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LETTERS

Cyanomethylene Cyclopropane, a useful Dipolarophile and Dienophile in [2+3] and [2+4] Cycloadditions.

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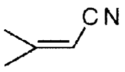
Abstract: Cyanomethylene cyclopropane, prepared for the first time on large scale, proved to be a reactive dipolarophile and dienophile in several cycloadditions. The reactivity of this compound has been compared with 3-methyl-2-butenenitrile, ethyl 3-methyl-2-butenoate and ethoxycarbonylmethylene cyclopropane. © 1998 Elsevier Science Ltd. All rights reserved.

During the course of natural product synthesis, we were faced with the poor reactivity of 3-methyl-2-butenenitrile **1** and ethyl 3-methyl-2-butenoate **2** in [2+3] cycloadditions with camphor derived oxazoline-*N*-oxides[1,2]. The use of cyclopropanic analogues in which the cyclopropane ring can be considered as a *gem* dimethyl surrogate seemed to be promising and this principle has been already used in several kind of cycloadditions[3,4,5]. The preparation of cyanomethylene cyclopropane **3** as well as a comparison of the reactivity of this compound and ethoxycarbonylmethylene cyclopropane **4a** in various [2+3] and [2+4] cycloadditions are presented in this communication.



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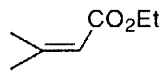

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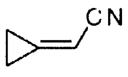

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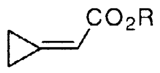

4a : R = Et
4b : R = Me

The only reference of cyanomethylene cyclopropane **3** in literature[6] is related to a pyrolysis of tetrahydrofuronitrile at 500-600°C over silica, affording **3** as by product. By analogy with the preparation of ethoxycarbonylmethylene cyclopropane **4a**[7], it was anticipated that Wittig condensation between triphenylcyanomethylenephophorane **6** and 1-ethoxy-1-hydroxycyclopropane **7**[8] might afford **3**.

The preparation of the required phosphorane **6**[9] proved troublesome, as also reported by others[10,11]. The use of a diluted solution of sodium hydroxyde for deprotonation of phosphonium salt **5** afforded large amount of triphenylphoshine oxide and very low yield of the anticipated phosphorane **6**. Nevertheless, it was found that by using 50% solution of sodium hydroxyde, **6** was isolated in 72% yield[12].

1-Ethoxy-1-hydroxycyclopropane **7** was prepared just before use by hydrolysis of 1-hydroxy-1-trimethylsilyoxy cyclopropane[8]. Wittig condensation between phosphorane **6** and hemiketal **7** can be performed in several solvents such as benzene, toluene or ethyl acetate at 80°C. After precipitation of triphenylphosphine oxide with pentane, the crude nitrile **3** was purified by silica gel column chromatography (pentane-ether 80 : 20) and afforded cyanomethylene cyclopropane **3** in solution in ether[12]. However, isolation of **3** was difficult because its tendancy to form azeotrope with various solvents. For this reason, yields were estimated by ^{1}H NMR to be in the range of 30-50% (Scheme 1).

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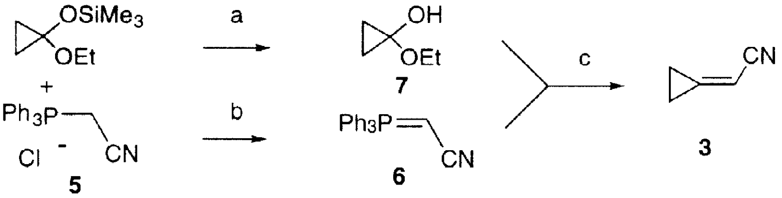
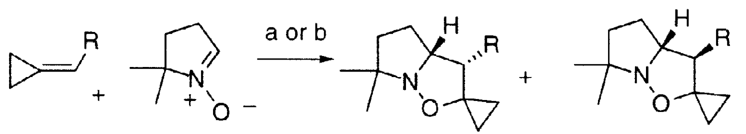


Scheme 1 : a) $ClSiMe_3$, 0.01 eq, MeOH, 20°C, 10 min. b) NaOH (50%), H_2O. c) $PhCO_2H$, 0.1 eq, C_6H_6, Rfx, 17 h.

Reactivity of cyanomethylene cyclopropane **3** was first evaluated in [2+3] cycloadditions with 5,5-dimethylpyrroline *N*-oxide **8** as dipole by comparison with [2+3] cycloaddition of the same dipole with methoxycarbonylmethylene cyclopropane **4b** as described by Brandi[13]. Results are summarized in Scheme 2. As expected, cyanomethylene cyclopropane **3** proved to be more reactive than **4b**. Cycloaddition is highly regioselective, only one regioisomer being detected. The *endo* stereoselectivity of this cycloaddition is more suprising, since generally esters give a better *endo* selectivity than nitriles. In this case, the effect of secondary orbital overlap in ester **4b** is probably overrided by the steric hindrance which is obviously minimized in nitrile **3** (Scheme 2).



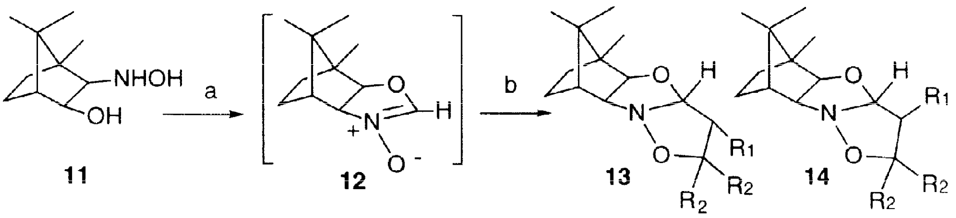
Yield %[c]

3 : R = CN **8** **9a** : R = CN (80%) **9b** : R = CN (20%) 87

4b : R= CO_2Me **10a** : R = CO_2Me (33%) **10b** : R = CO_2Me (67%) 63 **(Ref. 13)**

Scheme 2 : a) **3**, 2 eq, toluene, 50°C, 1h. b) **4b**, 2 eq, 50°C, 40h, whithout solvent.
c) For **9a-9b** yield is calculated from **8**.

Asymmetric [2+3] cycloadditions with camphor derived oxazoline-*N*-oxide **12** with **3** and **4a** have also been studied and compared with cycloaddition of 3-methyl-2-butenenitrile **1** and of ethyl 3-methyl-2-butenoate **2** (Scheme 3, table 1). As previously described[1], *N*-oxide **12** was prepared by condensation of hydroxylamino*iso*borneol **11** with trimethyl orthoformate and submitted directly to cycloaddition reaction condition. Cyclopropane derivatives **3** and **4a** gave much better yields than the *gem*dimethyl derivatives **1** and **2** (Table 1). The high yield obtained in cycloaddition with **3** affording adducts **13c-14c** is specially worthy of note. *Endo* selectivity is observed in both cases with **3** and **4a**. This can be due to the decreasing steric hindrance at the α position from nitrogen which is linked in dipole **12** to tertiary carbon and in dipole **8** to a quaternary carbon. A secondary orbital interaction with endocyclic oxygen in dipole **12** may also reenforce the *endo* selectivity.



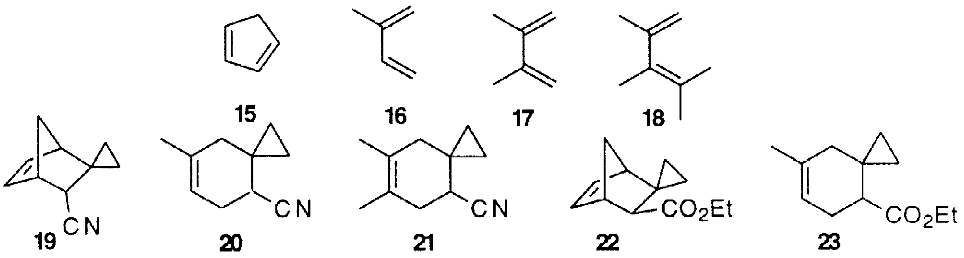
13a, 14a : R_1 = CN ; R_2 = Me
13b, 14b : R_1 = CO_2Et ; R_2 = Me
13c, 14c : R_1 = CN ; R_2 = $(CH_2)_2$
13d, 14d : R_1 = CO_2Et ; R_2 = $(CH_2)_2$

Scheme 3 : a) $HC(OMe)_3$, 4 eq, $CaCO_3$, 1.1 eq, toluene, 40°C, 4h. b) see table 2.

Dipolarophile (eq)^{a}	Time h	Yield %	**13** (*endo*)	**14** (*exo*) (ratio)
1 (10)	21	16	>95	<5
2 (10)	19	11	50	50
3 (2)	1.10	84	88	12
4a (2)	1.30	54	83	17

Table 1 : a) cycloadditions were performed at 80°C in toluene.

Finally, the reactivity of cyanomethylene cyclopropane **3** and of ethoxycarbonylmethylene cyclopropane **4a** in Diels-Alder reaction have been also evaluated. These compounds reacted as dienophiles in the presence of zinc chloride, with a variety of dienes (Table 2). Except in one case with the reactive cyclopentadiene, **3** gave better yields and stereoselectivity than **4a**. However, no cycloaddition was observed with highly sterically demanding 1,1,2,3-tetramethyl butadiene **18** (Scheme 4, table 2).



Scheme 4

It is worth noting that with nitrile **3** cycloaddition with cyclopentadiene **15** was *endo* selective affording **19** as the major adduct, whereas **4a** gave rise exclusively to the *exo* adduct **22**[14]. In this latter case, steric hindrance probably overlap a possible secondary orbital interaction[15].

Dienophile	Diene	Time (h)	Yield	*endo*	*exo*	Adduct
3^{a}	**15**	2	62	70	30	**19**
3^{b}	**16**	19	70			**20**
"	**17**	30	50			**21**
"	**18**	24	0			-
4a^{a}	**15**	2	40	0	100	**22**
4a^{b}	**16**	24	50			**23**

Table 2 : $ZnCl_2$, 0.5 eq, Et_2O. a : 20°C. b: 40°C.

Further uses of the [2+3] cycloadditions between compound **3** and dipole **12** in β-lactam synthesis are in current development.

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References and Notes:

1) For a review, see : Langlois, Y.; Pouilhès, A.; Kouklovsky, C.; Morelli, J.-F.; Haudrechy, A.; Kobayakawa, M.; André-Barrès, C.; Berranger, T.; Dirat O. *Bull. Soc. Chim. Belg.* **1996**, *105*, 639-657.

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3) a) For a review on alkylidenecyclopropane in cycloaddition, see : Goti, A.; Cordero, F. M.; Brandi, A. *Top. in Curr.Chem.*, **1996**, *178*, 1-98. b) For a recent use of alkylidenecyclopropane as dienophile in intramolecular Diels-Alder reaction see, Heiner, T.; Michalski, S.; Gerke, K.; Buback, M.; de Meijere, A. *Synlett*, **1995**, 355-357 and references there in.

4) For the use of alkylidenecyclopropanes as dienes, see: Thiemann, T.; Kohlstruck, S.; Schwär, G.; de Meijere, A. *Tetrahedron Letters*, **1991**, *32*, 3483-3486 and references there in.

5) For a review on the synthesis of alkylidenecyclopropanes, see : Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589-635.

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11) Novikov, S. S.; Shvekhgeimer, G. A. *Izvest. Akad. Nauk.* **1960**, 2061-2063. (*Chem. Abstr.* **1961**, 13353g). Increasing yield (85%) in the preparation of **6** has been described by these authors, but we have been unable to obtain their results.

12) Same yield is obtained if a 5% aqueous solution of sodium hydroxyde is carefully degassed before use. This observation suggests that oxygen reacts with phosphorane **6** affording phosphine oxide.
Preparation of **6** : To a solution of cyanomethyltriphenylphosphonium chloride **5** (39,6g, 117,3 mmol) in water (790 mL) was added dropwise at room temperature an aqueous solution of sodium hydroxyde (50%, 19,8mL). After ten minutes the white solide was filtered off and dried in vacuum. Recrystallisation in ethyl acetate (1,3L) give cyanomethylene triphenylphosphorane **6** (25g, 72%, m.p. 195,4°C, litt. (ref 9) m.p. 195-196°C.
Preparation of **3** : A solution of freshly distillated 1-ethoxycyclopropanol **7** (4,6g, 45,1 mmol), benzoic acid (550mg, 4,51 mmol) and cyanomethylene triphenylphosphorane **6** in benzene (250mL) was refluxed for 17 hours. After cooling at room temperature the reaction mixture was concentrated in vacuum. Triphenyl phosphine oxide was precipitate by addition of pentane and filtered off. The filtrate was concentrated in vacuum and chromatographied (silica gel, pentane-ether : 8/2) affording **3** in solution in diethyl ether. Due to the volatitlity of **3**, yield was estimated by ^{1}H NMR in the range of 30-50%. ^{1}H NMR (200MHz, $CDCl_3$) : 1.45 (broad s, 4H), 5.8 (broad s, 1H). ^{13}C NMR : 4.22, 5.34, 90.51, 116.95, 152.08.

13) Brandi, A.; Carli, S.; Goti, A. *Heterocycles*, **1988**, *27*, 17-20.

14) Configurations in adducts **19** and **22** were confirmed by ^{1}H NMR NOESY experiments. Under thermodynamic conditions whithout Lewis acid, the *exo* adduct **22** is still the major isomer.

15) For the same cycloaddition between **4b** and **15** whithout Lewis acid catalyst, see: Seyed-Mahdavi, F.; Teichmann, S.; de Meijere, A. *Tetrahedron Letters*, **1986**, *27*, 1685-1688.