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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6747–6750

Aza-Diels–Alder reaction of α,β-unsaturated sulfinylimines derived from α-amino acids with enolethers and enamines

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Received 5 June 2007; revised 12 July 2007; accepted 16 July 2007
Available online 25 July 2007

Abstract—α,β-Unsaturated sulfinylimines derived from α-amino acids undergo aza-Diels–Alder reaction with electron rich dienophiles such as enolethers and enamines. Subsequent elimination of sulfinyl and amine or alkoxy moiety on the resulting cycloadducts affords pyridines derived from α-amino acids.

Aza-Diels–Alder (ADA) reaction[1,2] of 1-aza-butadienes are gaining widespread acceptance as tools in heterocyclic synthesis and have found their use in the preparation of compounds containing pyridine, quinoline, mono- and diazaanthracene and other nitrogen rings. α,β-Unsaturated dimethylhydrazones have been widely used in hetero Diels–Alder reactions, as 1-azadienes[3] (Fig. 1, **I**) with electron-deficient dienophiles, as key steps in a variety of syntheses of natural products and other biologically relevant heterocycles.[4] However, the introduction of electron-withdrawing groups in the position 1 of 1-azadienes changes the reactivity pattern of these compounds and the inverse electronic demand aza-Diels–Alder (IADA) reaction is then feasible if electron rich dienophiles are used. For example, Boger et al. found that *N*-sulfonyl imines (Fig. 1, **II**) can participate as dienes in inverse electron demand aza-Diels–Alder (IADA) reactions with enolethers[5] and that the reactivity of these heterodienes is increased if electron-withdrawing substituents are introduced in C-2.[5b] Moreover, an elegant approach has been recently reported for asymmetric variant of 1-azadiene Diels–Alder reaction, using reactive α,β-unsaturated *N*-sulfonyl imines and chiral enolethers.[6]

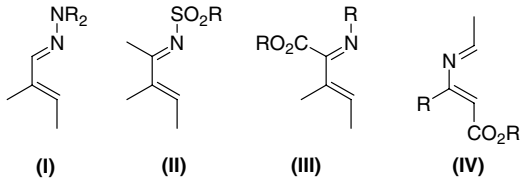

Figure 1. 1- and 2-azadienes.

We have been involved in the synthesis of 2-aza-butadienes,[7] (Fig. 1, **IV**) as well as in the design of new strategies for the preparation of nitrogen heterocyclic compounds[8] including the synthesis and aza-Diels–Alder reaction (ADA) of electron rich 1-azadienes (Fig. 1, **I**).[9] In this context, we developed two approaches for the preparation of 1-azadienes involving as the key step (i) the formation of C=C conjugated olefinic bond through olefination reaction of β-phosphorylated imines[10] or (ii) the aza-Wittig reaction[11] between phosphazenes and β,γ-unsaturated α-ketoesters derived from α-amino acids or α-aminophosphonates[12] and 1-azadienes derived from α-amino esters have also been used for the preparation of acyclic[13] and heterocyclic derivatives.[14]

A recent publication[15] reporting the first catalytic asymmetric inverse electron demand aza-Diels–Alder (AIADA) reaction of *N*-sulfonyl-1-azadienes with enolethers prompted us to report our own results concerning a high yield synthesis of a new family of *N*-sulfinyl-1-aza-1,3-butadienes **III** (Fig. 1, R = Ar SO) from β,γ-unsaturated α-ketoesters derived from α-amino acids and their use for the preparation of six membered heterocycles.

The formation of C=N imine bond through condensation of carbonyl compounds and amine derivatives is

Keywords: Aza-Diels–Alder; 1-Azadienes; α-Amino acids; Pyridines.
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0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.07.101

the simplest method for the preparation of imine compounds.[16] However, in the case of α,β-unsaturated carbonyl compounds, especially in the case of ketones, this presents frequent regioselectivity problems and conjugate addition or double addition products has been observed.[17]

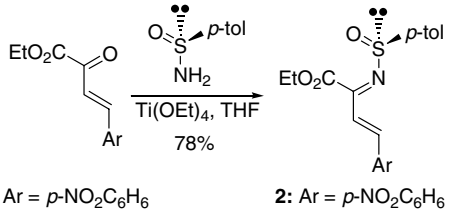
Taking into account the considerations mentioned above, we explored the direct condensation of (*S*)-*p*-toluenesulfinimide and β,γ-unsaturated α-ketoester **1**, activated by the addition of two equivalents of titanium tetraethoxide and only the regioselective preparation of α,β-unsaturated sulfinylimine **2** derived from α-amino acids was observed with good yield (Scheme 1).[18] The presence of an electron-withdrawing group in position 2 of α-ketoester **1** seems to increase the reactivity of the carbonyl group and then the exclusive condensation reaction with the formation of the C=N imine double bond is favoured.

Keeping in mind the good results observed before in inverse electron demand aza-Diels–Alder (IADA) reactions with α,β-unsaturated sulfonylimines,[5,6] we thought that the sulfinylimine derivative **2** would also be a good candidate for [4+2] cycloaddition reactions with electron rich dienophiles. We were aware of the lower electron-withdrawing character of sulfinyl group compared to the sulfonyl moiety but, in our case, we expected an additional activation due to the presence of a carboxylate substituent in C-2 as well as a *p*-nitrophenyl moiety in C-4.

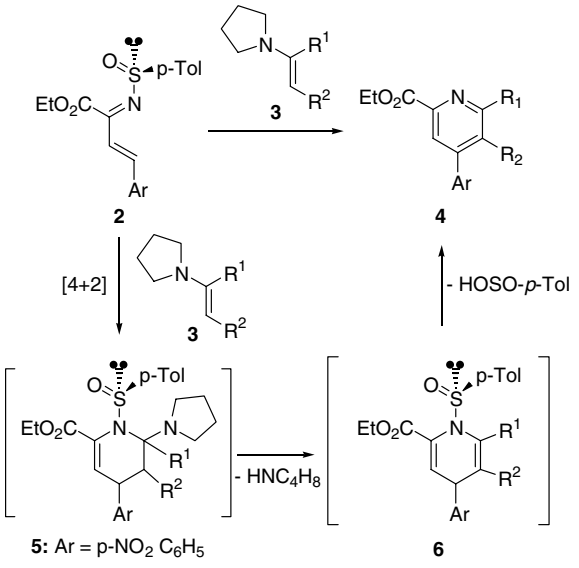
Thus, when 1-azadiene **2** was refluxed overnight with pyrrolidinecyclohexene **3a** (R^1 R^2 = –(CH_2)–), substituted tetrahydroquinoline **4a** (R^1 R^2 = –(CH_2)–) was obtained (Scheme 2, Table 1, entry 1).[19] Formation of quinoline derivative **4a** could be explained through a mechanism where an initial inverse electron demand aza-Diels–Alder (IADA) reaction between 1-azadiene **2** and the enamine afforded cycloadduct **5**, which underwent spontaneous double elimination of pyrrolidine and *p*-toluensulfinyl group, leading to the formation of heterocycle **4a**. An alternative mechanism involving the elimination *N*-pyrrolidine (*S*)-*p*-toluensulfinimide and subsequent aromatization from cycloadduct **5** could not be excluded for the formation of quinoline derivative **4a**.

The reaction can also be extended to deactivated enamine, **3b** (R^1 = H, R^2 = CO_2Et), and when 1-azadiene **2** was refluxed overnight with enamine **3b**, substituted pyridine **4b** (R^1 = H, R^2 = CO_2Et) derived from α- and β-aminoesters was recovered from the reaction (Scheme 2, Table 1, entry 2).

When the reaction was extended to the use of enolethers as electron rich dienophiles, mixtures comprising the unaltered starting materials and the products resulting from the hydrolysis of imine functionality were recovered after refluxing for several days. Diverse Lewis acids were tested in order to activate the cycloaddition reaction but the use of $Yb(OTf)_3$, BF_3, $AlCl_3$ or $TiCl_4$ afforded yet again the starting 1-azadiene **2** together with its hydrolysis products.



Scheme 1. Synthesis of α,β-unsaturated *N*-sulfinylimine **2**.



Scheme 2. Aza-Diels–Alder reaction of 1-azadiene **2** derived from α-amino acids with enamines.

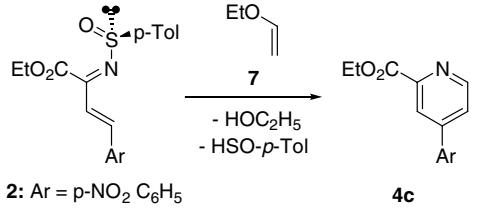
Table 1. Tetrahydroquinoline **4a** and pyridine derivatives **4b, 4c, 9** and **12** obtained by reaction of azadiene **2** and enamines **3** or enolethers **7** and **8**

Entry	Pyridine	Dienophile	Temperature (°C)	R^1	R^2	Yield (%)
1	**4a**	**3a**	39–40			71
2	**4b**	**3b**	39–40	H	CO_2Et	73
3	**4c**	**7**	Sealed tube	H	H	84
4	**9**	**8**	55			75
5	**12**	—				95

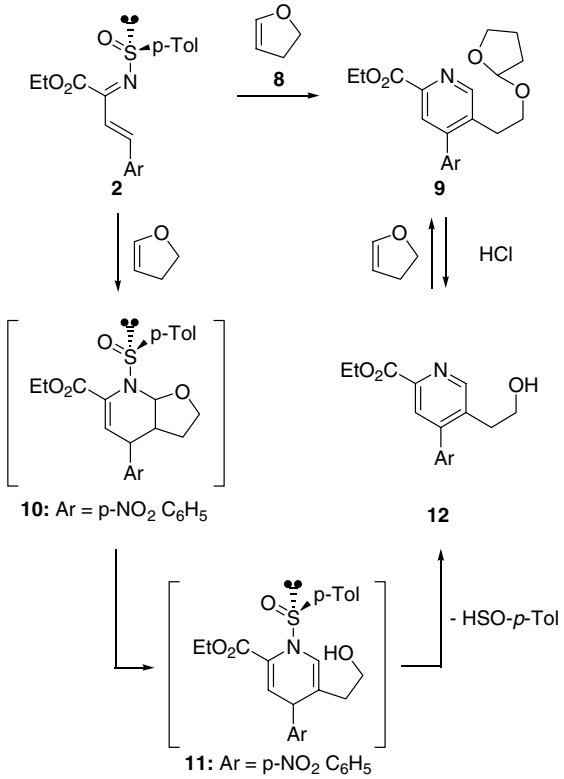
Unsuccessful cycloaddition was once again obtained when 1-azadiene **2** was refluxed at 33 °C in neat ethylvinylether **7** but, however, when a solution of 1-azadiene **2** in ethylvinylether was stirred in a sealed tube and heated in an oil bath at 110 °C until liquid–vapour equilibrium was reached, pyridine **4c** was obtained. In a similar way to that reported for enamines (see Scheme 2), a mechanism comprising [4+2] cycloaddition and subsequent double elimination of ethanol and the sulfinyl group could explain the formation of pyridine **4c** derived from α-aminoester (Scheme 3, Table 1, entry 3).

A remarkable result was obtained when a cyclic enolether was used as the dienophile. In this case, refluxing overnight a solution of 1-azadiene **2** in dihydrofuran **8** afforded pyridine **9** in very good yield (Scheme 4, Table 1, entry 4).

The formation of functionalized pyridine **9** can be explained initially by the [4+2] cycloaddition process



Scheme 3. Aza-Diels–Alder reaction of 1-azadiene **2** with ethylvinylether **7**.



Scheme 4. Aza-Diels–Alder reaction of 1-azadiene **2** with dihydrofuran **8**.

of 1-azadiene **2** and dihydrofuran **8**, followed by bond cleavage of the C–O bond and sulfinyl elimination from cycloadduct **10**. The addition of a second molecule of dihydrofuran **8** to pyridine–ethanol **12** could give functionalized pyridine **9**. The concomitance of the alcohol and dihydrofuran is known to afford tetrahydrofuranyl ethers. Tetrahydrofuranyl ethers can be deprotected under acidic conditions and, therefore, in order to prove the structure assigned to pyridine **9** the acid cleavage of the protecting group was carried out by treatment with HCl to give pyridine **12** with the expected hydroxy moiety (Scheme 3, Table 1, entry 5).

In conclusion, it has been demonstrated that α,β-unsaturated chiral *N*-sulfinylimines can participate as 4π systems with electron rich dienophiles in intermolecular inverse electron demand aza-Diels–Alder reaction. The cycloaddition reaction in all the cases is followed by double elimination of the labile sulfinyl group and amine or alkoxy groups, implying the aromatization of the cycloadducts, which prevents the determination of the stereochemistry of the [4+2] cycloadduct. It should be mentioned that the pyridine heterocyclic core is a widespread subunit in numerous natural products.[20]

Acknowledgements

The present work has been supported by the Dirección General de Investigación del Ministerio de Ciencia y Tecnología (MCYT, Madrid DGI, CTQ2006-09323) and by the Universidad del País Vasco (UPV, GIU 06/51). J.V. thanks the Departamento de Educación, Universidades e Investigación del Gobierno Vasco, for a postdoctoral fellowship.

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18. For the synthesis of α,β-unsaturated sulfinylimine **2**, a solution of (*E*)-4-*p*-nitrophenyl-2-oxo-3-butenoate **1** (1.25 g, 5 mmol) (5 mmol), (*S*)-*p*-toluensufinynimide (0.78 g, 5 mmol) and $Ti(OEt)_4$ (2.10 mL, 10 mmol) in THF (20 mL) was stirred and refluxed for 2 h. The reaction was allowed to warm to room temperature and a solution of aqueous saturated NH_4Cl (20 mL) was then added. The mixture was filtered through celite, washed with H_2O (50 mL) and extracted with CH_2Cl_2 (3×25 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure and the crude residue was purified by chromatography (SiO_2, AcOEt/hexanes 1:4), affording 1.30 g (78%) of **2** as a pale yellow oil. $R_f = 0.89$ (AcOEt). $[\alpha]_D^{20}$ +121.2 (*c* 1.04, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.23$ (d, $^3J_{HH} = 7.0$ Hz, 2H), 7.69 (d, $^3J_{HH} = 7.0$ Hz, 2H), 7.65 (d, $^3J_{HH} = 8.0$ Hz, 2H), 7.34 (d, $^3J_{HH} = 8.0$ Hz, 2H), 7.23 (d, $^3J_{HH} = 16.6$ Hz, 1H), 6.99 (d, $^3J_{HH} = 16.6$ Hz, 1H), 4.51 (q, $^3J_{HH} = 6.9$ Hz, 2H), 2.41 (s, 3H), 1.47 (t, $^3J_{HH} = 6.9$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.1$, 161.2, 148.2, 142.0, 141.1, 140.3, 139.4, 129.7, 128.4, 127.7, 124.8, 123.8, 62.6, 21.2, 13.8 ppm. IR (film): $\nu_{max} = 1725$ (C=O st), 1607 (C=N st) cm^{-1}. EIMS $m/z = 385$ ([M^+], 81), 312 ([M^+]–CO_2Et, 100), 246 ([M^+] – SOTol, 33) amu. Elem. Anal. Calcd for $C_{19}H_{18}N_2O_5S$: C, 59.06; H, 4.70; N, 7.25. Found: C, 59.27; H, 4.66; N, 7.31.
19. Representative example for the cycloaddition reaction of 1-azadiene 2 and electron rich dienophiles is described for the synthesis of pyridine **4a**. A solution of ethyl 2-(*S*)-*p*-tolylsulfinimido-4-*p*-nitrophenyl-(*E*)-3-butenoate **2** (0.39 g, 1 mmol) and 1-cyclohex-1-enyl-pyrrolidine **3a** (0.15 g, 1 mmol) in CH_2Cl_2 (3 mL) was stirred and refluxed overnight. The resulting solution was concentrated under reduced pressure and the crude residue was purified by chromatography (SiO_2, AcOEt/hexanes 1:3) to afford 0.23 g (71%) of pyridine **4a** as a white solid. Mp 132–133 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.26$ (d, $^3J_{HH} = 8.9$ Hz, 2H), 7.71 (s, 1H), 7.41 (d, $^3J_{HH} = 8.9$ Hz, 2H), 4.41 (q, $^3J_{HH} = 7.0$ Hz, 2H), 3.07 (t, $^3J_{HH} = 6.4$ Hz, 2H), 2.57 (t, $^3J_{HH} = 6.4$ Hz, 2H), 1.87 (m, 2H), 1.70 (m, 2H), 1.18 (t, $^3J_{HH} = 7.0$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.3$, 159.1, 148.0, 145.6, 145.3, 133.6, 129.6, 123.8, 122.8, 62.0, 33.2, 27.7, 22.6, 22.5, 14.3 ppm. IR (KBr): $\nu_{max} = 1718$ (C=O st) cm^{-1}. EIMS $m/z = 326$ ([M^+], 100), 253 ([M^+]–CO_2Et, 61) amu. Elem. Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.39; H, 5.65; N, 8.65.
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