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Selective α-monoallylation of phenyl ketones and benzocycloalkanones under microwave irradiation

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Abstract—A method for the selective α-monoallylation of phenyl ketones and benzocycloalkanones with allyl alcohol under microwave irradation is described. The corresponding α-allyl ketones are obtained in moderate to good yields with only minor quantities of diallylation by-products.

α-Allyl ketones are highly valuable intermediates for organic synthesis due to the presence of a functionalized three-carbon moiety.[1] As part one of our Drug Discovery Programs we became interested in the synthesis of α-allyl phenyl ketones (**A**) and α-allyl benzocycloalkanones (**B**) (Fig. 1), in a High Throughput Chemistry (HTC) environment, as versatile intermediates for further modification.

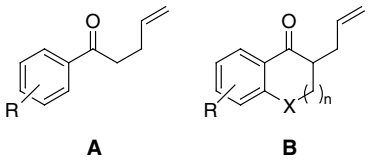
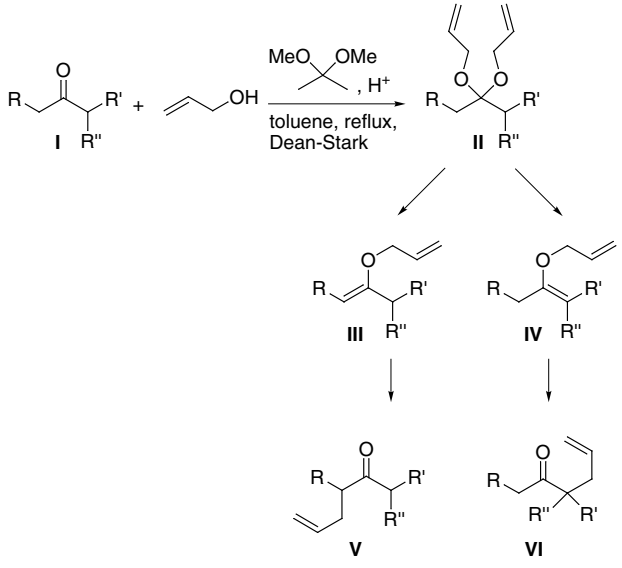


Figure 1.

While the Claisen rearrangement[2,3] is a versatile and well-documented reaction, few examples of its use for the direct allylation of ketones have been reported. In 1961 Lorette and Howard[4] described the synthesis of several α-allylketones **V**, **VI** (Scheme 1) by acid-catalyzed cracking of the corresponding ketone diallyl ketals **II** and in situ Claisen rearrangement of the intermediate enol ethers **III**, **IV**. The use of 2,2-dimethoxypropane made possible the preparation of α-allyl-substituted ketones from dialkyl ketones (**I**) and allyl alcohol without isolation of the intermediate diallyl ketals (**II**). Although the method has proved its value for the synthesis of valuable intermediates,[5–10] it presents some drawbacks such as the long reaction times (10–20 h) required for completion of the reaction and the need for the continuous removal of azeotropes from the reaction media.



Scheme 1.

Microwave Assisted Organic Synthesis (MAOS) has become increasingly popular in recent years to improve

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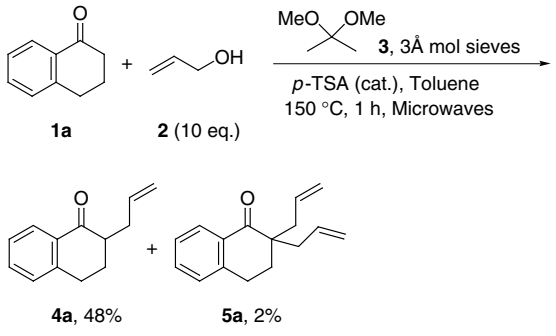
the yields and shorten reaction times in a variety of reactions.[11] Dedicated microwave reactors enable on-line temperature and pressure monitoring, for the rapid heating of samples under controlled reaction conditions. To the best of our knowledge, microwave-mediated methodology for the α-allylation of ketones via Claisen rearrangement of allyl enol ethers has not yet been reported.[12,13] This paper describes an efficient, operationally simple and parallel method for the selective α-allylation of phenyl ketones and benzocycloalkanones under microwave irradiation.

Scheme 2 shows the preliminary experiment in our study. Treatment of α-tetralone (**1a**) with a 10-fold molar excess of allyl alcohol (**2**), 2,2-dimethoxypropane (**3**, 1.5 equiv) and a catalytic amount of *p*-toluenesulfonic acid in toluene, in the presence of 3 Å molecular sieves at 150 °C for 1 h under microwave irradiation led, after aqueous work-up and chromatographic purification, to the α-allyl ketone **4a** in 48% yield. The diallylated product **5a** and starting ketone **1a** were isolated in 2% and 39% yields, respectively.

Encouraged by this result, investigations into the conditions suitable for this allylation reaction under microwave irradiation were initiated. The results obtained are summarized in Table 1. Firstly, the reaction temperature and time were optimized using a 10-fold excess of allyl alcohol (Table 1, entries 1–4). Heating at 200 or 225 °C for either 1 h (Table 1, entries 1 and 3) or 1.5 h (Table 1, entries 2 and 4) resulted in better chemical yields and an increase in the amount of the diallylation product **5a**. Attempts to reduce the number of equivalents of **2** were also performed. Treatment of α-tetralone **1a** with 5 equiv of **2** under microwave irradiation for 1.5 h at 200 °C (Table 1, entry 5), led to satisfactory results: the chemical yield increased to 98% and the ratio **4a**/**5a** was 95/5. The use of 2 equiv of **2** at 200 °C for 1.5 h (Table 1, entry 6) gave the best ratio **4a**/**5b** (99/1) although the chemical yield was substantially lower (76%).



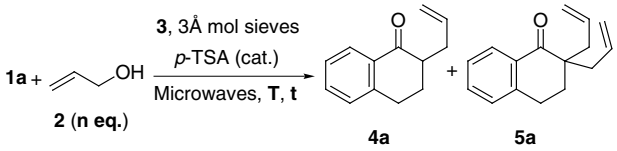
Scheme 2.

We chose as the standard reaction conditions for the monoallylation of ketones, microwave irradiation of the ketone with 5 equiv of allyl alcohol **2**, 1.5 equiv of **3**, 3 Å molecular sieves, a catalytic amount of *p*-toluenesulfonic acid and toluene, heated at 200 °C for 1.5 h.[14]

Figure 2 displays a set of representative phenyl ketones and benzocycloalkanones chosen to explore the scope and limitations of this process. The results for each ketone are summarized in Table 2.

As shown in Table 2, our microwave conditions worked well for a variety of aryl-, heteroaryl- and benzocycloalkyl ketones (Table 2, entries 1–4, 7–12). In all cases the reactions were clean and the only significant products formed were those resulting from monoallylation **4** and diallylation **5** of the starting ketone **1**. A variable amount of starting material **1** was recovered during the chromatographic isolation of the reaction products. Methyl ketones **1b–d** (Table 2, entries 1–3) were allylated under standard microwave conditions to give the monoallylated products **4b–d** with satisfactory yields after purification by column chromatography

Table 1. Allylation reaction of α-tetralone (**1a**) with allyl alcohol (**2**) under microwave conditions



Entry	**2** (eq)	*T* (°C)	*t* (h)	**4a**:**5a**[a]	Yield (%)[b]
1	10	200	1	96:4	67
2	10	200	1.5	91:9	83[c]
3	10	225	1	93:7	75
4	10	225	1.5	88:12	75
5	5	200	1.5	95:5	98[d,e]
6	2	200	1.5	99:1	76

[a] The ratio was determined by GCMS spectroscopy of the crude reaction mixture.
[b] Yield of isolated products **4a**/**5a** based on α-tetralone **1a**.
[c] After traditional heating for 1.5 h at reflux **4a** and **5a** were detected in 27% and 5% yields, respectively.
[d] When the reaction was carried out without 3 Å molecular sieves, compound **4a** was detected by GCMS spectroscopy in 12% yield in a complex mixture of products.
[e] **4a** was detected in 31% yield when 2,2-dimethoxypropanne (**3**) was not added to the reaction mixture.

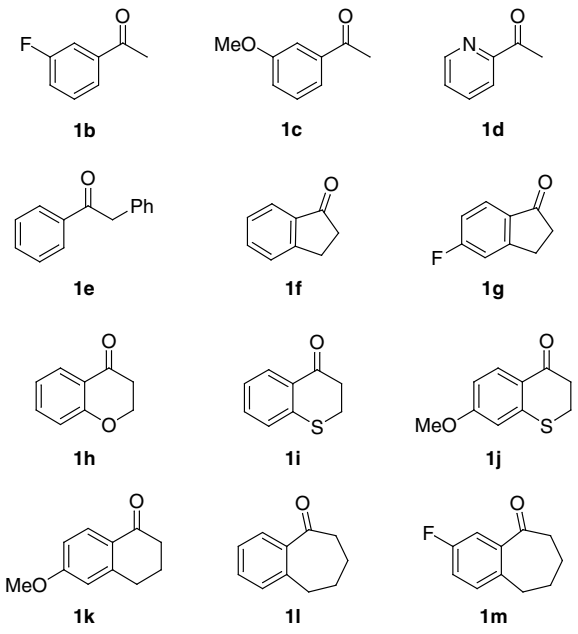


Figure 2. The set of phenyl ketones and benzocycloalkanones used in microwave assisted allylation.

(60–66%). The amount of diallylated compounds **5b–d** for these open-chain ketones was variable and somewhat higher than that obtained with α-tetralone (Table 1, entry 5). The monoallylation reaction occurred with complete selectivity in the case of deoxybenzoin **1e** affording **4e** in good yield (Table 2, entry 4). To our surprise, indanone (**1e**) was selectively transformed into the corresponding diallyl compound **5e** in 96% yield (Table 2, entry 5). A slightly better result was achieved with the indanone derivative **1f** allowing the isolation of the corresponding monoallyl compound **4f** in 60% yield together with a large amount (29%) of **5f** (Table 2, entry 6). Six- and seven-membered benzocycloalkanones **1h–m** are good substrates for this alkylation reaction affording the monoallyl products (**4h–m**) with good yields (73–87%) and high selectivities (Table 2, entries 7–12). It should be pointed out that neither the yield nor the selectivity was greatly influenced by the presence of electron-donating or electron-withdrawing groups on the ketone **1** (Table 2, entry 2 vs 3, 8 vs 9, 11 vs 12) and only in the case of indanone derivatives did the introduction of an electron-withdrawing group substantially affect to the selectivity of the reaction (Table 2, entry 5 vs 6).

In summary, we have developed an operationally simple and efficient method for the selective monoallylation of aryl and benzocycloalkanones under microwave irradiation. Studies on the scope and limitations of this methodology are continuing and will be reported in due curse.

Acknowledgements

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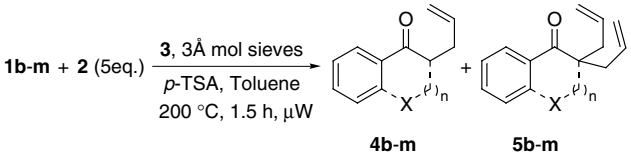
Table 2. Microwave assisted allylation of ketones **1** with allyl alcohol **2**[15,16]



Entry	Ketone **1**[a]	**4**:**5**[b]	Yield (%)[c]		Recovered **1** (%)[c]
			4	**5**	
1	**1b**	92:8	66	7	15
2	**1c**	86:14	66	11	12
3	**1d**	83:17	64	14	10
4	**1e**	100:0	77	—	14
5	**1f**	0:100	—	96	—
6	**1g**	65:35	60	29	1
7	**1h**	90:10	77	5	6
8	**1i**	100:0	83	—	10
9	**1j**	98:2	87	1	3
10	**1k**	90:10	74	6	7
11	**1l**	96:4	73	2	14
12	**1m**	97:3	75	2	12

[a] The reactions were done on a 3 mmol scale.
[b] The ratio was determined by GCMS spectroscopy of the crude reaction mixture.
[c] Isolated yield.

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14. As a control experiment, the same mixture (using 5 equiv of **2**) was heated at 200 °C for 1.5 h in a sealed tube using an oil bath, and the allylated products **4a** and **5a** were obtained in 46% and 4% yields, respectively. This observation demonstrates the advantage of microwave irradiation over conventional heating techniques.
15. In any case the reaction pressure exceeded 17 bars.
16. Representative procedure: To a solution of thiochroman-4-one (**1i**, 328 mg, 2 mmol) allyl alcohol (**2**, 0.68 mL, 10 mmol) and toluene (3 mL) in a microwave Emrysprocess™ vial were added 2,2-dimethoxypropane (**3**, 0.370 mL, 3 mmol), *p*-toluenesulfonic acid (69 mg, 0.4 mmol) and 3 Å molecular sieves (ca. 600 mg). The vial was sealed and heated in an Emrys™ Optimizer microwave at 200 °C for 1.5 h. The cooled reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed successively with $NaHCO_3$ (aqueous saturated solution) and brine. The volatiles were evaporated and the residue thus obtained was purified by HPLC chromatography to give 3-allyl thiochroman-4-one (**4i**, 339 mg, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.37 (dt, $J = 7.9$, 1.5 Hz, 1H), 7.25 (dd, $J = 7.8$, 1.0 Hz, 1H), 7.17 (dt, $J = 8.0$, 1.0 Hz, 1H), 5.87–5.77 (m, 1H), 5.17 (dd, $J = 13.7$, 1.5 Hz, 1H), 5.13 (dd, $J = 6.6$, 1.3 Hz, 1H), 3.25 (dd, $J = 13.3$, 3.9 Hz, 1H), 3.08 (dd, $J = 13.3$, 10.0 Hz, 1H), 2.90–2.81 (m, 1H), 2.78–2.70 (m, 1H), 2.40 (dt, $J = 13.7$, 8.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.7, 142.2, 135.4, 133.4, 131.0, 130.0, 127.7, 125.2, 118.4, 46.8, 33.5, 30.7. MS (EI): m/z (%) 204 (20).