1,3-DIPOLAR CYCLOADDTIONS OF PYRIDINIUM DICYANOMETHYLIDE UNDER MICROWAVE IRRADIATION

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Abstract- Microwave irradiation induces a specific effect on the reactivity on the title reaction. Selectivity may be increased using a neutral bentonite as support.

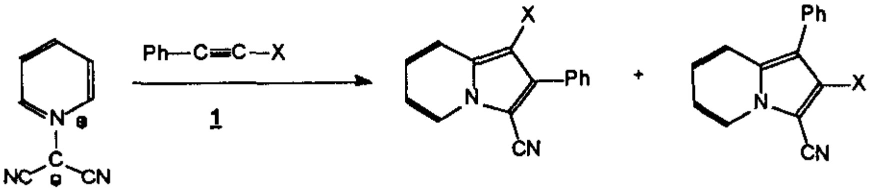
Pyridinium *N*-dicyanomethylide was first prepared by Linn.[1] Since then, several reports on the cycloaddition of this substrate have been reported for the synthesis of indolizine derivatives.[2-20] They usually take place in rather difficult conditions needing high temperatures for long reactions times (many hours or days at reflux of the solvent).

We report here the first 1,3-dipolar cycloaddition of pyridinium *N*-dicyanomethylide under microwave irradiation in solvent-free conditions.

Microwave irradiation have showed to be an efficient technique for the selective synthesis of several substrates.[21-24] Accelerations have been reported with the subsequent shortening in time and increased products purity and yields. No changes in selectivity have been observed in relation to classical heating.[25-27]

We have studied the reaction of pyridinium *N*-dicyanomethylide with ethyl phenylpropiolate and phenylacetylene under microwave irradiation in solvent-free conditions.

We choose this cycloaddition because it is an irreversible reaction, as elimination of hydrogen cyanide takes place after the cycloaddition. In this way, it can be posible to study the effect of microwave irradiation on the selectivity. Ethyl phenylpropiolate and phenylacetylene were chosen as dipolarophiles. Cycloaddition with ethyl phenylpropiolate affords a mixture of the two possible regioisomers (2a) and (2b) in a 88:12 ratio *(yield, 77% in refluxing toluene.*[28] *In these conditions* phenylacetylene affords traces of the expected cycloadducts while in solvent-free conditions both isomers were obtained in a 80:20 ratio.



X = $CO_2CH_2CH_3$ 88% 2a 12% 2b
X = H 80% 3a 20% 3b

Reactions were performed in a Prolabo Maxidigest MX 350 *monomode reactor modified in order to* have an accurate control of the temperature. A computer was attached to the commercial reactor to *measure and control* the temperature. Reactions mixtures were heated from room temperature to the desired temperature within 3 min. Temperature was controlled automatically by decreasing the field power to 20 W. In this way, microwave field was always present.

Table 1. Reaction of pyridinium *N*-dicyanomethylide with ethyl phenylpropiolate (**1a**) under microwave irradiation

Entry	Power (W)	T (°C)[a]	t (min.)	Molar ratio[b]	Yield (%)[c]	2a/3a	Remaining 1a
1	120	150	25	1 : 1	64	87 : 13	25
2	120	150	25	1.5 : 1	87	86 : 14	12
3	120	150	25	1 : 1.5	84	88 : 12	53
4	60	90	25	1 : 1	*traces*	-------	95
5	180	150	25	1 : 1	54	88 : 12	40
6	120	120	25	1 : 1	56	88 : 12	25
7	120	120	25	1 : 1	52	85 : 15	40

[a] Temperature fixed in the computer and controlled using a Luxtron optical fibre; [b] Ylide : dipolarophile; [c] *Determined by gc.*

We have studied the effect of several parameters (molar ratio, incident power, temperature and irradiation time) on the yield and selectivity using ethyl phenylpropiolate. The extend of the cycloaddition depends on the temperature necessary to the reaction and to prevent the decomposition of pyridinium *N*-dicyanomethylide (ethyl phenylpropiolate is stable under these conditions).

In this way the best results were obtained using a molar ratio ylide:dipolarophile 1:1.5 or 1.5:1 (Table 1, Entries 2 and 3), and irradiation at 120 W during 25 min at 150°C .

Lower temperatures decrease in yield while higher temperatures favor the decomposition of the ylide (Entry 1 vs 6-7). The same effect is observed with the field power, as a lower power do not induce a sufficient temperature (Entry 4) to produce the reaction, while a higher field favors the decomposition of the ylide (Entry 1 vs 4-5). Finally, extending the reaction time to 60 min yield is not increased significantly.

Table 2 presents a comparison with classical methods. Solvent-free conditions produce better yields than reactions in solution in the same conditions (Entry 2 vs 3) and 24 h are at least necessary to obtain poorer or comparable results (Entries 4 and 5). Microwave irradiation introduces an specific effect (non thermal effect) on the reaction. Yields increase from 61 to 87% when compared with conventional heating in the same experimental conditions. However the selectivity is not affected neither by solvent-free conditions nor by microwave irradiation.

Table 2. Comparision Microwave irradiation (M.W.)-Conventional heating (C.H.)

Entry	**Technique**	**Solvent**	**T (°C)**	**t (min)**	**Molar ratio**[a]	**Yield (%)**[b]	**2a : 3a**
1	M.W. (120 W)	-----	150	25	1.5 : 1	87	86 : 14
2	C. H.	-----	150	25	1.5 : 1	61	88 : 12
3	C. H.	DMF	150	25	1.5 : 1	15	88 : 12
4	C. H.	DMF	113	48 h	1 : 1	70	88 : 12
5	C. H.	Xylene	145	24 h	1 : 1	59	88 : 12

[a] Ylide : dipolarophile; [b] Determined by gc.

In order to change the selectivity we have performed the reaction in the presence of various solid supports in solvent-free conditions and under microwave irradiation or classical heating (Table 3).

Adsorption on solid supports may affect the dipolarophile by increasing the polarity and as a consecuence, may change the selectivity. On the other hand a specific effect can occur due to the different mode of heating. Many solid supports absorb microwaves efficiently and homogeneously while they absorb and transmit heat poorly.[29-30]

Reactions with different supports were performed under microwave irradiation (120 W, 25 min) considering a mixture of pyridinium *N*-dicyanomethylide and ethyl phenylpropiolate (molar ratio, 1:1.5, w/w) (Table 3).

Table 3. Reactions of pyridinium *N*-dicyanomethylide with ethyl phenylpropiolate (**1a**) on solid supports. (Power = 120 W; ylide : dipolarophile = 1 : 1.5; time = 25 min; support : ylide = 15 : 1 w/w)

Entry	**Support**	**Final temperature (°C)**	**Yield (%)**[a]	**2a : 3a**	**Remaining 1a**
1	Montmorillonite K-10	150	31	94 : 6	---
2	Bentonite neutre[b]	90	20	97 : 3	80
3	Tonsyl[b]	110	38	94 : 6	44
4	Bentonite Fluka	125	22	92 : 8	57
5	Talc	101	7	93 : 7	75
6	Celite[c]	110	45	87 : 13	59
7	Hyflo superCell[c]	75	0	-------	91
8	Basic Alumine	100	4	91 : 9	59
9	Florisil	90	33	93 : 7	55
10	Silicagel[d]	150	40	96 : 4	38

[a] Determined by gc.; [b] Süd Chemie ; [c] Support : ylide = 5 : 1, w/w; [d] 230-400 mesh.

The best selectivity was obtained using a neutral bentonite (Entry 2)[31] or silica gel (Entry 10). Better yields were obtained with silica gel but most of the starting material was recovered.

Using a neutral bentonite yields were improved to 69% using a ratio bentonite:ylide 5:1 w/w and irradiation during 60 min (Table 4, Entry 3) with an excellent selectivity. However, best results were obtained now by conventional heating in solvent-free conditions (Table 4, Entry 7). This fact can be explained because decomposition of the ylide and the cycloadduct takes place by dilution in the solid support and prolonged exposure to microwave irradiation (Entries 3 and 6).

Table 4. Reaction of pyridinium *N*-dicyanomethylide with ethyl phenylpropiolate **1a** on a bentonite neutre at 150°C

Entry	Power (W)	Bentonite : ylide w/w	t (min)	Yield (%)[a]	2a : 3a	Remaining 1a
1	120	15 : 1	25	20	97 : 3	80
2	180	15 : 1	25	35	98 : 2	74
3	120	5 : 1	60	69	97 : 3	59
4	180	5 : 1	60	47	96 : 4	53
5	120[b]	5 : 1	60	56	95 : 5	61
6	120	5 : 1	120	43	95 : 5	46
7	-----[c]	5 : 1	120	82	98: 2	62

[a] Determined by gc.; [b] T, 160°C; [c] Conventional heating at 150°C.

Table 5. Reactions of pyridinium *N*-dicyanomethylide with phenylacetylene (**1b**) (Power = 120 W, T = 150°C, ylide : phenylacetylene = 1 : 1.5)

Entry	t (min)	Yield (%)	2b : 3b
1	25	24	80:20
2	60	46	80:20
3	180	50	80:20
4[a]	180	26	79:21
5[b]	180	traces	80:20
6[b,c]	60	traces	80:20

[a] Neutral betnonite , ylide : bentonite = 5 : 1 w/w; [b] Conventional heating;
[c] Dimethylformamide 10 ml/mmol.

Phenylacetylene is a very unreactive dipolarophile. Yield was only 24% in the best conditions used with ethyl phenylpropiolate, but it was increased up to 46% within 60 min (Table 5, Entry 2). Again microwave irradiation introduce a specific effect in the cycloaddition. Only traces of cycloadducts were detected by conventional heating in solvent-free conditions or in solution in DMF and yields are not improved extending the reaction time to seven days.

Adsorption on solid support does not affect the selectivity. This fact confirms that adsorption of the carbonyl group is responsible of the change in the selectivity observed with ethyl phenylpropiolate.

In conclusion, microwave irradiation introduce a specific effect on reactivity for the 1,3-dipolar cycloaddition of pyridinium dicyanomethylide producing higher yield, but no changes in selectivity are observed.

Selectivity is improved using a neutral bentonite as solid support. Dilution and decomposition of the ylide and cycloadducts is responsible of the reverse result obtained in these conditions.

EXPERIMENTAL

All reagents were of commercial quality from freshly opened containers. Tetracyanoethylene oxide[32] and pyridinium dicyanomethylide were prepared as reported.

Microwave experiments were performed in a Problabo Maxidigest MX350 monomode reactor. Yields were determined by gc.

1. Reactions under microwave irradiation

1a. Without control of temperature

A mixture of the reagents placed in a cylindrical flask was stirred under microwave irradiation. Power, time and proportion of reagents are indicated in Tables. The crude mixtures were extracted with ethyl acetate (25 ml/mmol of ylide).

1b. With control of temperature

Similar to 1a. Temperature was controlled heating from room temperature to the desired temperature whitin 3 min and maintaining it as reported in the discussion during the time indicated in Tables.

1c. With solid supports

Both reagents were adsorbed in the amount of solid support indicated in Tables and irradiated as in 1a or 1b. Crude mixtures were extracted with ethyl acetate (5 x 5 ml/mmol of ylide).

2. Reactions by conventional heating

2a. Solvent-free conditions

Similar to 1a or 1c and using a spherical flask attached to a reflux condenser and submerged in an oil bath.

2b. In solution

Similar to 2a, using the appropriate solvent (10 ml/mmol of ylide). When reaction is completed, ethyl acetate (15 ml/mmol of ylide) was added.

3-Cyano-1-methoxycarbonyl-2-phenylindolizine (2a)

The crude mixture was chromatographed on silica gel (20 g/mmol of ylide). Elution with pentane:ethyl acetate 9:1 afforded a mixture of both regioisomers. Recrystallization from ethanol afforded the pure compound. mp 120-122°C.

^{1}H-Nmr ($CDCl_3$) δ (ppm) 1.18 (t, J=7, CH_3); 4.23 (q, J=7, CH_2); 7.06 (td, J=0.8, 6.8, H-6); 7.37 (ddd, J=1.2, 6.6, 9, H-7); 7.4-7.6 (m, Ph); 8.35 (dd, J=1.2, 6.8, H-5); 8.39 (dd, J=0.8, 9, H-8).

3-Cyano-2-phenylindolizine (3a)

The crude mixture was chromatographied on silica gel (20 g/mmol of ylide). Elution with light petroleum : ethyl acetate 4 : 1 afforded a first fraction that contains the pure compound. mp 91-93°C. A second fraction contains a mixture of both isomers.

^{1}H-Nmr ($CDCl_3$) δ (ppm) 6.68 (d, J=0.7, H-1); 6.83 (td, J=6.9, 1.2, H-7); 7.04 (ddd, J=1, 6.8, 8.9, H-6); 7.42 (tt, J=7.3, 1.5, H-4'); 7.49 (t, J=7.3, H-3'); 7.52 (dd, J=6.5, 1, H-8); 7.82 (dd, J=7.3, 1.5, H-2'); 8.3 (dq, J=8.5, 1, H-5).

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