α-Acetyl- and α-Cyanovinyl 2,4-Dinitrophenyl Carboxylate as Useful Ketene Equivalents for the Diels-Alder Reaction

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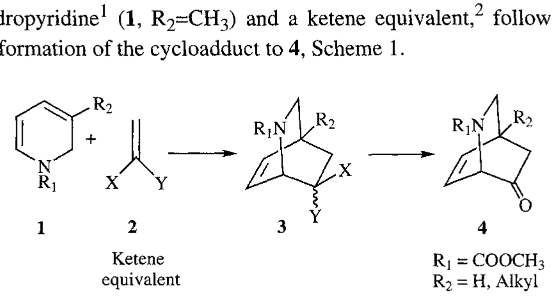
Abstract: Two ketene equivalents (**5** and **35**) have been developed for use in the Diels-Alder reaction. These dienophiles exhibit a marked increase in reactivity in comparison with the more conventional acetoxyacrylonitrile. Conversions of the cycloadducts to the requisite ketones occurs under mild, and moderate to high yielding conditions.

In a program directed towards the synthesis of manzamine A, we recently had a need for 1-(methoxycarbonyl)-4-methyl-7-ketoisoquinuclidene (**4**, R_2=CH_3) as an intermediate. It appeared that the most judicious approach to this compound was *via* a [4+2]-cycloaddition between N-(methoxycarbonyl)-3-methyl-1,2-dihydropyridine[1] (**1**, R_2=CH_3) and a ketene equivalent,[2] followed by transformation of the cycloadduct to **4**, Scheme 1.

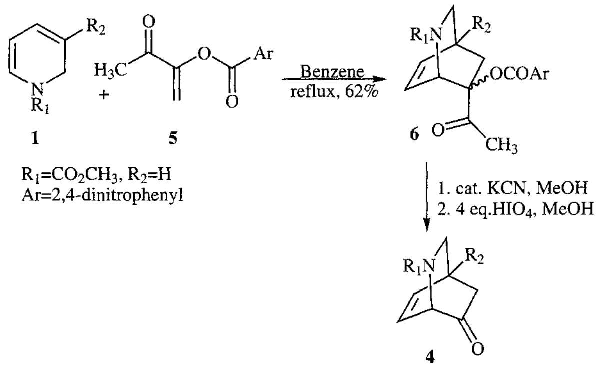


Scheme 1

Relevant examples for this type of strategy are limited. However, Mariano has recently demonstrated that cycloaddition between **1** (R_2=H) and acetoxyacrylonitrile **2** (X=OAc, Y=CN) can be effected in 40% yield.[3] When we repeated this reaction we got identical results, but attempted cycloaddition with more substituted variants of **1** (R=CH_3) gave disappointing results (<10% cycloadduct). The use of the more reactive chloroacrylonitrile **2** (X=Cl, Y=CN) gave acceptable levels of cycloadduct (ca. 80%-85%), but unfortunately all endeavours at hydrolysis failed. The adequacy of other ketene equivalents (**2**) such as nitroethylene (X=H, Y=NO_2) proved unsuccessful. In addition, efforts to use higher temperatures (>120°C) or Lewis acids ($ZnCl_2$, Eu(fod)$_3$, $SnCl_4$) only led to decomposition of the diene. From the above results it was clear that for our purposes, not only was a reactive dienophile needed, but one that allowed the cycloadduct to be easily transformed into the desired azabicycle.

Some years ago Vogel[4] reported that 1-acetylvinyl 2,4-dinitrobenzoate (**5**) had approximately the same dienophile reactivity as methyl vinyl ketone (MVK) in the Diels-Alder reaction. This fact caught our attention since MVK was known to readily react with the types of dienes we were interested in,[5] and in principle, simple hydrolysis of the ester followed by oxidative cleavage would furnish **4** (R_2=H), Scheme 2. In order to establish the feasibility of this approach, N-(methoxycarbonyl)-1,2-dihydropyridine (**1**) and dienophile **5** were refluxed in benzene for 72 hours to generate adduct **6** in good yield (2:1 endo/exo mixture of stereoisomers), Scheme 2.

Ensuing hydrolysis of the aryl-ester (**6**) with potassium cyanide (4 mol %)[6] followed by oxidative cleavage with HIO_4 produced ketone **4** in 60% overall yield! This was a marked improvement over the Mariano procedure which had generated the product in only 32%.



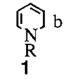
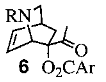
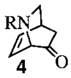
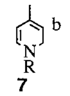
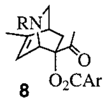
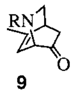
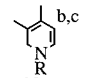
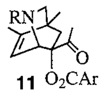
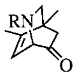
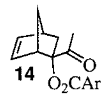
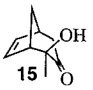
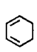
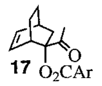
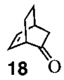
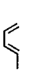
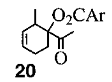
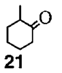
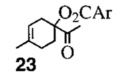
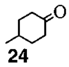
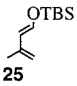
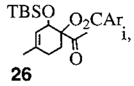
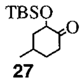
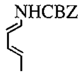
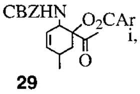
Scheme 2

With the success of this result, this inspired us to undertake a study to probe the versatility of this dienophile (**5**), and the generality of the procedure for this transformation. Our results are presented in Table 1.[7] As hoped for, the dienophile was sufficiently reactive to undergo the [4+2]-cycloaddition with all of the dienes investigated under simple thermal conditions (benzene, CH_3CN). In all cases examined, except diene **10**, the cycloadducts were produced in good to excellent yields as a mixture of stereoisomers (endo/exo ratios ranging from 1:1 for cycloadducts **6**, **8**, **11**, **14** and **17** to >98:2 for adducts **20**, **26** and **29**, with no traces of the minor diasteromers being observed by ^1H NMR). The generally poor endo/exo selectivities for our purposes were of no consequence, but the observed results agree with the previous studies of Vogel.[4]

Having demonstrated that the dienophile (**5**) was effective in the [4+2]-cycloaddition reaction with a wide variety of dienes, attention was now focused on elaborating the Diels-Alder products into the "ketene" adducts, Table 1. For all examples studied, smooth hydrolysis could be effected simply by treating the aryl-esters with a catalytic amount of potassium cyanide in methanol; use of more basic conditions (5% NaOH) led to significant decomposition. For cycloadducts **6**, **8**, **11** and **17** simple oxidative cleavage with periodic acid (HIO_4) furnished the bicycloketones in good to excellent overall yields (66%-95%). For the monocyclic examples, this did not prove practical. In most instances oxidation proceeded as expected, however, the alkene tended to partially and/or completely isomerize, thus making product isolation and characterization difficult. To alleviate this, the alkenes were hydrogenated before oxidation. As shown in Table 1 (adducts **20**, **23**, **26** and **29**) this sequence proved viable, generating the desired saturated ketones in good overall yields. Of note is that oxidants other than HIO_4 could be used without any deleterious effects on the efficiency of the process (**26**-**27**).

Of particular interest in Table 1 is the [2.2.1]-bicycloadduct **14**. Attempted hydrolysis under a variety of conditions only led to the rearranged bicyclohydroxyketone (**15**), presumably by an α-ketol rearrangement. A similar behaviour was noted by Corey in a related example.[8] A partial solution to this problem was found by reducing the initial hydrolysis product to generate a 3:1 mixture of diols (**31**, **32**), Scheme 3. Separation followed by periodic acid oxidation gave the norcamphor derivative **33** in low yield (ca. 20-25%). All effort expended to improve this result proved fruitless.

Table 1. Reaction of α-acetylvinyl 2,4-dinitrophenylbenzoate (**5**) as a ketene equivalant

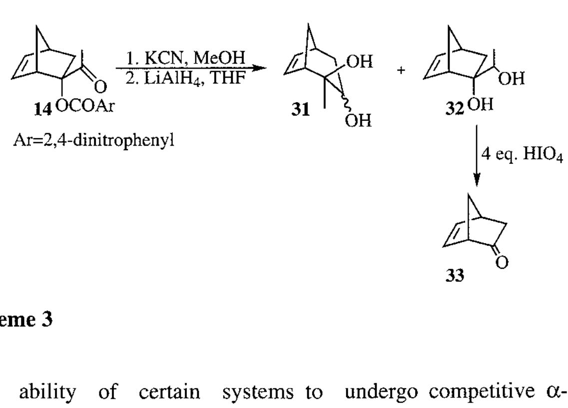
Diene	Conditions yield(%)[a]	Cycloadduct	Reaction conditions	Ketone	Yield[a] (%)
 **1** [b]	A (63%)	 **6**	i, ii	 **4**	>95
 **7** [b]	A (63%)	 **8**	i, ii	 **9**	73
 **10** [b,c]	A (32%)	 **11**	i, ii	 **12**	74
 **13**	B (95%)	 **14**	i	 **15**	92
 **16**	A (64%)	 **17**	i, ii	 **18**	66
 **19**	C (95%)	 **20**	i, iii, ii	 **21**	56
 **22**	C (95%)	 **23**	i, iii, ii	 **24**	49
 **25**	D (91%)	 **26**	i, iv, v	 **27**	77
 **28**	D (91%)	 **29**	i, iv, ii	 **30**	80

Ar = 2,4-dinitrophenyl, R = CO_2CH_3

Conditions for Cycloadditions: **A**. C_6H_6, reflux, 72 h; **B**. CH_3CN, rt, 15 h; **C**. CH_3CN, 100°C, 72 h; **D**. C_6H_6, reflux, 15 h.

Conditions for Generating Ketene Adducts: **i**. 4 mole % KCN, MeOH; **ii**. 4 eq. HIO_4, aq. 66% EtOH; **iii**. 10% Pd/C, MeOH; **iv**. PtO_2, MeOH; **v**. $RuCl_3.xH_2O$, CCl_4, H_2O, CH_3CN.

[a] Isolated yields and all new compounds were characterized by ^1H and ^{13}C NMR, IR and HREIMS or FABMS. [b] 1,2-dihydropyridine dervivatives were prepared according to ref. 1. [c] mixture of 1,2-, 1,4- and 1,6-regiosiomers.



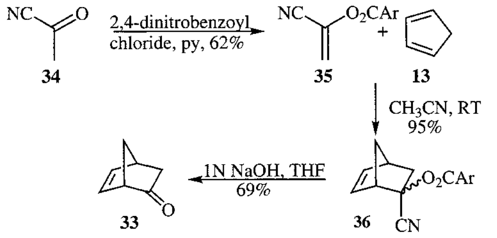
Scheme 3

The ability of certain systems to undergo competitive α-ketol rearrangement clearly demonstrated a potential limitation of this strategy. However, it was felt that if a similar dienophile lacking the acetyl functionality could be constructed, then this problem would be alleviated.

To investigate this possibility, pyruvonitrile (**34**) was treated with 2,4-dinitrobenzoyl chloride according to the conditions reported by Oku[9] to produce α-cyanovinyl 2,4-dinitrophenyl carboxylate (**35**) in 62% yield, Scheme 4.[10] This dienophile when treated with excess cyclopentadiene (**13**) at room temperature for 22 h gave cyano-ester **36** as a mixture of endo/exo stereoisomers (7:3) in 95% yield. Although cyclopentadiene is an extremely reactive diene, it appeared that this dienophile also had marked reactivity.[11] A quick study of the reactivity of this alkene as a dienophile in the Diels-Alder reaction (using cyclopentadiene as a diene) bore this out. It was found, as expected, that analogue **35** had reactivity comparable to acrylonitrile, but was approximately 5-6 times more reactive than acetoxyacrylonitrile, Table 2. These rates were determined using the rate expression given by Vogel,[4] and as in his examples, reactions were monitored over 2 half-lives.

Table 2. Rate data (± 5%) for reaction of various dienophiles with cyclopentadiene at 40°C in toluene-d8 according to the rate expression given in ref. 4.

Dienophile	Rate (10^{-5} $l.mol^{-1}.s^{-1}$)
acetoxyacrylonitrile (**2**, X=CN, Y=OAc)	0.37
α-cyanovinyl 2,4-dinitrophenyl carboxylate (**35**)	1.97
acrylonitrile (**2**, X=CN, Y=H)	1.84



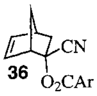
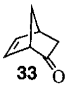
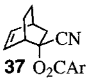
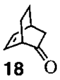
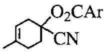
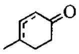
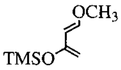
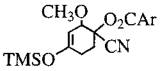
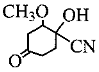
An expeditious examination of the utility of this dienophile as a ketene equivalent was done and the results are presented in Table 3. As seen, the yields of cycloadducts are analogous to the former study, however, the stereoselectivity of this dienophile is superior to **5** (endo/exo ratios(cycloadduct): 4:1 (**38**), 7:3 (**36**), 83:17 (**37**) and >98:2 (**41**)). Unfortunately, attempts at cycloaddition using dienes such as **1**, **7**, or **10** only led to complete decomposition of the dienophile. The reasons for this are not clear, although traces of pyridine (or its analogues) remaining from the reduction appear to catalyze the observed decomposition, presumably by either a Michael type addition or hydrolysis of the ester.

Gratifyingly, simple hydrolysis (1M NaOH or KCN, MeOH) generated the desired ketones (**33**, **18** and **39**) in good yields, Table 3. In one example, the cyanohydrin (**42**) was obtained in lieu of the ketone. Due to the sensitivity of this compound, further hydrolysis to the dione proved elusive.

Although not shown in Table 3, cycloadditions with acyclic dienes (i.e. **19**, **22** and **25**) were equally feasible, however, upon hydrolysis double bond isomerization became a serious problem. In many runs the major product obtained after work-up was the deconjugated product, usually contaminated with 10%-15% of the conjugated isomer, but upon standing or attempted purification the olefin typically migrated into conjugation. Regardless of the limitations imposed by the types of dienes that can be used, conversion of the cycloadducts to the corresponding ketones in one step was seen as an attractive advantage.

In summary, we have developed two ketene equivalents for the Diels-Alder reaction. Both compounds are stable for long periods of time (ca months at <0°C) and are easily synthesized in one step from readily available starting materials. These dienophiles (**5**, **35**) show a marked increase in reactivity compared to other conventional ketene equivalents such as acetoxyacyrlonitrile. Also their transformation into the desired

Table 3. Reaction of α-cyanovinyl 2,4-dinitrophenylbenzoate (**35**) as a ketene equivalant.

Diene	Conditions yield(%)	Cycloadduct	Reaction conditions	Ketone	Yield[a] (%)
 **13**	B (95%)	 **36**	i	 **33**	67
 **16**	A (32%)	 **37**	i	 **18**	66
 **22**	C (83%)	 **38**	ii	 **39**[b]	66
 **40**	D (92%)	 **41**	ii	 **42**	76

Ar = 2,4-dinitrophenyl, E = CO_2CH_3

Conditions for Cycloadditions: **A**. $C_6H_5CH_3/CH_3CN$ (3:1), 120°C, sealed tube, 48 h; **B**. CH_3CN, rt, 22 h; **C**. $C_6H_5CH_3/CH_3CN$ (3:1), sealed tube, 120°C, 96 h; **D**. toluene, reflux, 16 h.

Conditions for Generating Ketene Adducts: **i**. aq. 1N NaOH, THF; **ii**. 4 mol % KCN, MeOH.

[a] Isolated yields and all new compounds were characterized by ^1H and ^{13}C NMR, IR and LREIMS or FABMS; [b] Mixture of double bond isomers.

"ketene" cycloadducts occurs under mild and generally good to high yielding conditions. As a result of their exceptional dienophilicity, ease of transformation into the desired cycloadducts and ready availability, these dienophiles should find wide application as ketene equivalents in natural product synthesis.

Acknowledgments:

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References and notes

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2. Tidwell, T.T.; In *Ketenes*; Wiley: New York, 1995; p 459-460.
3. Mariano, P.S.; Ammon, H.L.; Labaree, D.; Barter, E.W. *J. Am. Chem. Soc.* **1990**, *112*, 7682.
4. Vogel, P.; Tamariz, J. *Helv. Chim. Acta.* **1981**, *64*, 188.
5. Unpublished results.
6. Herzig, J.; Nudelman, A.; Gottlieb, H.E.; Fischer, B. *J. Org. Chem.* **1986**, 51, 727.
7. **General procedure for the hydrolysis of cycloadducts**: To a stirred solution of cycloadduct (1 mmol) in anhydrous methanol (10 ml) was added potassium cyanide (0.04 mmol). The reaction mixture was stirred at room temperature for 1.5 to 3 hours, where upon completion, the reaction mixture was filtered through a short pad of silica gel. The filtrate was concentrated in vacuo and the residue was purified by silica gel chromatography.

   General procedure for the oxidation of hydroxy ketones: To a stirred solution of hydroxy ketone (1 mmol) in aq. 66% ethanol (3.5 ml) at 0°C was added periodic acid (4 mmol) in ethanol (1.5 ml). The reaction mixture was stirred at room temperature until TLC showed complete consumption of starting material. The reaction mixture was extracted with CH_2Cl_2 (3x10 ml) and the combined organic layers were washed with brine, dried over anhydrous potassium carbonate and evaporated under reduced pressure. The crude products were purified by silica gel chromatography.
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10. **Preparation of 2-cyanovinyl 2,4-dinitrophenyl carboxylate (7)**: To an RBF cooled to 0°C was added 2,4-dinitrobenzoyl chloride (84 mmol), pyruvonitrile (30 mmol) and benzene (17 ml). To this was added pyridine (42 mmol) in benzene (10 ml), and the reaction mixture was allowed to slowly warm to room temperature and stir for 24 hours. The solution was filtered through a short pad of silica gel and the filtrate was washed with water (3x30 ml), brine (1x25 ml) and dried over anhydrous K_2CO_3. After evaporation of solvent, the residue was purified by SiO_2 chromatography (4:1 hexane/ethyl acetate as eluant) to give 4.9 g (62%) of **7** as a pale yellow solid. An analytical sample was obtained by recrystallization from hexane/ethyl acetate. M.Pt. 102-103°C; IR ($CHCl_3$) cm^{-1}: 3102, 3005, 2878, 2230, 1778, 1601, 1540, 1345; ^1H NMR ($CDCl_3$): 5.97 (d, 1H, J=3.4), 6.01 (d, 1H, J=3.4), 8.04 (d, 1H, J=8.4), 8.65 (dd, 1H, J=8.3, 2.0), 8.94 (d, 1H, J=2.0); ^{13}C NMR ($CDCl_3$): 112.2, 120.0, 121.1, 126.9, 128.3, 130.6, 131.1, 131.5, 149.6, 160.7; LREIMS m^+/z (%): 263.3 (3), 194.3 (100), 68.8 (89).
11. A similar experiment with acetoxyacrylonitrile gave substantially less conversion after an identical time period primarily due to the rate of dimerization of cyclopentadiene being competitive with the desired [4+2]-cycloaddition.