Carboannulation Reactions of Cyclohexenone Derivatives: Synthesis of Functionalized α-Tetralones

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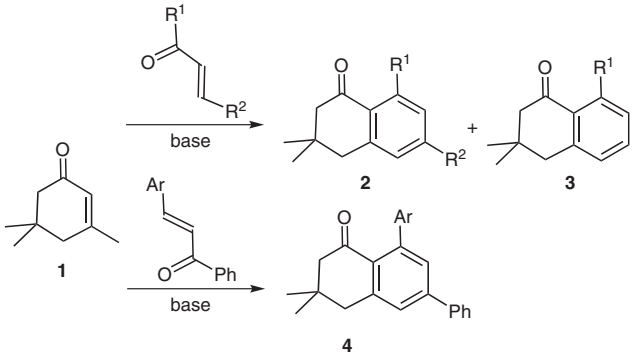
Abstract: The base-mediated cyclocondensation reactions of 3-(ethoxycarbonylmethylene)- and 3-(cyanomethylene)cyclohexenones with ethoxymethylenemalonate derivatives lead to two functionalized α-tetralones with selectivities which depend on the stoichiometric ratio of the reactants. α-Tetralones are selectively obtained when excess Michael acceptor is used.

Key words: carboannulation, Michael additions, condensation, carbocycles, α-tetralones.

The α-tetralone skeleton is the basic core of numerous natural products such as (–)-arnottin II,[1] (–)-regiolone,[2] berchemiaside A and B,[3] or pyrolone A and B.[4] Some of them have been demonstrated to present interesting biologic activities. Xylarenone and hypoxylonol B, both isolated from xylariaceous fungus PSU-A80, displayed good radical scavenging potency,[5] and daldinone C and D are cytotoxic against SW1116 cells.[6] The α-tetralone structure is also the basic unit of numerous synthetic bioactive compounds such as the antitumor 2-arylidene-1-tetralones[7] and QF0104B,[8] an 4-amino-1-tetralone antagonist of dopamine D_2 and serotonin 5-HT_2 receptors. Thus, α-tetralones still remain prime targets and have become valuable synthetic intermediates for the preparation of numerous biologically active substances and their analogues.[9] In industry, α-tetralones are important in different chemical areas such as agrochemistry (pest control as antifeedants against spruce budworm[10]) or fragrances.[11]

However, synthetic routes to α-tetralones are scarce. The most classic access to these compounds is based on the intramolecular Friedel–Crafts reaction of arylbutyric acids and its variants.[12] Other routes include Diels–Alder reactions between cyclohexenones and various dienes,[13] the tandem Michael addition–Dieckmann condensation,[14] the aryne condensation of α,β-unsaturated ketone enolates,[15] the aluminum- and nickel-mediated cyclotrimerization of cyclohexenone with alkynes[16] or the radical cyclization of γ-phenacyl xanthates to olefins.[17]

With the aim of developing an alternative approach to α-tetralones, we focused our attention on the possible carboannulation reactions of 3-methylcyclohexenones with activated olefins. This methodology has been previously considered by Wiemann and Cyrot who studied the magnesium oxide catalyzed condensation in the vapor phase between isophorone **1** and conjugated aldehydes or ketones (Scheme 1).[18] They obtained differently alkyl-substituted α-tetralones **2** and **3**. However, the selectivities and yields were modest. Later, Loupy, Fkih–Tétouani and co-workers described a straightforward access to aryl substituted α-tetralones **4** from isophorone and chalcones via Michael addition and subsequent Robinson annulation reactions followed by a base-induced oxidative dehydrogenation (Scheme 1).[19]



Scheme 1 Carboannulation reactions of isophorone **1** with enones

Consequently, we expected that the base-mediated cyclocondensation of 3-methylcyclohexenones **I** with ethoxymethylenemalonate derivatives **5** might lead to new functionalized α-tetralones **II** and/or **III** (Scheme 2), and now report herein our preliminary results.

Our first experiments demonstrated that the base-catalyzed reactions (20 mol% piperidine or 10 mol% DMAP) of isophorone **1** with diethyl ethoxymethylenemalonate **5a** gave no cyclocondensation product of type **II** or **III** in refluxing ethanol or even at 180 °C without solvent.[20] However, when the reaction was carried out in refluxing ethanol in the presence of 2 equivalents of sodium hydride, we could isolate the keto-malonate **6** in 20% yield (Scheme 3).

So, in order to favor the enolization of the 3-methylcyclohexenone structure and of the presumed reaction intermediates, it seemed advantageous to start from activated substrates such as 3-(ethoxycarbonyl)methylene[21] or 3-cyanomethylenecyclohexenones **7a–c**.[22] This turned out

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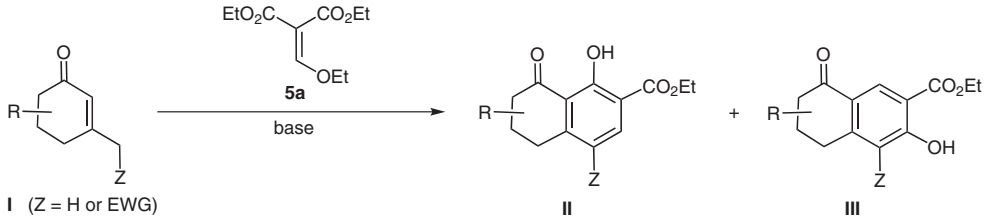
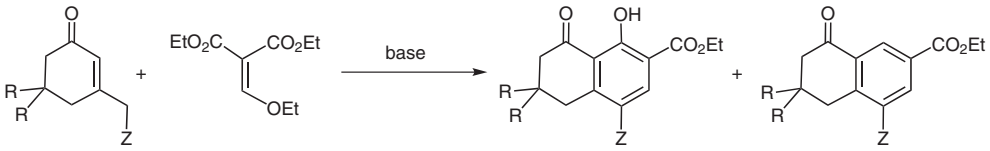


Scheme 2 New approach to α-tetralones **II** and **III**

to be fruitful since we observed the formation of two α-tetralones **8** and/or **9** (Table 1).

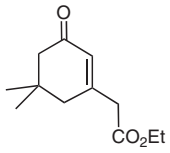
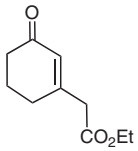
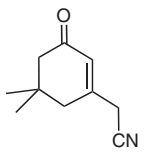
The reaction of cyclohexenone **7a** with diethyl ethoxymethylenemalonate **5a** in the presence of sodium hydride in refluxing THF led to no cyclocondensation product (Table 1, entry 1). However, in DMF it afforded α-tetralone **8a** in a low 9% yield (Table 1, entry 2). The DMAP-catalyzed reaction of **7a** with **5a** (1 equiv) at 180 °C with-

Table 1 Cyclocondensations of 3-Methylcyclohexenones **7a–c** with Ethoxymethylenemalonate **5a**

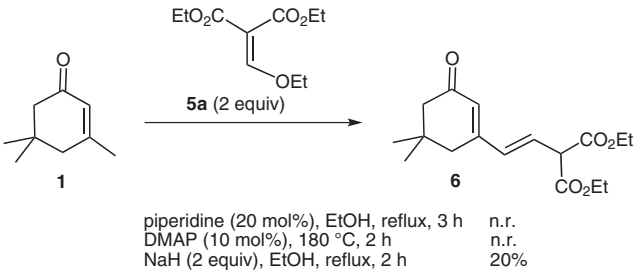


7a R = Me Z = CO_2Et **5a**
7b R = H Z = CO_2Et (n equiv)
7c R = Me Z = CN

8a–c **9a–c**

Entry	Cyclohexenone **7a–c**	**5a** (n equiv)	Base	Solvent	Temp (°C)	Time (h)	Products **8** and **9**	Yield of **8** (%)[a]	Yield of **9** (%)[a]
1	 **7a**	1.2	NaH (1.1 equiv)	THF	66	9	n.r.		
2	**7a**	1.2	NaH (2 equiv)	DMF	85	9	**8a**	9	
3	**7a**	1	DMAP (10 mol%)	–	180	1	**8a**, **9a**	62	2
4	**7a**	2	DMAP (10 mol%)	–	180	1	**9a**		43
5	**7a**	2	NaH (1 equiv) + DMAP (10 mol%)	–	180	1	**8a**, **9a**	15	53
6	**7a**	4	NaH (1 equiv) + DMAP (10 mol%)	–	180	1	**9a**		62
7	 **7b**	1	DMAP (10 mol%)	–	180	1	**8b**, **9b**	30	10
8	**7b**	2	DMAP (10 mol%)	–	180	1	**9b**		41
9	**7b**	2	NaH (1 equiv) + DMAP (10 mol%)	–	180	1	**9b**		50
10	**7b**	4	NaH (1 equiv) + DMAP (10 mol%)	–	180	1	**9b**		60
11	 **7c**	2	DMAP (10 mol%)	–	145	1	**9c**		30
12	**7c**	2	NaH (1 equiv) + DMAP (10 mol%)	–	145	1	**9c**		45

[a] Refers to yield of isolated product after flash chromatography.



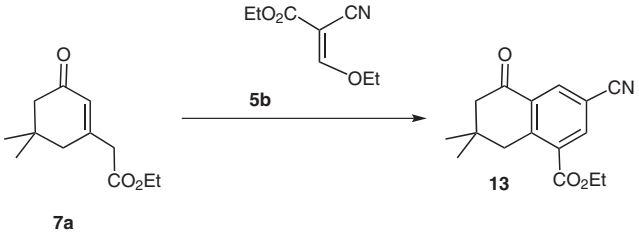
Scheme 3 Reactions of isophorone **1** with **5a**

out any solvent gave α-tetralones **8a** (62%) and **9a** (2%; Table 1, entry 3). The former product **8a** was one of the expected cyclocondensation products (type II α-tetralone). The latter product **9a** seemed to result from the cyclocondensation of cyclohexenone **7a** with two molecules of the activated olefin **5a**. A plausible mechanism depicted in Scheme 4 would involve the formation of intermediates **10**–**12**, the latter **12** giving access to α-tetralone **9a** via elimination of the anion of tri(ethoxycarbonyl)methane. A similar reaction using two equivalents of **5a** gave only α-tetralone **9a** (Table 1, entry 4). By using a more basic system (1 equiv NaH and 10 mol% DMAP) we observed the formation of α-tetralone **9a** as the major cyclocondensation product (53% yield; Table 1, entry 5).[23] The yield of **9a** was optimized to 62% by carrying out the reaction with four equivalents of **5a** (Table 1, entry 6).

Analogous results were obtained for the reactions of cyclohexenone **7b** with ethoxymethylenemalonate **5a** (Table 1, entries 7–10). Thus, both α-tetralones **8b** and **9b** were obtained for the reaction of **7b** with one equivalent of **5a** in the presence of 10 mol% of DMAP (Table 1, entry 7). Use of increased amounts of ethoxymethylenemalonate **5a** provided only α-tetralone **9b** (Table 1, entries 8–10) which was obtained in an optimal 60% yield (entry 10).

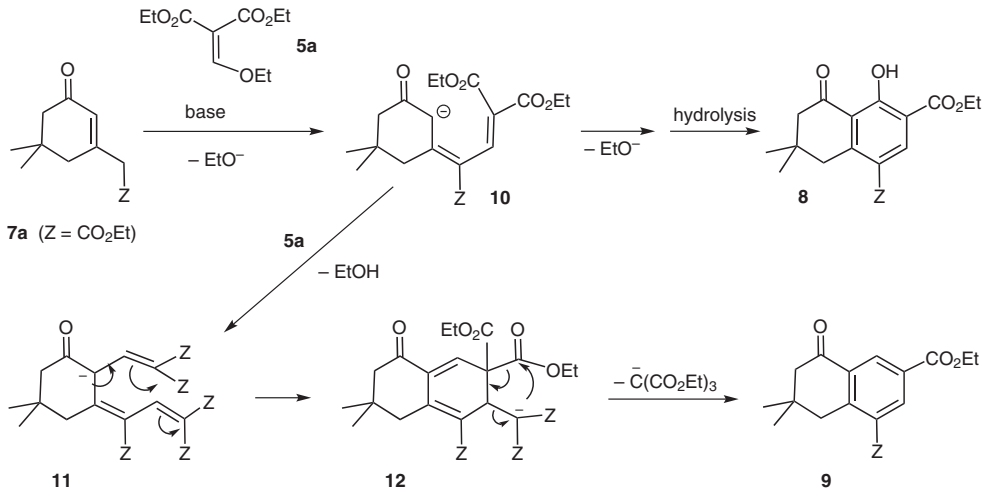
The cyclocondensation reactions of 3-cyanomethylenecyclohexenone **7c** were performed at a lower 145 °C temperature, because of presumed unwanted polycondensation reactions of the comparatively less sterically demanding cyano group (Table 1, entries 11 and 12). α-Tetralone **9c** was then obtained in an optimal 45% yield.

This carboannulation reaction of activated 3-methylenecyclohexenones **7a**–**c** was extended to the use of α-cyano-β-ethoxyacrylate **5b** as Michael acceptor. Thus, several reactions of cyclohexenone **7a** with **5b** were carried out under similar conditions which are summarized in Scheme 5. They all gave α-tetralone **13** as a single product which was obtained in an optimized 65% yield when four equivalents of acrylate **5b** were used.



Scheme 5 Cyclocondensation reactions of cyclohexenone **7a** with **5b**

In summary, we have shown that the cyclocondensation of activated 3-methylenecyclohexenones **7a**–**c** with ethoxymethylenemalonate derivatives **5** gives α-tetralones **8** and **9** with selectivities which mainly depend on the number of equivalents of the derivative **5**. This opens an attractive route to polyfunctionalized α-tetralones **9** which are obtained in one step as single products when excess of the Michael acceptor **5** is used. Further study on the cyclocondensation reactions of cyclohexenone derivatives with other activated olefins is in progress in our laboratory.



Scheme 4 Mechanism of formation of α-tetralones **8** and **9**

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(22) Kazarian, J.; Geribaldi, S.; Ferrero, L.; Rouillard, M.; Azzaro, M. *J. Org. Chem.* **1978**, *43*, 1817.
(23) **Typical Experimental Procedure (Table 1, entry 5) – Synthesis of Diethyl 5,6,7,8-Tetrahydro-7,7-dimethyl-4-hydroxy-5-oxo-1,3-naphthalenedicarboxylate (8a) and Diethyl 5,6,7,8-Tetrahydro-7,7-dimethyl-5-oxo-1,3-naphthalenedicarboxylate (9a)**
Sodium hydride (50% oil, 48 mg, 1 mmol) was added to a mixture of ester **7a** (211 mg, 1 mmol), DMAP (12 mg, 0.1 mmol) and diethyl ethoxymethylenemalonate (433 mg, 2 mmol) stirred at 0 °C under nitrogen. The reaction mixture immediately became yellow with release of hydrogen. After stirring for 10 min at r.t., the mixture was heated at 180 °C for 1 h. After cooling at r.t., the mixture was diluted with CH_2Cl_2 and hydrolyzed with sat. aq NH_4Cl. Workup gave an oil which was purified by flash chromatography (SiO_2, PE–Et_2O, 80:20) to afford α-tetralone **8a** (50 mg, 15%) and α-tetralone **9a** (170 mg, 53%).
Compound **8a**: mp 62–64 °C. TLC (SiO_2, PE–Et_2O, 50:50): R_f = 0.39. IR (KBr film): 2950, 1717, 1701, 1635, 1605, 1443, 1228, 1208, 1191, 1150, 867, 774, 683 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 14.18 (s, 1 H, OH), 8.62 (s, 1 H, H-2), 4.32 (q, ^3J = 7.1 Hz, 4 H, 2 × OCH_2CH_3), 3.25 (s, 2 H, H-8), 2.55 (s, 2 H, H-6), 1.38 (t, ^3J = 7.1 Hz, 6H, 2 × OCH_2CH_3), 1.06 [s, 6 H, *gem*-$(CH_3)_2$]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 206.1 (C=O), 166.1 (OC=O), 166.0 (OC=O), 165.0 (C-4), 151.9 (C-8a), 141.4 (C-2), 120.7 (C-1), 117.9 (C-4a), 117.6 (C-3), 61.7 (OCH_2CH_3), 61.6 (OCH_2CH_3), 52.0 (C-6), 42.2 (C-8), 33.1 (C-7), 28.5 [*gem*-$(CH_3)_2$], 14.7 (OCH_2CH_3), 14.6 (OCH_2CH_3). ESI-HRMS: *m/z* calcd for $C_{18}H_{22}O_6$ [MNa^+]: 357.1314; found: 357.1320.
Compound **9a**: mp 78 °C. TLC (SiO_2, PE–Et_2O, 50:50): R_f = 0.56. IR (KBr film): 2977, 2958, 2870, 1715, 1691, 1605, 1466, 1449, 1418, 1389, 1225, 1195, 1148, 1022, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.81 (d, ^3J = 1.8 Hz, 1 H, H-4), 8.68 (d, ^3J = 1.8 Hz, 1 H, H-2), 4.32 (q, ^3J = 7.1 Hz, 4 H, 2 × OCH_2CH_3), 3.24 (s, 2 H, H-8), 2.54 (s, 2 H, H-6), 1.42 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 1.40 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 1.07 [s, 6 H, *gem*-$(CH_3)_2$]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 197.5 (C=O), 166.6 (OC=O), 166.5 (OC=O), 148.4 (C-8a), 136.3 (C-4a), 133.6 (C-2), 131.9 (C-4), 131.7 (C-1), 129.2 (C-3), 61.9 (2 × OCH_2CH_3), 52.0 (C-6), 42.0 (C-8), 33.3 (C-7), 29.0 [*gem*-$(CH_3)_2$], 14.7 (OCH_2CH_3), 14.6 (OCH_2CH_3). ESI-HRMS: *m/z* calcd for $C_{18}H_{22}O_5$ [MNa^+]: 341.1359; found: 341.1357.