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Diels-Alder Reactions with 2-Substituted-α,β-Unsaturated Hydrazones in Concentrated Organic Solutions of $LiNTf_2$ ‡

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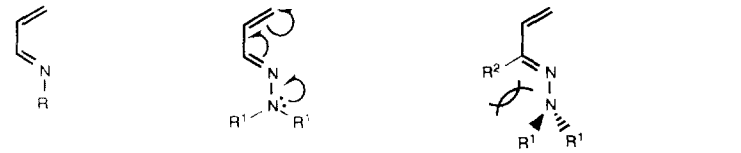
Abstract: *α,β-Unsaturated hydrazones bearing an ester or a nitrile at C-2 position have been synthesized. They are unreactive towards electron-rich dienophiles but react with electron-poor dienophiles. Dramatic rate enhancements have been observed in concentrated organic solutions of $LiNTf_2$.*

INTRODUCTION

Earlier reports from our laboratory have shown that α,β-unsaturated hydrazones could be used as 1-azadiene reagents for the Diels-Alder reaction with electron-deficient dienophiles.[1] More recently we reported the first examples of asymmetric hetero Diels-Alder reactions using α,β-unsaturated hydrazones derived from Enders' chiral hydrazines.[2] These results confirmed our assumption that the presence of a tertiary amine group on the nitrogen atom of an α,β-unsaturated imine would reverse its natural electron-deficient character by virtue of the interaction of the lone pair of the nitrogen atom with the π–system (Scheme 1).



electron-deficient | electron-rich | electron deficient (steric inhibition of conjugation)

Scheme 1

The presence of an alkyl substituent at C-2 suppresses this conjugative interaction as a result of steric hindrance between R^1 and R^2 substituents which force the lone pair out of the plane of the π electrons.[1]

In order to overcome this limitation we have considered the introduction of electron-withdrawing groups at C-2. It has indeed been recently shown[3] that α,β-unsaturated imines bearing a nitrile group at C-2 position reacted surprisingly well with both electron-deficient and electron-rich dienophiles. The corresponding hydrazones should exhibit a higher reactivity towards electrophilic dienophiles and, furthermore, they would readily allow for asymmetric cycloadditions.

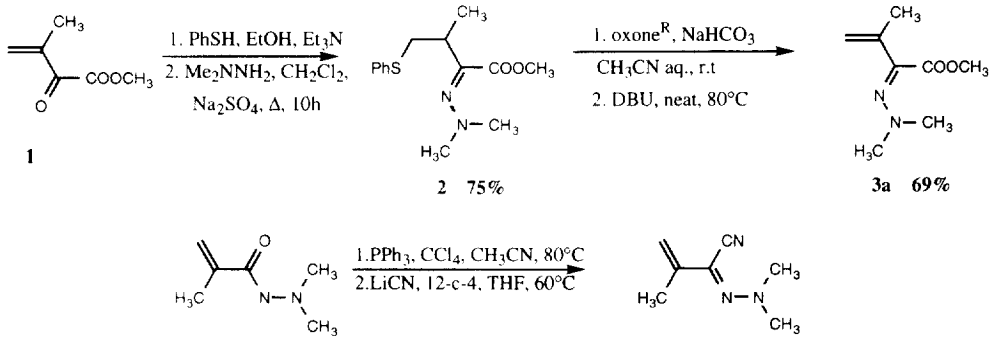
‡ Dedicated to Professor Manfred Regitz on the occasion of his 60th birthday.

In this communication we report our preliminary studies on the synthesis and reactivity of these new 1-azadienes as well as the use of lithium trifluoromethanesulfonimide, $LiNTf_2$ as an efficient and safe catalyst for these hetero Diels-Alder reactions.

RESULTS AND DISCUSSION

The azadiene **3** was synthesized in three-steps (Scheme 2). Methyl β,γ-unsaturated-α-oxo-ester **1** was produced by vinyl Grignard addition on dimethyl oxalate according to the method reported by Rambaud et al.[4] The direct condensation of **1** with N,N-dimethylhydrazine or the corresponding N-aminoiminophosphorane was uneffective as a result of a competitive Michael addition. Thus, the double bond was protected by addition of thiophenol and the resulting adduct was condensed with N,N-dimethylhydrazine to give a good yield of the hydrazone **2.** Oxidation of **2** with oxone® followed by treatment with DBU at 80°C gave the diene **3a** in 69% yield (50% overall).

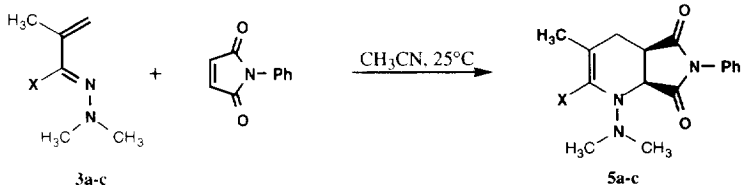
On the other hand, azadiene **3b** bearing a cyano group at C-2 position was readily synthesized in a one-pot sequence from hydrazide **4** (Scheme 2).



Scheme 2

Both azadienes **3a** and **3b** were obtained as single stereoisomers as shown by H^1-NMR.[5]

In contrast to Fowler-Grierson's dienes, both **3a** and **3b** were unreactive towards ethylvinylether or p-methoxystyrene (e.g. refluxing acetonitrile). However they slowly react with N-phenylmaleimide in acetonitrile at room temperature to give high yields of adducts **5** (Scheme 3 and Table 1). As expected from the introduction of an electron-withdrawing group at C-2, both **3a** and **3b** were less reactive than the corresponding unsubstituted diene **3c** (X=H).



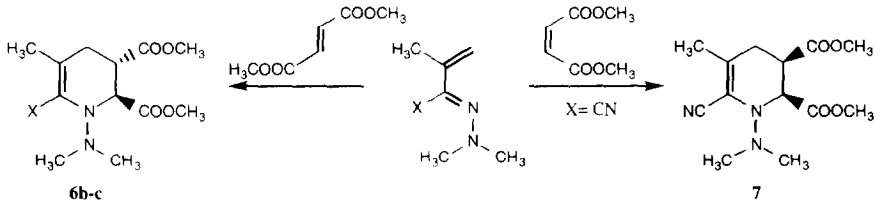
Scheme 3

Table 1

entry	1-azadiene	cycloadduct	Yield (%)	reaction time
1	**3c**, X=H	**5c**	95%[a]	1 day
2	**3a**, X=$COOCH_3$	**5a**	76%	3 days
3	**3b**, X=CN	**5b**	91 (86)%[b]	14days
4	**3b**, X=CN	**5b**	82%	3h [c]

[a] ^{1}H-NMR estimated yield, not isolated. [b] Value in parentheses given for the reaction in toluene. [c] reaction carried out in 2.5M $LiNTf_2$-acetonitrile.

There are several reports of strong acceleration of Diels-Alder reactions when performed in concentrated solutions of lithium perchlorate in organic solvents.[6] We and Grieco's group have recently found that the hazardous lithium perchlorate can be efficiently replaced by lithium trifluromethanesulfonimide, $LiNTf_2$, which is highly soluble in many organic solvents.[7] A spectacular rate increase was indeed observed when the reaction of **5** with N-phenylmaleimide was run in 2.5 M $LiNTf_2$-acetonitrile (Table 1, entry 4). These conditions also allow to perform successfully cycloadditions with less reactive dienophiles (Scheme 4, Table 2).[8] Moreover, we observed the complete stereospecificity of the reaction in this medium.



Scheme 4

Table 2

Adducts, X=	Reaction conditions	% Yield
H, **6c**	$LiNTf_2$ - CH_3CN 2.8M, r.t., 3d.	75
H, **6c**	$LiNTf_2$ - Et_2O 4M, r.t., 19h.	90(crude)
CN, **6b**	$LiNTf_2$ - CH_3CN 2.5M, 50°C, 3d.	60
CN, **7**	$LiNTf_2$ - CH_3CN 2.5M, 50°C, 3d.	68

These results show that Diels-Alder reactions can now be performed with α,β-unsaturated hydrazones bearing functional groups at C-2. They also confirm the usefulness of $LiNTf_2$ in organic solvents as a reaction medium for Diels-Alder reactions. An extension of this methodology using enantiomerically pure hydrazones is presently being studied.

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4. Rambaud M.; Bakasse M.; Duguay G.; Villieras J. *Synthesis* **1988**, 564-566.
5. **N,N-dimethylamino-2-methoxycarbonyl-3-methyl-1-azabutadiene 3a:**
   Yellow oil (one isomer). IR(CCl_4): 3095, 2929, 1742, 1731, 1434, 1242,1085. ^1H NMR ($CDCl_3$, 300MHz) δ 5.34 (m,1H,CH_2=), 5.08 (m,1H,CH_2=), 3.84 (s,3H,OCH_3), 2.72 (s,6H,NMe_2), 1.95 (s,3H,CH_3). ^{13}C NMR ($CDCl_3$, 75MHz) δ 167.1 ($COOCH_3$), 149.8, 139.9, 117.5 (CH_2=), 51.6 (OCH_3), 46.6 (NMe_2), 18.8 (CH_3). Anal. Calcd for $C_8H_{14}O_2N_2$: C,56.45; H,8.29; N,16.45. Found: C,56.74; H, 7.97; N,16.04.
   N,N-Dimethylamino-2-cyano-3-methyl-1-azabutadiene 3b:
   Yellow oil. IR(CCl_4): 3097, 2926, 2201, 1543, 1420, 1067. ^1H NMR ($CDCl_3$, 300MHz) δ 5.37 (s,1H,CH_2=), 5.15 (s,1H,CH_2=), 3.38 (s,6H,NMe_2), 1.90 (s,3H,CH_3). ^{13}C NMR ($CDCl_3$, 75MHz) δ 141.0, 114.7, 112.2, 109.4 (CN), 45.4 (NMe_2), 19.2 (CH_3). Anal. Calcd for $C_7H_{11}N_2$: C,61.29; H,8.08; N,30.63. Found: C,61.91; H, 8.08; N,30.10.
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8. Typical procedure for the cycloadditions:
   3b (0.28g, 2mmoles) is treated with N-phenylmaleimide (0.35g, 2mmoles) in acetonitrile (6ml) under argon at 20°C for 14 days. After removal of the solvent, the crude reaction mixture is purified by chromatography on silicagel (hexane - ethyl acetate: 75/25) to give pure cycloadduct **5b**. Yield 91%; pale yellow crystals; mp 62-63°C. IR(CCl_4): 2952, 2819, 2201, 1729, 1551, 1376. ^1H NMR ($CDCl_3$, 300MHz) δ 7.55-7.41 (m,3H,Ph), 7.30-7.27 (m,2H,Ph), 4.41 (d,1H,J=8.5Hz,H-2), 3.09 (ddd,1H,J=7.5 & 15.8Hz,H-3), 2.68-2.59 (m,7H,NMe_2 & H-4), 2.27 (dd,1H,J=7.5Hz,H-4), 2.01 (s,3H,CH_3). ^{13}C NMR ($CDCl_3$, 75MHz) δ 175.5 (CON), 174.3 (CON), 131.3, 129.2, 128.8, 126.1; 125.1, 118.0, 114.5 (CN), 51.2 (C-1), 42.6 (NMe_2), 37.3 (C-3), 27.9 (C-4), 20.6 (CH_3). Anal. Calcd for $C_{17}H_{18}N_4O_2$: C,65.79; H,5.85; N,18.05. Found: C,65.56; H,5.70; N,17.67.

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