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α-Methylenation/Diels-alder tandem reaction promoted by ammonium salts generated *in situ* from secondary–tertiary diamines and alkoxymethyl chlorides

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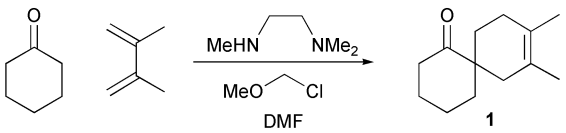
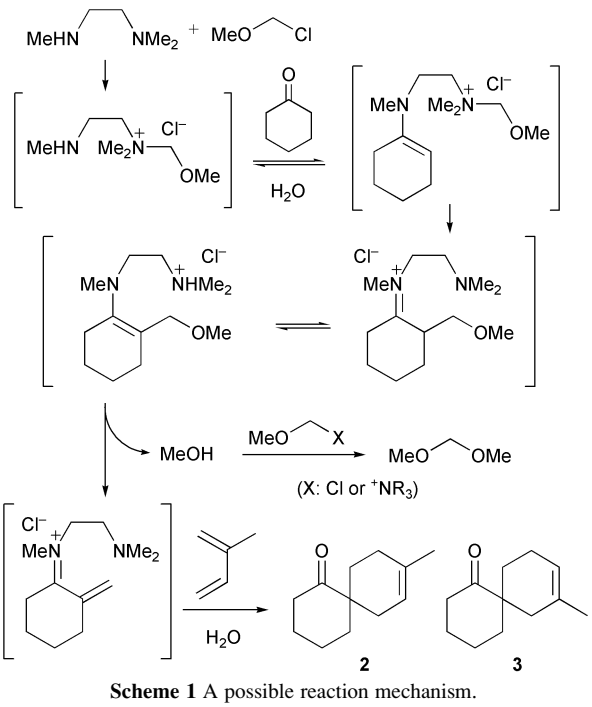
A simple one-pot synthesis of spiranones from cycloketones and dienes promoted by an ammonium salt generated *in situ* from diamine and alkoxymethyl chloride through a tandem α-methylenation/Diels–Alder reaction is described.

Tandem reactions offer many advantages compared to a stepwise processes: they shorten and simplify the experimental operation, minimize the loss of products and discharge of wastes, and avoid the isolation of unstable intermediates. Spiranones, a possible building block for the synthesis of natural products that have spiro-systems,[1] are synthesized by Diels–Alder reaction from dienes and methylenecycloketones which are prepared from corresponding ketones generally in one or two steps.[2] Herein we report a simple one-pot synthesis of spiranones through tandem α-methylenation/Diels–Alder reaction using commercially available reagents: diamine, chloromethyl methyl ether (MOMCl), cycloketones and dienes [eqn. (1)].



(1)

N,*N*,*N*′-trimethylethylenediamine, MOMCl, cyclohexanone, isoprene and DMF were charged in a sealed bottle, kept at room temperature for 1 day, then heated to 80 °C. After 12–24 h, standard work-up followed by purification with flash chromatography afforded the spiranones[3] as a 65 : 35 mixture of *para* and *meta* adducts (**2** and **3**, Scheme 1).[4] Various secondary–tertiary diamines were examined[5] and *N*,*N*,*N*′-trimethylethylenediamine led to the best results. Although solvent was not necessary in these reactions with a great excess of diene, DMF contributed to a slight improvement of the yields. When the reaction mixture of cyclohexanone, diamine and MOMCl in DMF was heated to 80 °C without diene, 2-methylenecyclohexanone dimer was obtained (run 8, Table 1). In this case, *N*,*N*,*N*′-trimethyl-1,3-propanediamine gave better yield. 2-(Trimethylsilyl)ethoxymethyl chloride (SEMCl) and benzyloxymethyl chloride (BOMCl) acted similarly to MOMCl, but BOMCl resulted in lower product yield. When SEMCl was used instead of MOMCl, di[2-(timethylsilyl)ethoxy]methane was obtained as a by-product.



Scheme 1 A possible reaction mechanism.

This transformation consists of some steps (Scheme 1). Alkoxymethyl chloride and tertiary amine are known to form an ammonium salt,[6] and we observed a white precipitate when MOMCl was added to a solution of *N*,*N*,*N*′-trimethylethylenediamine in THF. Thus, the first step would be the formation of an ammonium salt from diamine and MOMCl. This ammonium salt and cyclohexanone would generate enamine, and then 2-methoxymethylation would proceed followed by elimination of methanol *via* the equilibrium between iminium salt and enamine. The intermediate, 2-methylenecyclohexanone was detected by GC analysis in the reaction at room temperature, whereas 2-methoxymethylcyclohexanone was not. The last Diels–Alder step did not occur until the mixture was heated. Although 2-methylenation was not completed after 3 days of stirring at room temperature, it might proceed after heating together with the Diels–Alder reaction because 2′-methylenated 2-methylenecyclohexanone dimer was obtained in the case without diene. The side reaction between methanol and MOMCl or its ammonium salt could generate dimethoxymethane, which explains the generation mechanism of di[2-(timethylsilyl)ethoxy]methane obtained in the reaction using SEMCl.

Table 1 shows results from the reaction of various cycloketones and dienes with *N*,*N*,*N*′-trimethylethylenediamine and MOMCl. The reactivities of these transformations were greatly influenced by the reactivities of Diels–Alder reaction. While it was slow, the reaction of cyclohexanone with 5 equiv. of cyclopentadiene proceeded even at room temperature. The role of diamine in the Diels–Alder step was examined using a stepwise procedure. A DMF solution of cyclohexanone, diamine and MOMCl was stirred at room temperature for 1 day, then quenched and the diamine removed, and the resulting mixture of cyclohexanone and 2-methylenecyclohexanone was treated with isoprene in DMF at 80 °C. After 1 day, 2-methylenecyclohexanone was totally consumed but only a trace of spiranone and an unknown by-product were obtained. It has also been reported that thermal dimerization of 2-methylenecyclohexanone proceeds at 150 °C,[7] which proceeded at 80 °C in our system. In view of these results, it was concluded that diamine played an important role in the Diels–Alder step as well as in the α-methylenation step. Recently, a highly enantioselective organocatalytic Diels–Alder reaction was published by MacMillan and co-workers.[8] If diamine salt catalyzes the Diels–Alder step in our system, it is possible to apply this tandem reaction to an asymmetric one using chiral diamines.†

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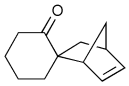
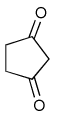
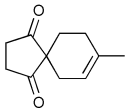
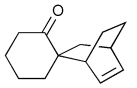
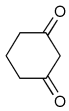
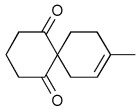
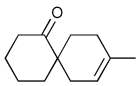
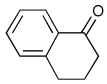
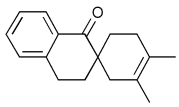
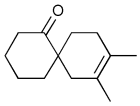
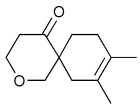
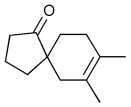
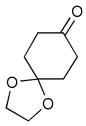
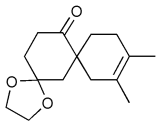
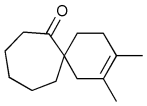
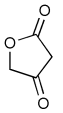
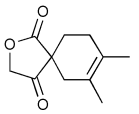
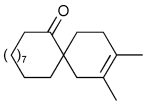
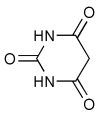
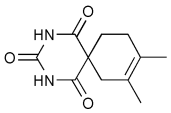
Table 1 Tandem α-methylenation/Diels–Alder reaction of cycloketones with *N*,*N*,*N*′-trimethylethylenediamine, MOMCl and dienes.[a]

Run	Ketone	Diene	Conditions	Product[b]	% Yield (*p*:*m*)[c]	Run	Ketone	Diene	Conditions	Product[b]	% Yield (*p*:*m*)[c]
1			rt, 24 h → 50 °C, 24 h		52	9			rt, 24 h → 70 °C, 24 h		26 (92:8)
2			rt, 24 h → 80 °C, 24 h		< 20	10			rt, 12 h → 50 °C, 24 h		47 (91:9)
3			rt, 24 h → 80 °C, 24 h		45 (65:35)	11			rt, 24 h → 100 °C, 24 h		46
4			rt, 24 h → 80 °C, 24 h		78	12			rt, 24 h → 80 °C, 24 h		65
5			rt, 24 h → 80 °C, 24 h		33	13			rt, 24 h → 80 °C, 24 h		65
6			rt, 24 h → 90 °C, 24 h		57	14			rt, 24 h → 80 °C, 24 h		75
7			rt, 24 h → 135 °C, 24 h		31	15			rt, 24 h → 80 °C, 24 h		91
8[e]		—	rt, 24 h → 80 °C, 24 h		46						

[a] Unless otherwise noted, reactions were carried out with 1 equiv. of ketone, 1.2 equivalent of *N*,*N*,*N*′-trimethylethylenediamine and MOMCl, and 50 equiv. of diene. [b] Only *para* adduct is shown when *para* and *meta* adduct are obtained. [c] Ratio of *para* and *meta* adduct. [d] 5 Equiv. of cyclopentadiene was used. [e] Reaction was run with 2 equiv. of cyclohexanone, 2.4 equiv. of *N*,*N*,*N*′-trimethyl-1,3-propanediamine and MOMCl.

Scheme 2

The application of this method in a formal synthesis of acoradiene, which is a component of essential oils, is illustrated in Scheme 2. Peterson Olefination[9] of the adduct **4** (run 9, Table 1)[10] and selective hydrogenation over Raney nickel gave key intermediates of acoradienes[11] as a 1:1 mixture of diastereomers.

In summary, we have developed a new one-pot synthesis of spiranones from cycloketones and dienes promoted by an ammonium salt generated *in situ* from diamine and MOMCl through a tandem α-methylenation/Diels–Alder sequence. This method is very easy: mix all reagents and heat. A formal synthesis of acoradiene based on our method was also shown.

HN thanks JSPS Fellowship for Japanese Junior Scientists.

Notes and references

† *Typical procedure for the synthesis of spiranone* (**1**): a dried sealed bottle was charged with *N*,*N*,*N*′-trimethylethylenediamine (78 μL, 0.6 mmol) and dry DMF (1 mL). MOMCl (46 L, 0.6 mmol), cyclohexanone (52 L, 0.5 mmol) and 2,3-dimethylbutadiene (2.8 mL, 25 mmol) were successively added to the solution at room temperature and stirred for 24 h. Then the reaction system was heated to 80 °C and stirred for another 24 h at the same temperature. After cooling to room temperature, the mixture was washed with water, concentrated and purified by flash column chromatography on silica gel to give an adduct. IR (neat): 2930, 1707, 1445, 1125, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 1.58 (s, 3H), 1.62 (s, 3H), 1.53–1.96 (m, 11H), 2.25–2.38 (m, 2H), 2.43–2.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz), δ 18.8, 19.3, 21.0, 28.1, 28.4, 29.9, 36.9, 38.6, 38.9, 48.2, 123.3, 124.0, 215.9. HRMS (FAB+): calc. for $C_{13}H_{20}O$: 192.1514, found: 192.1506.

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