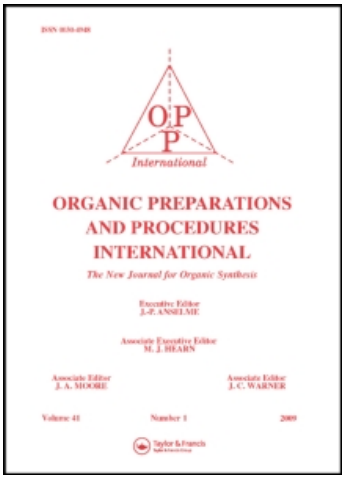

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MICROWAVE-ASSISTED SYNTHESIS OF SUBSTITUTED CYCLOPROPYL, FERROCENYL KETONES BY A SULFUR YLIDE REACTION UNDER SOLID-STATE CONDITIONS

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MICROWAVE-ASSISTED SYNTHESIS OF SUBSTITUTED CYCLOPROPYL FERROCENYL KETONES BY A SULFUR YLIDE REACTION UNDER SOLID-STATE CONDITIONS

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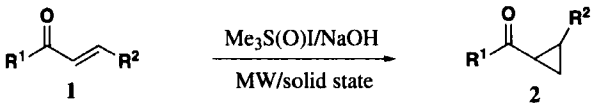
Ferrocene derivatives are of considerable interest because of their possible biological activities.[1] A few substituted cyclopropyl ferrocenyl ketones have been described and they were synthesized by a sulfur ylide reaction in solution.[2] This method has limitations such as harsh reaction conditions, liberation of H_2, long reaction time and tedious work-up. Toda has reported a simple method for synthesizing some cyclopropyl ketones in the absence of solvent at room temperature,[3] but chalcone-containing ferrocenes have not yet been investigated. To seek a simple, efficient procedure for the synthesis of substituted cyclopropyl ferrocenyl ketones, we applied the reported method[3] to ferrocene derivatives and found that the reactions do not take place at room temperature. Further, substituted cyclopropyl ferrocenyl ketones can be obtained in only moderate yields at elevated temperature (≥ 75°); the high temperature leads to the formation of many by-products. Hence, there is a need for a rapid and efficient general method for synthesizing cyclopropyl ferrocenyl ketones. In recent years, considerable interest has arisen in microwave-induced reactions in organic synthesis.[4-5] In view of the potential uses of cyclopropyl ferrocenyl ketones[1] and substantial reduction in reaction times using microwave (MW), we now report a novel procedure involving MW for the synthesis of cyclopropyl ferrocenyl ketones as shown in the Scheme.



1 2

R^1= Fc: a) R^2=C_6H_5; b) *p*-Br-C_6H_4; c) *p*-Cl-C_6H_4; d) *p*-MeO-C_6H_4; e) 3,4-OCH_2O-C_6H_3, f) (*E*)-CH=CHPh; g) Furyl; h) Fc; R^2 = Fc; i) R^1=Ph; j) *p*-Br-C_6H_4; Fc = ferrocenyl

A mixture of powdered ferrocenylchalcone (***1a***), trimethylsulfonium iodide and NaOH was reacted for several minutes in the presence of focused MW to give substituted cyclopropyl ferrocenyl ketones in good yields (Method B). During the reaction process, the reaction mixture was irradiated 3-4 times for 2-2.5 min intervals; each irradiation was separated by 15-20 s.

By comparison, at room temperature, the yields were very small after several days. The reaction was accelerated and completed after 3 h under traditional heating at 75-80° (Method A).

The results of this reaction are listed in the Table. It can be seen that the reaction can be carrying out without solvent using MW irradiation. This method seems to be advantageous over conventional methods in terms of high yields, rapid reaction rates, no requirement for inert atmosphere and an environmentally friendly procedure.

TABLE. Comparative Results using Conventional Heating (Method A) and Microwave Activation (Method B).

Entry	Product	Method	Reaction Time	Yield (%)	Final Temp.[a] (°C)	mp. (°C) (*lit.*[2])
1	***2a***	A	3hr	70		98-100 (91-100)
		B	8.2min	87	83-87	
2	***2b***	A	3hr	63		123-125
		B	6.5min	85	80-82	
3	***2c***	A	3hr	74		130-131
		B	7.2min	87	84-86	
4	***2d***	A	3hr	60		119-121 (125)
		B	6.8min	86	82-86	
5	***2e***	A	3hr	67		–
		B	7.3min	93	85-90	
6	***2f***	A	3hr	74		–
		B	7.8min	94	85-90	
7	***2g***	A	3hr	60		84-85
		B	8.4min	92	85-90	
8	***2h***	A	3hr	73		173.5-174
		B	8.3min	94	84-90	
9	***2i***	A	3hr	75		100-102
		B	8.5min	90	85-90	
10	***2j***	A	3hr	60		122-125
		B	7.4min	87	82-87	

[a] Final temperature was measured by immersion of a glass thermometer at the end of exposure to microwave irradiation (approximate temperature range)

It is notable that when the substrate is ***1f***, highly regioselective methylene transfer product, ferrocenyl phenylvinylcyclopropyl ketone ***2f*** was obtained in 94% yield. The C=C of the phenylvinyl fragment was not affected.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. MW irradiation was carried out with a commercial microwave oven Meidi WT022J at 2450MHz. An approximate temperature measurement was performed by introducing a glass thermometer into the sample at the end of each irradiation. ^{1}H NMR spectra were measured on a FC-80A

spectrometer in $CDCl_3$ with TMS as an internal standard. IR spectra were performed as KBr pellets on a Nicolet 179SX FT-IR spectrometer. Mass spectra (MS) were taken on a ZAB-HS mass spectrometer by Fast Atom Bombardment (FAB). Elemental analyses were performed using a Carlo-Erba 1106 element analyzer.

Ferrocenylchalcone and trimethylsulfonium iodide were prepared as described earlier.[6,7] All other reagents were commercially available AR grade.

General Procedure for the Reaction by Method A.-A mixture of powdered ferrocenylchalcone (***1a***) (1.58 g, 5 mmol), trimethylsulfonium iodide (2.2 g, 10 mmol) and NaOH (2.0 g) was ground together thoroughly with a mortar and pestle, then kept at 75-80° for 3 h. After the reaction was complete (by TLC), the mixture was washed with water and the residue was taken up in ethyl acetate. The ethyl acetate solution was dried over anhydrous Na_2SO_4 and the crude product was concentrated and purified by column chromatography on silica gel using ethyl acetate/petroleum ether (1/20, v/v) as the eluant to give the title compound (***2a***) (1.14 g, 70%).

General Procedure for the Reaction by Method B.-A finely powdered mixture, as above, was introduced to a glass vessel and irradiated in a domestic microwave oven (350 W) for the indicated period (see Table). The reaction mixture was irradiated 3-4 times for 2-2.5 min intervals; each irradiation was separated by 15-20 s. Isolation and purification were the same as described for method A.

Ferrocenyl Phenylcyclopropyl Ketone (*2a*): ^{1}H NMR: δ 7.21 (5 H, m, Ph), 4.87 (2 H, br s, J = 2.0 Hz, Cp), 4.53 (2 H, t, J = 1.8 Hz, Cp), 4.18 (5 H, s, Cp), 2.86-2.41 (2 H, m), 2.0-1.78 (1 H, m) and 1.62-1.30 (1 H, m); IR: 3034, 2986, 1640, 1488, 1102, 803 and 477 cm^{-1}; MS (FAB): *m/z* (%) 331 (M^++1, 12), 330 (M^+, 40).

Anal. Calcd for $C_{20}H_{18}FeO$: C, 72.73; H, 5.45. Found: C, 72.48; H, 5.58

Ferrocenyl *p*-Bromophenylcyclopropyl Ketone (*2b*): ^{1}H NMR: δ 7.30 (4 H, 2d, J = 12 Hz, Ph), 4.76 (2 H, br s, J = 1.9 Hz, Cp), 4.47 (2 H, br s, J = 2.1 Hz, Cp), 4.23 (5 H, s, Cp), 2.59 (2 H, m), 1.58 (1 H, m), and 1.28 (1 H, m); IR: 3050, 2925, 2811, 1660, 1488, 1102, 803 and 477 cm^{-1}; MS (FAB): *m/z* (%) 410 (M^++2, 41), 408 (M^+, 42).

Anal. Calcd for $C_{20}H_{17}BrFeO$: C, 58.82; H, 4.17. Found: C, 59.18; H, 4.14

Ferrocenyl *p*-Clorophenylcyclopropyl Ketone (*2c*): ^{1}H NMR: δ 7.26 (4 H, 2d, J = 8.8 Hz, Ph), 4.85 (2 H, t, J = 2.1 Hz, Cp), 4.53 (2 H, t, J = 1.9 Hz, Cp), 4.16 (5 H, s, Cp), 2.56 (2 H, m), 1.88 (1 H, m) and 1.41 (1 H, m); IR: 3104, 1639, 1456, 1103, 806 and 502 cm^{-1}; MS (FAB): *m/z* (%) 366 (M^++2, 34), 365 (M^++1, 36), 364 (M^+, 100).

Anal. Calcd for $C_{20}H_{17}ClFeO$: C, 65.93; H, 4.67. Found: C, 65.66; H, 4.44

Ferrocenyl *p*-Methoxyphenylcyclopropyl Ketone (*2d*): ^{1}H NMR: δ 6.96 (4 H, 2d, J = 8.4 Hz, Ph), 4.86 (2 H, t, J = 2.0 Hz, Cp), 4.52 (2 H, t, J = 2.0 Hz, Cp), 4.21 (5 H, s, Cp), 3.82 (3 H, s, OCH_3), 2.66-2.42 (2 H, m), 1.91-1.60 (1 H, m) and 1.56-1.29 (1 H, m); IR: 3056, 2926, 2854, 1640, 1456, 1248, 1021, 807 and 501 cm^{-1}; MS (FAB): *m/z* (%) 361 (M^++1, 15), 360 (M^+, 38).

Anal. Calcd for $C_{21}H_{20}FeO_2$: C, 70.00; H, 5.56. Found: C, 70.38; H, 6.01

Ferrocenyl 3,4-Methylenedioxyphenylcyclopropyl Ketone (*2e*): ^{1}H NMR: δ 6.74 (1 H, s, Ph), 6.67

(1 H, s, Ph), 6.63 (1 H, s, Ph), 5.96 (2 H, s, OCH_2O), 4.85 (2 H, t, J = 1.1 Hz, Cp), 4.53 (2 H, t, J = 1.8 Hz, Cp), 4.21 (5 H, s, Cp), 2.74 (2 H, m), 1.83 (1 H, m) and 1.39 (1 H, m); IR: 3053, 2909, 1644, 1453, 1240, 1033, 796 and 499 cm^{-1}; MS (FAB): *m/z* (%) 375 (M^++1, 17), 374 (M^+, 46).

Anal. Calcd for $C_{21}H_{18}FeO_3$: C, 67.38; H, 4.81. Found: C, 66.98; H, 4.53

Ferrocenyl Phenylvinylcyclopropyl Ketone (*2f*): ^1H NMR: δ 7.33 (5 H, m, Ph), 6.67 (1 H, d, J = 15.8 Hz), 6.07 (1 H, dd, J = 15.8 Hz, 8.8 Hz), 4.87 (2 H, t, J = 1.5 Hz, Cp), 4.52 (2 H, t, J = 2.0 Hz, Cp), 4.25 (5 H, s, Cp), 2.50-2.45 (2 H, m), 1.90-1.69 (1 H, m) and 1.35-1.22 (1 H, m); IR: 3051, 2978, 1658, 1635, 1452, 1245, 1020, 808 and 500 cm^{-1}; MS (FAB): *m/z* (%) 357 (M^++1, 34), 356 (M^+, 90).

Anal. Calcd for $C_{22}H_{20}FeO$: C, 74.16; H, 5.62. Found: C, 74.51; H, 5.58

Ferrocenyl 2-Furylcyclopropyl Ketone (*2g*): ^1H NMR: δ 7.33 (1 H, m, furyl), 6.33 (1 H, m, furyl), 6.11 (1 H, d, J = 3.0 Hz, furyl), 4.86 (2 H, t, J = 0.6 Hz, Cp), 4.53 (2 H, t, J = 1.8 Hz, Cp), 4.24 (5 H, s, Cp), 2.76-2.47 (2 H, m) and 1.89-1.28 (2 H, m); IR: 3053, 937, 1645, 1458, 1249, 1021, 808 and 493 cm^{-1}; MS (FAB): *m/z* (%) 320 (M^+, 45).

Anal. Calcd for $C_{18}H_{16}FeO_2$: C, 67.50; H, 5.00. Found: C, 67.64; H, 4.94

Ferrocenyl Ferrocenylcyclopropyl Ketone (*2h*): ^1H NMR: δ 4.85 (4 H, br s, Cp), 4.52 (4 H, br s, Cp), 4.23-3.94 (10 H, m, Cp), 2.35 (2 H, m), 1.83 (1 H, m) and 1.28 (1 H, m); IR: 3084, 2931, 1638, 1456, 1082, 818 and 504 cm^{-1}; MS (FAB): *m/z* (%) 439 (M^++1, 18), 438 (M^+, 43).

Anal. Calcd for $C_{24}H_{22}Fe_2O$: C, 65.75; H, 5.02. Found: C, 65.33; H, 4.83

Phenyl Ferrocenylcyclopropyl Ketone (*2i*): ^1H NMR: δ 8.12-8.00 (2 H, m, Ph), 7.06-7.36 (3 H, m, Ph), 4.18-4.13 (9 H, m, Cp), 2.91-2.35 (2 H, m), 1.93 (1 H m) and 1.49-1.26 (1 H, m); IR: 3094, 2978, 1649, 1372, 1223, 993, 817 and 502 cm^{-1}; MS (FAB): *m/z* (%) 330 (M^+, 51).

Anal. Calcd for $C_{20}H_{18}FeO$: C, 72.73; H, 5.45. Found: C, 72.48; H, 5.47

***p*-Bromophenyl Ferrocenylcyclopropyl Ketone (*2j*):** ^1H NMR: δ 7.29 (4 H, m, Ph), 4.52-4.32 (9 H, m, Cp), 2.57 (2 H, m), 1.58 (1 H, m) and 1.28 (1 H, m); IR: 3100, 2985, 1639, 1488, 1102, 803 and 497 cm^{-1}; MS (FAB): *m/z* (%) 410 (M^++2, 87), 408 (M^+, 85).

Anal. Calcd. for $C_{20}H_{17}BrFeO$: C, 58.82; H, 4.17. Found: C, 58.79; H, 4.40

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A SIMPLE SYNTHESIS OF 1-ARYL-POLYENES

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The delocalization of π electrons (conjugation) in linear molecules has been and continues to be of great interest in modern chemistry, physics and technology since these systems can display relevant and unique physical properties such as high electrical conductivity and large optical non-linearities.[1] The prototype of polyconjugated linear molecules is polyacetylene (PA) first synthesized by Natta;[2] it shows large electrical conductivity if suitably doped with electron donors or acceptors.[3] PA is however, a difficult material to handle and is totally insoluble in most common solvents; it is highly unstable and structurally very complex, possibly due to cross-linking. The interest of researchers then turned to a class of polyconjugated oligomers which could be used as model compounds whose chain-length dependent properties could be extrapolated to the "infinite" chain of PA. Very short oligoenes are chemically stable and tractable, *t*-butyl capped oligoenes[4] and α,ω-diphenylpolyenes[4,5] became available, but their chain lengths have been very limited. The stability and solubility of these materials allows the systematic characterization of their physical properties as a function of chain-length (and conjugation length, CL). The set of molecules one-ten conjugated carbon-carbon double bonds can be taken as suitable models for the entire series of polyconjugated materials.

In addition physicists and chemists dealing with electrical conductivity and nonlinear optical properties of polyene-like systems also turned their attention to the class of natural and synthetic carotenoids of various lenghts.[6] The role of carotenoids in bioscience is well acknowledged and is the subject of extensive studies.[7] The idea of adopting carotenoids as model compounds for the PA system was not successful probably because of methyl groups regularly placed as substituents along the oligoene chain which greatly affects their properties compared to the corresponding demethylated polyenes. Since demethylated carotenoids are not easily available, the synthesis of 1-arylpolyenes can offer new materials with increasing CL. This work presents a general method for the synthesis of 1-arylpolyenes having with from three to nine conjugated carbon-carbon double bonds.