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Michael Addition of Malononitrile to Indenones: Synthesis and Characterization of 2-(1-oxo-2,3-dihydro-1*H*-inden-2-yl) (Aryl)(Methyl)malononitrile Derivatives

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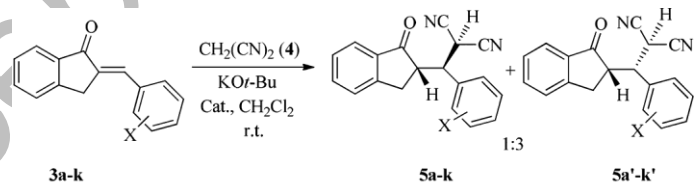
Abstract

Indanones **3** were prepared from the reaction of indanone (**1**) with corresponding benzaldehyde derivatives **2,** as described in the literature. Then, indenones **3** were subjected to *KOt*Bu-catalyzed Michael addition with malononitrile to give a mixture of diastereomers **5** with a low conversion and no diastereoselection. Employment of phase transfer catalyst such as benzyltriethylammonium chloride or N-Benzylcinchonidinium chloride had a positive effect on both conversion and diastereoselection. The structure of diastereomers **5** was determined by spectroscopic methods (NMR, IR).

Graphical Abstract



KEYWORDS: Indenones, Malononitrile, Michael addition, Phase transfer catalyst

INTRODUCTION

The Michael addition of active methylene compounds to α,β-unsaturated carbonyl compounds is a general route to construct for carbon-carbon bond.[1–7] An active methylene compounds, malononitrile, has been widely used as Michael donor, since it serves as an equivalent of 1,3-diketone and offers an access to preparation carboxylic acids,[8] esters,[9] amines,[10–12] polyfunctional aromatics, pyridines, pyridones, pyridazines and pyrazoles.[13–17]

For Michael addition of malononitrile to α,β-unsaturated carbonyl compounds, a variety of catalysts, including acids, bases and organocatalysts have been used.[18–23]

In this paper, we report KO*t*Bu-catalyzed Michael addition of malononitrile to indenones **3** in the presence of benzyltriethylammonium chloride (TEBAC) as a phase transfer catalyst to furnish addition products as a mixture of diastereomers in a ratio of 3:1.

RESULTS AND DISCUSSION

The starting compounds, 2-benzylidene-2,3-dihydro-1*H*-inden-1-one derivatives **3a-k**, were synthesized from the addition of benzaldehyde derivatives to 1-indanone in the presence of NaOH in EtOH for 6 hours at room temperature (Scheme 1).[30–33] The products were purified by means of crystallization and their structures were determined by spectroscopic methods (NMR, IR and Elemental Analysis) and compared with the reported data.[32–39]

After preparation and characterization of the starting materials, we focused on optimization of reaction conditions for the Michael addition of malononitrile (**4**) to indenones **3**. For this purpose, addition of malononitrile (**4**) to indenone **3a** was chosen as the model reaction (Scheme 2). The results were given in Table 1. The reaction of **3a** (1 equiv.) with **4** (1.2 equiv.) and KO*t*Bu (20 % mmol) was performed in CH_2Cl_2 (5 ml) for 24 hours at room temperature. The reaction resulted in the formation of a mixture of diastereomer (**5a** and **5a'**) in a ratio of 1:1 with 20 % conversion (Table 1, entry 1). When the reaction was conducted in the presence of benzyltriethylammonium chloride (TEBAC) (act as a Brønsted acid) (10 % mmol) diastereoselectivity and conversion increased up to 3:1 and 100%, respectively, (Table 1, entry 2). Replacement of TEBAC with N-Benzylcinchonidinium chloride did not affect outcome of the reaction (Table 1, entry 3). For this reason, we continued our work with TEBAC.

The structure of isolated compounds **5a** and **5a'** were determined on the basis of spectral data. In the ^{1}H-NMR spectrum of compound **5a**, the proton HC(4) resonates as a doublet at 7.75 ppm (J = 4.8 Hz), and the proton HC(3) resonates as a doublet of doublet at 4.27 (J = 12.0, 4.8 Hz), and the proton HC(2) resonates as a doublet of doublet of doublet at 3.37 (J = 12.0, 7.6, 4.8 Hz), These coupling constants indicate that the protons HC(4) and HC(3) are *cis* and the HC(3) and HC(2) are *trans*.

In the ^{1}H-NMR spectrum of compound **5a'**, the proton HC(4) resonates as a doublet at 7.55 ppm (J = 11.2 Hz), and the proton HC(3) resonates as a doublet of doublet at 4.61 (J = 11.2, 4.8 Hz). These coupling constants indicate that the protons HC(4) and HC(3) are

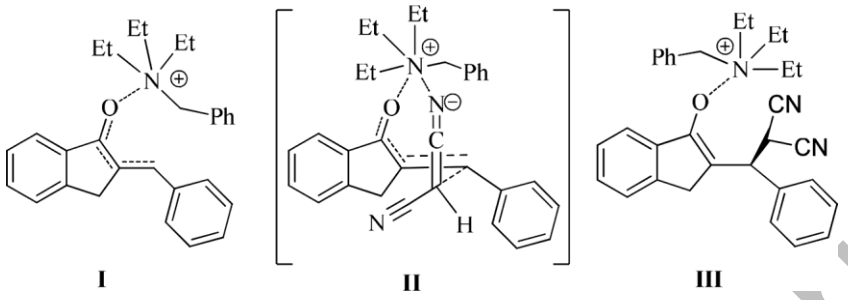
trans to each other. Furthermore, all these results show that the compounds **5a** and **5a'** are diastereomers. Summary, the reaction of malononitrile (**4**) with the inonones (**3**) can gives 4 possible stereoisomer having SS, RR, RS and SR configurations. From the NMR studies, we assume that the a-isomer has SS or RR configurations and a'-isomer has RS or SR configurations.

After these results, we continued the reactions with others indenones (**3b-k**) using TEBAC (10 % mmol) and KO*t*Bu (20 % mmol) (Scheme 3). The results were presented in Table 2.

The products were separated by crystallization, thin layer- and column chromatography and/or HPLC. The diastereomers **5a-k** and **5a'**, **5b'**, **5e'**, **5f'**, **5i'** and **5j'** were isolated as pure products. Despite all our efforts, the other diastereomers **5c'**, **5d'**, **5g**', **5h**' and **5k'** could not be isolated as pure products.

The reaction mechanism can be illustrated as shown below. We assume that the benzyltriethylammonium chloride interacts with oxygen atom of carbonyl group to form the enolate form I. Then, malononitrile anion (iminium ion), formed by acting of KO*t*Bu, interacts with I and formed the transition state II. In the transition state II, the formation of C-C bond takes place rather one side of the transition state II. Removing of the benzyltriethylammonium ion from III give the malononitrile adducts.

Addition, we assume that, the *m*-substituents on phenyl ring increase the energy of the transition state II due to the steric effect and reduce product yield.



I II III

CONCLUSION

In summary, KO*t*Bu-catalyzed addition of malononitrile to indenones **3** in the presence of TEBAC gave addition products with acceptable yields. These products may find synthetic utility for the preparation valuable intermediates in organic chemistry.

EXPERIMENTAL

All the reagents and solvents for synthesis were purchased from Sigma-Aldrich and Fluka. Thin layer chromatography was carried out on Merck silica F_{254} 0.255-mm plates, and spots were visualized by UV fluorescence at 254 nm. Classic column chromatography was performed using Merck 60 (70-230 mesh) silica gel. Melting points were measured on Electrothermal 9100 apparatus. IR spectrums (KBr disc) were recorded on a Jasco FT/IR-430 spectrometer. ^{1}H- and ^{13}C-NMR spectrum was recorded on a Bruker Avance DPX-400 instrument. As internal 0.00) for standards served TMS (^{1}H NMR and $CDCl_3$ δ(77.0) for ^{13}C NMR spectroscopy *J* values are given in Hz. Elemental analyses were obtained from a LECO CHNS 932 Elemental Analyzer.

General Procedure For The Synthesis Of 2-(Benziliden)-2,3-Dihidro-1H-Inden-1-One (Chalcone Analogues) Derivatives (3a-K)

The chalcone analogues, 2-(benziliden)-2,3-dihidro-1*H*-inden-1-one derivatives, (**3a-k**) were synthesized by previously published methods.[30–33]

General Procedure For The Addition Of Malononitrile To Chalcone Analogues (3a-K): Synthesis Of 5a-K And 5a'-5k'

The mixture of chalcone analogue **3** (0.5 g, 1 mmol) and malononitrile (**4**) (0.16 g, 1.2 mmol) was dissolved in 5 ml of CH_2Cl_2. To this solution was added benzyltriethylammonium chloride (10% mmol) and KO*t*-Bu (20%mmol) and the mixture was stirred for 6 hours at room temperature. Reaction mixture was diluted with CH_2Cl_2 (50 ml) and added solution of 5% HCl. Organic layer was washed with H_2O and dried with Na_2SO_4. The solvent was removwed. The crude product was submitted to crystallization (using different solvent mixture: 2:1 ether: ethanol; CH_2Cl_2: hexane), and/or colon chromatography (silica gel), and/or thin layer chromatography (silica gel) and/or HPLC for separation of isomers.

2-((R)-(2-Bromophenyl)((S)-1-Oxo-2,3-Dihydro-1H-Inden-2-Yl)Methyl)Malononitrile. (5a)

White cyrstals, Yield: 40%. mp: 145-148°C. **IR (**KBr, cm^{-1}): 3064, 2900, 2254, 1697, 1602, 1565, 1475, 1463, 1434, 1274, 1211, 1186, 1076, 997, 925, 796, 763, 736, 665, 615. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.6 Hz, 1H), 7.76-7.73 (m, 2H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 8.0 Hz,

1H), 7.34 (t, *J* = 8.0 Hz, 1H), 5.75 (d, *J* = 4.8 Hz, 1H), 4.27 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.37 (ddd, *J* = 12.6, 7.6, 4.8 Hz,1H), 3.13 (dd, *J* = 17.2, 7.6 Hz, 1H), 2.64 (dd, *J* = 17.2, 4.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 205.8, 152.2, 135.9, 135.8, 135.5, 133.9, 130.6, 128.7, 128.3, 128.2, 126.3, 125.9, 124.4, 111.9, 111.3, 47.2, 43.8, 32.5, 26.5. Anal. calc. for $C_{19}H_{13}BrN_2O$: C, 62.48; H, 3.59; N, 7.67. Found: C, 62.36; H, 3.47; N, 7.63.

2-((S)-(2-Bromophenyl)((S)-1-Oxo-2,3-Dihydro-1H-Inden-2-Yl)Methyl)Malononitrile. (5a')

White cyrstals, Yield: 15%. mp: 196-199°C. **IR (**KBr, cm^{-1}): 3079, 3064, 2942, 2252, 1698, 1604, 1473, 1434, 1294,1280, 1205, 1024, 759, 750, 715, 651, 578. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.26 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 5.55 (d, *J* = 11.2 Hz, 1H), 4.61 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.51-3.41 (m, 2H), 2.81 (dd, *J* = 16.0, 3.6 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.6, 153.0, 136.4, 135.7, 133.9, 133.6, 130.5, 128.7, 128.1, 127.9, 126.6, 126.4, 124.0, 112.5, 111.6, 47.0, 45.5, 30.1, 26.0. Anal. calc. for $C_{19}H_{13}BrN_2O$: C, 62.48; H, 3.59; N, 7.67. Found: C, 62.36; H, 3.48; N, 7.56.

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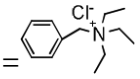
Table1. Optimization studies

Entry	Compound	Catalyst	Time(h)	Conv.%	Product ratio 5a:5a’
1	**3a**	-	24	20	1:1
2	**3a**	A	6	100	3:1
3	**3a**	B	6	100	3:1

A = Benzyltriethylammonium chloride = 

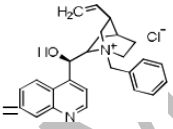
B = N-Benzylcinhoninium chloride = 

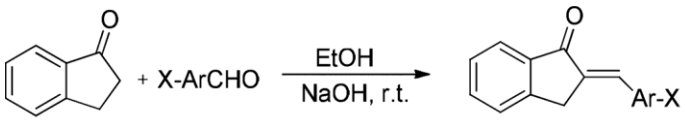
Table 2. Synthesized diastereomers **5a-k** and **5a'-k'**

Entry	**X**	**Comp.**	**Yield%**	**Comp.**	**Yield%**
1	2-Br	**5a**	40[a)]	**5a'**	15[a)]
2	3-Br	**5b**	43[a)]	**5b'**	17[a)]
3	4-Br	**5c**	67[a)]	**5c'**	17[b)]
4	3-Cl	**5d**	60[a)]	**5d'**	23[b)]
5	4-Cl	**5e**	65[a)]	**5e'**	25[a)]
6	3-OCH_3	**5f**	56[a)]	**5f'**	21[a)]
7	4-OCH_3	**5g**	62[a)]	**5g'**	21[b)]
8	2-CH_3	**5h**	45[a)]	**5h'**	19[b)]
9	3-CH_3	**5i**	64[a)]	**5i'**	23[a)]
10	2,5-diOCH_3	**5j**	63[a)]	**5j'**	22[a)]
11	2-Cl,5-NO_2	**5k**	71[a)]	**5k'**	16[b)]

[a)] Isolated yield;

[b)] Calculated yield from ^{1}H-NMR spectrum of mixture of isomers

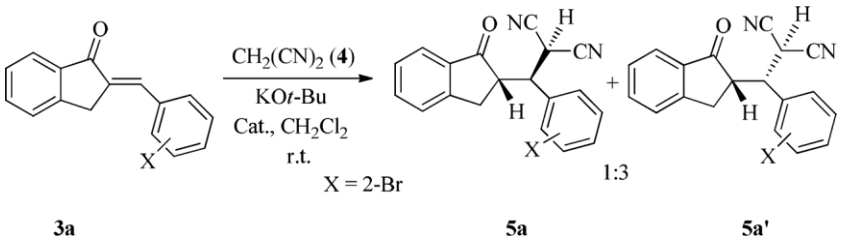
Scheme 1. Synthesis of indenones (**3a-k**)



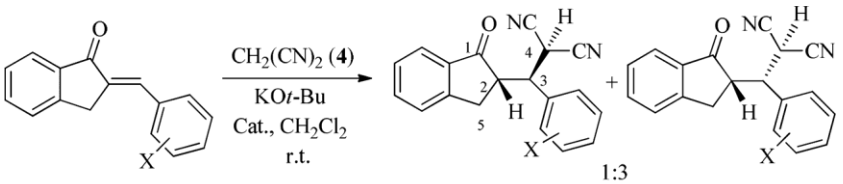
1 **2a-k** **3a-k**

X= (a) 2-BrPh, (b) 3-BrPh, (c) 4-BrPh, (d) 3-ClPh, (e) 4-ClPh, (f) 3-OCH_3Ph, (g) 4-OCH_3Ph, (h) 2-CH_3Ph, (i) 3-CH_3Ph, (j) 2,5-diOCH_3Ph, (k) 2-Cl,5-NO_2Ph

Scheme 2. Determination of the optimum reaction conditions



Scheme 3. Michael Additof of Malanonitrile to Indenones



3a-k **5a-k** **5a'-k'**

X= (a) 2-BrPh, (b) 3-BrPh, (c) 4-BrPh, (d) 3-ClPh, (e) 4-ClPh, (f) 3-OCH_3Ph, (g) 4-OCH_3Ph, (h) 2-CH_3Ph, (i) 3-CH_3Ph, (j) 2,5-diOCH_3Ph, (k) 2-Cl,5-NO_2Ph