles (deg)		
C(1)-C(2)-O(8)	119.1 (7)	C(4)-C(3)-O(9)-C(10)	99.42 (0.66)		
C(1)-C(2)-C(3)	120.6 (6)	C(2)-C(3)-O(9)-C(10)	(-) 83.55 (0.64)		
C(3)-C(2)-O(8)	120.3 (6)	C(6)-N(5)-C(4)-C(3)	(-) 178.68 (0.66)		
C(2)-C(3)-O(9)	114.2 (5)	C(7)-N(5)-C(4)-C(3)	4.15 (1.09)		
C(4)-C(3)-O(9)	120.8 (7)	N(5)-C(4)-C(3)-O(9)	(-) 1.16 (1.04)		
C(3)-C(4)-N(5)	133.0 (6)	N(5)-C(4)-C(3)-C(2)	(-) 177.86 (0.63)		
C(4)-N(5)-C(6)	120.6 (6)	O(9)-C(3)-C(2)-O(8)	5.87 (0.81)		
C(4)-N(5)-C(7)	125.2 (5)	O(9)-C(3)-C(2)-C(1)	(-) 174.84 (0.51)		
C(6)-N(5)-C(7)	114.2 (7)	C(4)-C(3)-C(2)-O(8)	(-) 177.24 (0.58)		
C(3)-O(9)-C(10)	115.3 (4)	C(4)-C(3)-C(2)-C(1)	2.05 (0.93)		

A computational optimization of the molecular structure and conformational study of 2a, using the AM1 algorithm of MOPAC V-6.0, showed that the minor rotamer s-cis had a lower enthalpy of formation than the s-

trans. This is contrary to X-ray and NMR analyses, and it could be attributed to solvent and crystalline lattice effects, not accounted for in MOPAC calculations.

Analogous low-temperature ¹H NMR experiments were undertaken with the thiol compounds 2g and 2h. In contrast with 2a, when the solution was cooling down to -90°C, a coalescence temperature was unobserved, showing that the *s*-*cis/s*-*trans* conformational barrier is very low. This suggests that the electronic interaction of the sulfur onto the enone system is less significant than that provided by the amino group.

In addition to the evidence given by the low temperature ¹H NMR experiments for the *s-trans* conformational preference of **2a** in solution, the ¹³C NMR shifts of the C(2), C(3) and C(4) signals could also be used as a conformational diagnosis for the enamino carbonyl compounds.²⁰ ¹³C NMR data of **2a-2h** and **4a** are listed in Table 4. Signals of olefinic carbon atoms C₃ and C₄ were distinguished by DEPT or APT spectra. For the β -amino compounds **2a-2f**, the deshielded signals at *ca*. 130-140 ppm corresponded to carbons C₄, while those occurring at *ca*. 123-131 ppm were attributed to C₃. The latter are upfield shifted with respect to the same carbon atom of olefins 1 (151 ppm),⁷ since a large charge density is centered on C₃ of **2** by the β -position electron-donor group, and by a compressing effect bearing on C₃, because of the steric repulsion between the groups in the *syn* relative position (γ effect).²¹ Nevertheless, the latter is minimized by the increase in the N-C₄-C₃ angle to 133° and the lengthening of the bond distance of **C₃-O**COAr more than expected for an enol ester,¹⁹ as shown by the crystal structure of **2a** (Tables 2 and 3). Chemical shifts of C₃ and C₄ of the sulphur and bromine derivatives **2g**, **2h** and **4a** are opposite, C₃ being at low field. A slight variation of δ_{C_2} (*ca*. 185 ppm) would suggest a similar conformation of the conjugated enone skeleton in the series **2a** to **2h**.^{21a} The *ca*. 4 ppm upfield shift of the C₂ resonance observed in this series in comparison with **1a** could be accounted for as a shielding effect caused by C₄ substitution.

Thermal reaction of the series of olefins 2a to 2h with cyclopentadiene (6) was unsuccessful, even at high temperatures (170°C) and for long periods of time (15-24 h). The mixture of reaction with 2a and 2b indicated both traces of expected adducts 7/8 (Scheme 4), and a high decomposition of the olefin. Even using Lewis acid catalysts, such as AlCl₃, ZnCl₂, TiCl₄, MgBr₂ and BF₃:Et₂O, which have been traditionally used to improve the cycloaddition even for unreactive olefins,²² failed to produce any cycloadduct and the olefin decomposition was increased. Other olefins of the series (2d and 2h) were treated under similar conditions, but they did not react either. Low dienophilicity has also been described for unactivated trisubstituted olefins^{2d} or they react preferentially as heterodienes.^{3,23}



Scheme 4. Diels-Alder reaction of olefins 2a, 2b and 4a with cyclopentadiene (6).



	22	2 b	2 c	2d	2 e	2 f	2 g	2 h	4a
C-1	23.6	23.8	23.8	23.5	23.7	23.7	24.5	24.8	25.5
C-2	185.1	185.1	185.1	184.7	186.0	185.8	186.7	187.3	188.6
C-3	123.5	123.2	123.7	131.1	127.2	127.0	141.4	142.3	148.8
C-4	142.5	140.6	135.6	139.5	133.2	131.3	138.5	135.4	115.3
C-5	162.9	162.6	162.5	163.1	162.5	162.5	161.4	161.3	161.3
C-6	134.6	134.8	134.8	134.7	135.2	135.3	133.3	133.5	132.7
C-7	131.0	131.0	130.9	131.0	131.3	131.3	131.9	131.5	131.4
C-8	123.9	124.0	124.0	123.9	123.6	123.6	124.1	124.4	124.4
C-9	150.3	150.5	150.4	150.3	150.1	150.2	150.4	151.2	150.9
C-10	42.0	47.5	47.9	52.3	138.3	134.0	34.9	131.4	_
C-11		14.4	21.8	24.9	129.7	117.6	23.5	129.8	
C-12					116.0	114.6	12.6	130.6	
C-13					131.5	155.0		128.3	
C-14					20.1	55.3			

Table 4. ¹³C NMR Spectral Data (DMSO-d₆) of Olefins 2a-2h and 4a.

The low reactivity provided by these olefins could be explained by an effective delocalization of the lonepair of the heteroatom on C_4 .²⁴ This effect decreases the double bond character of the olefin; hence, the dienophile character is decreased as well. From the point of view of the perturbational theory.²⁵ the Diels-Alder reaction is slowed down when the dienophile is electron rich, because the electron releasing substituents will produce a LUMO destabilization and, consequently, the energy gap of the frontier orbital interaction with the HOMO of the diene, under normal electronic demand conditions, will be greater.²⁶ Therefore, the interaction between these cycloaddents, as well as their reactivity, will decrease. This could account for the low reactivity of olefins 2a-2h as dienophiles towards dienes 6 and 11 (vide infra). A further support for this picture with respect to this olefins 2g and 2h, is the role of sulfur as a control element by an electron donnating distribution, rather than oxygen, onto the regiochemistry of disubstituted dienes.²⁷ In the particular case of α -alkylthio acrylates and cyanoacrylates, the captodative effect was invoked to compensate for this deactivation.²⁸ Even though our low temperature ¹H NMR experiments with these olefins suggested rather that sulfur lone pair delocalization to the enone π system is not as strong as for the amino group for freezing the s-cis/s-trans conformation, this electronic interaction could participate by decreasing the dienophilic character of these olefins. In addition to this, the steric hindrance provided by the thioalkyl and thiophenyl substituents would improve the destabilizing interactions at the transition state. Other contributing causes such as closed-shell repulsions²⁹ might also be considered.

A higher reactivity was observed for **4a** in the presence of diene **6**. Thus, when they were heated to 130°C or the reaction was carried out in the presence of catalysts, the addition occurred in modest yields (-34%) to give the desired adducts **9/10** (Scheme 4). Surprisingly, for the thermal trials, *exo* stereoisomer **10** was the only observed adduct; whereas, the Lewis acid catalyzed trials were less selective (Table 5). This contrasts with the usual role of Lewis acids in improving selectivity.²² The multiple complexation sites on dienophile **4a** and the great number of possible conformeric species formed with the Lewis acid³⁰ prevent a prediction about the stereocontrol factors in this process. The *exo* selectivity could be associated with a low stability of the transition state leading to *endo* isomer **9**, since repulsive non-bonding interactions of the methylene bridge of **6** with the two bulky groups of the dienophile would destabilize this approach (Figure 4).³¹ It has been argued that electronic effects in the transition state play a major role in determining stereoselectivity; however, these studies have been generally restricted to unsubstituted enones.³² On the other hand, secondary orbital interactions from the donor group on the *alpha* carbon might also stabilize the *exo* transition state.³³ The *exo* approach preference of **4a** in this cycloaddition also reflect minimal contribution from possible electrostatic repulsions between the heteroatom lone pairs, i.e., bromine and oxygen, and the cyclopentadiene π electrons,³⁴ since this factor would predict the unobserved *endo* transition state (Figure 4) to be more stable.³⁵

The relative configuration of the major adduct 10 was established by NMR. A J = 3.4 Hz coupling was determined between the bridgehead proton H-4 and the *exo* bromo base proton H-3.³⁶



Figure 4. Steric interactions in the endo approach of 4a and 6.

Dienea	Lewis Acid ^b	Solvent	T (°C)	t (h)	Productsc	Yield (%) ^d
6 b		xylene	100	31	9/10 (<5 : >95)	25
6	AICl ₃	CH ₂ Cl ₂	25	72	9/10 (25 : 75)	37
6	ZnCl ₂	CH2Cl2	25	72	9/10 (37 : 63)	40
11 ^b		xylene	130	15	14/15 (70 : 30)	41
11	AlCl3	CH ₂ Cl ₂	25	5	14/15 (85 : 15)	43
11	ZnCl ₂	CH ₂ Cl ₂	25	5	14/15 (90 : 10)	41

Table 5. Diels-Alder Cycloadditions of Olefin 4a with Diene 6 and 11.

^a 5 mol eq. ^b 10 mol eq. ^c Ratio determined by ¹H NMR of the crude mixture. ^d After recrystallization.

The non-reaction and gradual decomposition of amino olefins 2a-2f with isoprene (11), under thermal and catalytic conditions, confirmed the low reactivity of 2 as dienophiles. Derivative 2h was added to 11 up to 170°C, giving very poor yields (<10%, estimated by NMR) of corresponding adducts 12/13 (Scheme 5), as a part of a complex side-product mixture. In contrast, thermal (130°C) cycloaddition of 4a with 11 furnished a mixture of isomers 14/15 (70:30), in which the *para* isomer 14 was the major one (Table 5). The regioselectivity obtained was comparable to that observed with the β -unsubstituted olefin 1a.⁴ This seems to support the assumption that the controling effect on the regioselectivity shown by 4a would be the electronic demand of the electron-withdrawing group, i.e., the acetyl group, on the LUMO energy and polarizability of the double bond, as suggested by FMO calculations.⁴ In such a case, a possible interaction of the bromine lone-pair on the π -system would also induce a regioselectivity as observed for 14, in accordance with the expected LUMO polarization of a π bond by an electron-donnor group.^{24a,b} The presence of ZnCl₂ improved the regioselectivity, which reached a ratio of *para/meta*, 14/15, 90:10. Other catalysts were used, such as BF₃:Et₂O and TiCl₄, without success.



Scheme 5. Diels-Alder reaction of olefins 2h and 4a with isoprene (11).

¹H NMR spectroscopy confirmed the structure of major isomer 14. NOE experiments revealed vicinal correlation between the signals of protons H-6 and the vinylic proton H-5. The differentiation of methylenes CH₂-3 and CH₂-6 was readily established by homonuclear decoupling, since the former is coupled with proton H-2.

In summary, an efficient and stereoselective synthesis of novel α,β -substituted enones 2a-2h was accomplished. They showed preferential Z configuration and s-trans conformation. These compounds failed to react with dienes 6 and 11. Brominated precursor 4a was a more efficient dienophile, since it was added to 6 and 11 in substantially high stereo- and regioselectivity, respectively.

EXPERIMENTAL SECTION

General. UV spectra were obtained on a Shimadzu 2100 spectrophotometer. ¹H and ¹³C NMR spectra were obtained on Varian Gemini-300 (300 MHz) and Gemini-200 (200 MHz) instruments, with TMS as internal standard. Further analytical procedures were described elsewhere.^{6a}

Refined Coordinates for the X-ray Crystallographic Data of Olefins 2a and 4a (Tables 6 and 7).

Formula	C ₂₀ H ₂₂ N ₂ O ₅	Cryst. dimens, mm	0.2 x 0.3 x 0.35
Mw	370.41	μ , cm ⁻¹	0. 87
Cryst syst	triclinic	D (calc), g cm ⁻³	1.289
Space group	PT	temp, °K	298
a, Å	8.060 (1)	Diffractometer	Enraf-Nonius CAD-4F
b, Å	11.667 (2)	Radiation	Мо
c, Å	11.836 (2)	Monochromator	graphite
V, Å ³	954.0 (3)	20 scan range, deg	2-44
α, deg	64.28 (1)	No. of rflns collected	2328
β , deg	73.64 (1)	No. of unique obsvd rflns	1323
γ, deg	73.74 (1)	R (merg)	
λ, Å	0.71073	Rf	0.0701
Z	2	Rwf	0.0655

Table 6. Crystallographic Data for 2a toluene.

Table 7. Crystallographic Data for 4a.

Formula	C11H8BrNO5	μ , cm ⁻¹	33.31
Mw	314.10	D (calc), g cm ⁻³	1.703
Cryst syst	monoclinic	temp, °K	298
Space group	P21	Diffractometer	Enraf-Nonius CAD-4F
a, Å	6.9537 (8)	Radiation	Мо
<i>b</i> , Å	16.418 (1)	Monochromator	graphite
<i>c</i> , Å	10.736 (1)	20 scan range, deg	2-44
V, Å ³	1225.2 (8)	No. of rflns collected	1718
β, deg	91.726 (1)	No. of unique obsvd rflns	1436
λ, Å	0.71073	R (merg)	0.028
Z	4	Rf	0.068
Cryst. dimens, mm	0.62 x 0.75 x 0.95	Rwf	0.081

3,4-Dibromo-3-(p-nitrobenzoyloxy)-2-butanone (3). To a solution of 0.5 g (2.1 mmol) of 1a in 15 mL of dry CH₂Cl₂ at room temperature was added dropwise 0.43 g (2.7 mmol) of bromine dissolved in 10 mL of CH₂Cl₂. The mixture was diluted with CH₂Cl₂ (40 mL) and was washed with a saturated solution of Na₂S₂O₃ (3 x 30 mL) and brine (3 x 30 mL). The organic layer was dried (Na₂SO₄) and the solvent was removed in vacuo. The amorfous crystals were recrystallized from EtOAc/MeOH, 7:3, to give 0.77 g (92%) of white crystals of 3: mp 63-64 °C; IR (KBr) 3100, 3060, 1720, 1600, 1520, 1420, 1370, 1280, 1190, 880, 750 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.5 (s, 3H, CH₃CO), 4.40 (d, J = 8.6 Hz, 1H, H-4), 4.69 (d, J = 8.6 Hz, 1H, H-4), 8.25 (m, 2H, ArH), 8.37 (m, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ 24.4 (C-1), 32.9 (C-4), 86.3 (C-3), 123.9 (C-8), 131.2 (C-7), 133.7 (C-6), 151.3 (C-9), 161.3 (C-5), 194.7 (C-2). Anal. Calcd for C₁₁H₉Br₂NO₅: C, 33.45; H, 2.30. Found: C, 33.41; H, 2.64.

(Z)-4-Bromo-3-(p-nitrobenzoyloxy)-3-buten-2-one (4a). To a solution of 0.1 g (0.254 mmol) of 3 in 3.0 mL of dry CH₂Cl₂ at room temperature was added dropwise 0.028 g (0.28 mmol) of triethylamine dissolved in CH₂Cl₂ (2.0 mL). The mixture was stirred for 1 h at room temperature, diluted with CH₂Cl₂ (30 mL) and washed with ice-cold aqueous 5% HCl (2 x 20 mL) and brine until neutral. The organic layer was dried (Na₂SO₄) and the solvent was removed under reduced pressure, giving a brown solid. This was recrystallized from EtOAc/MeOH, 7:3 to yield 0.057 g (72%) of 4a as pale yellow crystals: mp 104-105 °C; UV (CH₃CN): 243 (19950); (EtOH): 245 (20000); IR (KBr) 1760, 1690, 1620, 1530, 1350, 1240, 1100 cm⁻¹; ¹H

NMR (300 MHz, CDCl₃) & 2.45 (s, 3H, CH₃CO), 7.52 (s, 1H, CH=), 8.34 (s, 4H, ArH); ¹³C NMR (75 MHz, CDCl₃), table 4. Anal. Calcd for C₁₁HgBrNO₅: C, 42.06; H, 2.57. Found: C, 41.83; H, 2.39.

General Procedure for the Preparation of β -Amino Olefins 2a-2d. A solution of 0.1 g (0.32 mmol) of 4a in dry CH₂Cl₂ (3.0 mL) was placed in a 25-mL round-bottom flask provided with a rubber septum, under an N₂ atmosphere at room temperature, and the corresponding amine was added: For 2a, 0.019 g (0.42 mmol) of dimethylamine; for 2b, 0.03 g (0.42 mmol) of diethylamine; for 2c, 0.042 g (0.42 mmol) of disopropylamine; and for 2d, 0.03 g (0.42 mmol) of pyrrolidine. The mixture was stirred for 1 h at room temperature, dissolved in CH₂Cl₂ (40 mL) and washed with ice-cold aqueous 5% HCl (2 x 20 mL) and brine until neutral. The organic layer was dried (Na₂SO₄) and the solvent was removed in vacuo. The amorfous crystals were recrystallized from EtOAc/MeOH, 9:1, to yield:

(Z)-4-(N,N-Dimethylamino)-3-(p-nitrobenzoyloxy)-3-buten-2-one (2a): 0.074 g (84%) as yellow crystals: mp 153-154 °C; UV (CH₃CN): 268 (17800), 293 (30000); (EtOH): 260 (23600), 297 (36300); IR (KBr) 1750, 1660, 1610, 1600, 1520, 1320, 1270, 1100 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 2.19 (br s, 3H, CH₃CO), 3.02 (br s, 6H, NMe₂), 7.08 (br s, 1H, CH=), 8.31 (br s, 4H, ArH); ¹³C NMR (50 MHz, DMSO-d₆), table 4; MS (70 eV) 278 (M⁺, 10), 207 (4), 150 (12), 128 (100), 100 (74), 58 (11). Anal. Calcd for C₁₃H₁₄N₂O₅: C, 56.11; H, 5.07. Found: C, 56.28; H, 5.16.

(Z)-4-(N,N-Diethylamino)-3-(p-nitrobenzoyloxy)-3-buten-2-one (2b): 0.082 g (84%) as yellow crystals: mp 155-156 °C; UV (CH₃CN): 293 (31800); (EtOH): 248 (41200), 297 (31500); IR (KBr) 1740, 1660, 1590, 1530, 1360, 1320, 1250, 1090 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.20 (br t, J = 6.7 Hz, 6H, N[CH₂CH₃]₂), 2.20 (br s, 3H, CH₃CO), 3.30 (br q, J = 6.7 Hz, 4H, N[CH₂CH₃]₂), 7.09 (br, 1H, CH=), 8.30 (br s, 4H, ArH); ¹³C NMR (50 MHz, DMSO-d₆), table 4; MS (70 eV) 306 (M⁺, 3), 156 (100), 150 (10), 128 (25), 86 (7). Anal. Calcd for C₁5H₁₈N₂O₅: C, 58.82; H, 5.92. Found: C, 58.69; H, 6.05.

(Z)-4-(N,N-Diisopropylamino)-3-(p-nitrobenzoyloxy)-3-buten-2-one (2c): 0.054 g (51%) as yellow crystals: mp 159-160°C; UV (CH₃CN): 260 (16600), 295 (28200); (EtOH): 260 (15500), 299 (23300); IR (KBr) 1740, 1660, 1590, 1520, 1300, 1260, 1090 cm⁻¹; ¹H NMR (90 MHz, CDCl₃) δ 1.30 (d, J = 7.0 Hz, 12H, N[CH(CH₃)₂]₂), 2.26 (br s, 3H, CH₃C=O), 4.05 (br, 2H, N[CH(CH₃)₂]₂), 7.38 (br s, 1H, CH=), 8.44 (br s, 4H, Ar-H); ¹³C NMR (75 MHz, DMSO-d₆), table 4; MS (70 eV) 334 (M⁺, 4), 319 (1), 291 (5), 249 (2), 184 (100), 150 (27), 142 (56), 114 (28), 104 (20), 72 (44). Anal. Calcd for C₁₇H₂₂N₂O₅: C, 61.07; H, 6.63. Found: C, 61.03; H, 6.36.

(Z)-4-Pyrrolidino-3-(p-nitrobenzoyloxy)-3-buten-2-one (2d): 0.015 g (16%) as yellow crystals: mp 163-164 °C; UV (CH₃CN): 260 (15600), 299 (33700); (EtOH): 260 (15600), 303 (29800); IR (KBr) 1740, 1650, 1600, 1270, 1100 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.90 (br s, 4H, 2 CH₂), 2.25 (br s, 3H, CH₃C=O), 3.50 (br s, 4H, (CH₂)₂N), 7.35 (br s, 1H, CH=), 8.36 (s, 4H, Ar-H); ¹³C NMR (75 MHz, DMSO-d₆), table 4. Anal. Calcd for C₁₅H₁₆N₂O₅: C, 59.21; H, 5.30. Found: C, 59.08; H, 5.36.

General Procedure for the Preparation of β -Anilino Olefins 2e-2f. A solution of 0.1 g (0.32 mmol) of 4a in 3.0 mL of dry DMF was placed in a 25-mL round-bottom flask provided with a rubber septum, under an N₂ atmosphere and at room temperature, and the corresponding aniline was added: For 2e, p-toluidine (0.043 g, 0.4 mmol); and for 2f, p-anisidine (0.052 g, 0.042 mmol). The mixture was vigorously stirred until complete dissolution and 0.042 g (0.42 mmol) of triethylamine were added. The mixture was stirred at room

temperature for 24 h, was dissolved in CH_2Cl_2 (30 mL); then, it was washed with ice-cold aqueous 5% HCl (2 x 20 mL) and brine until neutral. The organic layer was dried (Na₂SO₄) and the solvent was removed in vacuo. The remaining solid was recrystallized from EtOAc/MeOH, 7:3, to give:

(Z)-3-(p-Nitrobenzoyloxy)-4-[N-(p-toluidino)]-3-buten-2-one (2e): 0.06 g (56%) as orange crystals: mp 172-173°C; UV (CH₃CN): 267 (15700), 293 (31400), 323 (50700); (EtOH): 260 (6000), 301 (5900), 331 (12900); IR (KBr) 3250, 1740, 1670, 1600, 1520, 1350, 1260, 1100 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.58 (s, 3H, CH₃Ar) , 2.33 (s, 3H, CH₃CO), 6.49 (br d, J = 13.5 Hz, 1H, CH=), 6.91 (m, 2H, p-toluidyl-H), 7.15 (m, 2H, p-toluidyl-H), 7.76 (d, J = 13.5 Hz, 1H, NH), 8.37 (s, 4H, PNB-H); ¹³C NMR (75 MHz, DMSO-d₆), table 4. Anal. Calcd for C₁₈H₁₆N₂O₅: C, 63.52; H, 4.74. Found: C, 63.17; H, 4.75.

(Z)-4-[N-(p-Anisidino)]-3-(p-nitrobenzoyloxy)-3-buten-2-one (2f): 0.046 g (41%) as yellow crystals: mp 168-169°C; UV (CH₃CN): 262 (33600), 297 (62200), 328 (63000); (EtOH): 260 (9400), 307 (8800), 334 (10600); IR (KBr) 3360, 1750, 1670, 1610, 1510, 1280, 1230, 1090 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 3.38 (s, 3H, CH₃CO), 3.74 (s, 3 H, OMe) , 6.92 (m, 2H, p-anisidyl-H), 7.28 (m, 2H, p-anisidyl-H), 8.05 (br d, J = 13.5 Hz, 1H, CH=), 8.33 (m, 2H, PNB-H), 8.42 (m, 2H, PNB-H), 9.10 (d, J = 13.5 Hz, 1H, N-H); ¹³C NMR (75 MHZ, DMSO-d₆), table 4. Anal. Calcd for C₁₈H₁₆N₂O₆: C, 60.67; H, 4.53. Obtenido: C, 60.42; H, 4.71.

General Procedure for the Preparation of β -Thio Olefins 2g-2h. A solution of 0.1 g (0.032 mmol) of 4a in 3.0 mL of dry DMF was vigorously stirred at room temperature under an N₂ atmosphere, and the corresponding mercaptan was added: For 2g, *n*-propanethiol (0.032 g, 0.42 mmol); and for 2h, thiophenol (0.046 g, 0.42 mmol). Then, triethylamine (0.042 g, 0.42 mmol) was added and the mixture was stirred for 1 h at room temperature. The mixture was diluted with CH₂Cl₂ (30 mL) and washed with ice-cold aqueous 5% HCl (2 x 20 mL) and brine until neutral. The organic layer was dried (Na₂SO₄) and the solvent was removed in vacuo. The remaining solid was recrystallized from EtOAc/MeOH, 7:3, to give:

(Z)-3-(p-Nitrobenzoyloxy)-4-(n-thiopropoxy)-3-buten-2-one (2g): 0.091 g (93%) as colorless needles: mp 119-120 °C; UV (CH₃CN): 265 (10300), 288 (12100); (EtOH): 267 (5900), 294 (7300); IR (KBr) 3050, 1750, 1680, 1600, 1540, 1360, 1275, 1230, 1110 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.05 (t, J = 7.3 Hz, 3H, CH₃CH₂CH₂), 1.75 (sext, J = 7.3 Hz, 2H, CH₃CH₂CH₂), 2.35 (s, 3H, CH₃CO), 2.89 (t, J = 7.3 Hz, 2H, CH₃CH₂CH₂), 7.48 (s, 1H, CH=), 8.35 (s, 4H, Ar-H); ¹³C NMR (75 MHz, DMSO-d₆), table 4. Anal. Calcd for C₁₄H₁₅NO₅S: C, 54.36; H, 4.89. Found: C, 54.16; H, 5.00.

(Z)-3-(p-Nitrobenzoyloxy)-4-thiophenoxy-3-buten-2-one (2h): 0.092 g (85%) as pale yellow crystals: mp 63-64 °C; UV (CH₃CN): 260 (31200), 294 (33000); (EtOH): 254 (30200), 297 (24700); IR (KBr) 1730, 1680, 1530, 1340, 1270, 1100 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 2.33 (s, 3H, CH₃CO), 7.40-7.50 (m, 5H, PhH), 7.52 (s, 1H, CH=), 8.45 (s, 4H, ArH); ¹³C NMR (75 MHz, DMSO-d₆), table 4. Anal. Calcd for C₁₇H₁₃NO₅S: C, 59.47; H, 3.81. Found: C, 59.44; H, 4.00.

2-endo-Acetyl-3-exo-bromobicyclo[2.2.1]hept-5-en-2-exo-yl p-Nitrobenzoate (9) and 2-exo-Acetyl-3-endo-bromobicyclo[2.2.1]hept-5-en-2-endo-yl p-Nitrobenzoate (10). Method A. A mixture of 0.1 g (0.32 mmol) of 4a, 0.21 g (3.2 mmol) of 6 and hydroquinone (3 mg) in anhydrous xylene (2 mL), under an N₂ atmosphere, was heated to 100 °C for 31 h. The crude was purified by column chromatography on silica gel (12 g, hexane/EtOAc, 9.5:0.5), giving a mixture of adducts 9/10 (<5 : >95) as white crystals, which were recrystallized from EtOAc/MeOH, 3:7, giving 0.03 g (25%): mp 149-150 °C; IR (KBr) 1730, 1680, 1510, 1210 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.78 (br s, 2H, H-7), 2.26 (s, 3H, CH₃CO), 3.30 (m, 1H, H-1), 3.45 (m, 1H, H-4), 5.05 (d, J = 3.4 Hz, 1H, H-3), 6.35 (dd, J = 5.5, 2.9 Hz, 1H, H-6), 6.48 (dd, J = 5.5, 3.3 Hz, 1H, H-5), 8.23 (m, 2H, ArH), 8.34 (m, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ 25.5 (C-9), 44.5 (C-7), 48.9 (C-1), 49.5 (C-4), 53.3 (C-3), 90.0 (C-2), 123.7 (C-13), 131.2 (C-12), 134.1 (C-6), 134.4 (C-11), 139.5 (C-5), 151.0 (C-14), 164.2 (C-10), 201.9 (C-8); MS (70 eV) 300 (M⁺-Br, 1), 270 (1), 151 (7), 135 (16), 120 (100), 93 (3). Anal. Calcd for C₁₆H₁₄BrNO₅: C, 50.55; H, 3.71. Found: C, 50.38; H, 3.88.

Method B. To a mixture of 4a (0.1 g, 0.32 mmol), $ZnCl_2$ (0.44 g, 3.2 mmol) or AlCl₃ (0.43 g, 3.2 mmol) in dry CH_2Cl_2 (2.0 mL), under an N₂ atmosphere at room temperature, was added 6 (0.053 g, 0.8 mmol). The mixture was stirred at room temperature for 48 h and 6 (0.053 g, 0.8 mmol) was added. The mixture was stirred for 24 h and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (15 g, hexane/EtOAc, 9:1), to yield: With $ZnCl_2$, 0.048 g (40%) of a mixture of adducts 9/10 (37:63); and with AlCl₃, 0.045 g (37%) of a mixture of adducts 9/10 (25:75).

 $(1R^*, 2R^*)$ -1-Acetyl-2-bromo-4-methylcyclohex-4-en-1-yl p-Nitrobenzoate (14) and $(1R^*, 2R^*)$ -1-Acetyl-2-bromo-5-methylcyclohex-4-en-1-yl p-Nitrobenzoate (15). Method A. A mixture of 4a (0.1 g, 0.32 mmol), 11 (0.109 g, 1.6 mmol) and hydroquinone (3 mg) in anhydrous xylene (5 mL) was placed under an N₂ atmosphere in a screw cap flask. After being stirred at 130 °C for 10 h, 0.109 g (1.6 mmol) of 11 was added. The mixture was heated for 5 h more. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (12 g, hexane/EtOAc, 9:1) to yield 0.05 g (41%) of a mixture of adducts 14/15 (7:3).

Method B. To a mixture of 4a (0.1 g, 0.32 mmol), AlCl₃ (0.43 g, 3.2 mmol) or ZnCl₂ (0.44 g, 3.2 mmol) in dry CH₂Cl₂ (2.0 mL) under an N₂ atmosphere at room temperature was added 11 in fourfold amounts of 0.027 g (0.4 mmol) every hour. The mixture was stirred at room temperature for 5 h and the solvent was removed in vacuo. The solid residue was purified by column chromatography on silica gel (12 g, hexane/EtOAc, 8:2), to yield: With AlCl₃, 0.052 g (43%) of a mixture of adducts 14/15 (85:15); and with ZnCl₂, 0.05 g (41%) of a mixture of adducts 14/15 (90:10). IR (KBr) 3020, 1710, 1520, 1300 cm⁻¹; data of 14: ¹H NMR (300 MHz, CDCl₃) δ 1.70 (br s, 3H, CH₃C=), 2.30 (s, 3H, CH₃CO), 2.80 (m, 2H, H-3), 3.02 (dm, J = 18.7 Hz, 1H, H-6), 3.14 (dm, J = 18.7 Hz, 1H, H-6), 4.58 (dd, J = 6.3, 6.0 Hz, 1H, H-2), 5.37 (br s, 1H, CH=), 8.25 (m, 2H, ArH), 8.35 (m, 2H, ArH). Further signals attributed to isomer 15: 2.33 (s, 3H, CH₃CO), 4.52 (dd, J = 11.0, 6.0 Hz, 1H, H-2); ¹³C NMR (75 MHz, CDCl₃) δ 22.5 (C-7), 26.5 (C-9), 30.4 (C-3), 39.0 (C-6), 50.0 (C-2), 86.2 (C-1), 116.6 (C-5), 123.7 (C-13), 131.1 (C-12), 131.5 (C-4), 135.0 (C-11), 151.0 (C-14), 163.7 (C-10), 204.0 (C-8). Anal. Calcd for C₁₆H₁₆BrNO₅: C, 50.28; H, 4.22. Found: C, 50.44; H, 4.46.

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