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A novel carbanion-olefin intramolecular cyclization: synthesis of substituted 2-aroyl-3,4-dihydro-2*H*-benzopyrans from salicylaldehydes

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ABSTRACT

Utilization of a novel carbanion-olefin intramolecular *6-endo-trig* cyclization reaction to provide 2-aroyl-3,4-dihydro-2*H*-benzopyrans is described. Through a sequence of a Wittig reaction, O-alkylation, and carbanion-olefin intramolecular cyclization, salicylaldehydes were converted into a series of new 2-aroyl-3,4-dihydro-2*H*-benzopyrans in two steps or in one-pot reaction.

The search for new cyclization methods for the construction of organic ring compounds from simple open chain starting materials is an attractive task for chemists. Carbon–carbon (C–C) bond formation reactions via intramolecular cyclization have been well documented and have become one of the most efficient methods in the synthesis of carbocyclic and heterocyclic compounds. In the previous reports, most of the intramolecular additions of nucleophiles to double bonds are initiated by the attack on the double bond by an external electrophile to generate a cationic intermediate that is subsequently cyclized by an internal nucleophile.[1] More recently, the intramolecular Heck reaction, which is known as a palladium-catalyzed coupling of haloarenes and haloalkenes with other double bonds, has become a powerful tool for synthesizing corresponding cyclic compounds.[2] Other cyclization reactions reported include the cyclization of unsaturated organolithium reagents for the preparation of benzoheterocyclic compounds,[3] the free radical cyclization for construction of both carbocycles and heterocycles,[4] the carbocyclization of *gem*-difluoroalkenes for the construction of naphthalene and indene frameworks,[5] the 6-*endo-trig* intramolecular cyclization of an enone-aldehyde using samarium (II) iodide for hydrindanone,[6] as well as other reactions. The lack of the regiochemical control between *6-endo-trig* and *5-exo-trig* closures as well the requirement for expensive transition metal catalysts, which may produce environmental hazardous toxic waste,[7] are shortcomings of some of these cyclization reactions. On the other hand, the preparation of 2-aroyl-3,4-dihydro-2*H*-benzopyrans is still undeveloped in the literature. Furthermore, its oxidation-dehydrogenation products, 2-aroylbenzopyran-4-ones exhibiting biological activities were reported.[8] Herein we report the results of our studies on the intramolecular carbanion-olefin cyclization via a 6-*endo-trig* cyclization leading to the synthesis of 2-aroyl-3,4-dihydro-2*H*-benzopyrans by the reaction of 1-aryl-2-(2-vinylphenoxy)ethanones (**3a–k**), which were prepared from salicylaldehydes (**1a–h**), with potassium *tert*-butoxide or by the reaction of **1a–h** through a sequence of reactions in one pot.

Based on the two-step strategy (Scheme 1), salicylaldehydes (**1a–h**) were reacted with methylene(triphenyl)phosphorane, which was generated from methyltriphenylphosphonium bromide (MTPPB) and potassium *tert*-butoxide (2.3 equiv) in situ at 0 °C, to undergo the Wittig reaction for 1 h. Without isolation of the intermediate, the reaction mixture was subsequently treated with 2-bromoacetophenones (**2a–c**) and refluxed for an additional 1 h. Following standard workup and isolation procedures, **3a**–**k** were afforded in 67–85% yield. The structure of **3a–k** can be confirmed by their spectral data.[9] Subsequently, as a model reaction, 2-(6-methoxy-2-vinylphenoxy)-1-phenylethanone (**3b**) was treated with various bases and in different solvents to optimize the reaction. When *n*-BuLi was used as a base, no desired cyclization product was observed resulting to the nucleophilic addition product 1-(2-methoxy-6-vinylphenoxy)-2-phenylhexan-2-ol,[10] instead (entry 1). Other bases either LDA (entries 2 and 3) or NaOEt (entries 4 and 5) gave no desired product or lower yield than that of *tert*-BuOK at either room temperature (entry 6) or reflux (entry 7) in THF. In addition to THF, CH_2Cl_2 (which is toxic and volatile) can also be used

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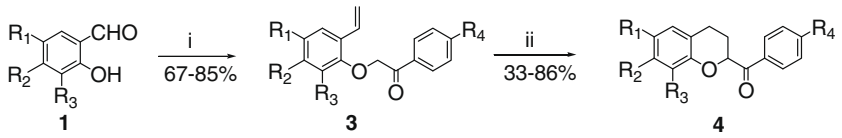


1 3 4

a. $R_1 = R_2 = R_3 = H$;
b. $R_1 = R_2 = H$, $R_3 = OMe$;
c. $R_1 = Br$, $R_2 = R_3 = H$;
d. $R_1 = Cl$, $R_2 = R_3 = H$;
e. $R_1 = Cl$, $R_2 = H$, $R_3 = Cl$;
f. $R_1 = R_3 = H$, $R_2 = OCH_3$
g. $R_2 = Cl$, $R_1 = R_3 = H$;
h. $R_2 = NO_2$; $R_1 = R_3 = H$

a. $R_1 = R_2 = R_3 = R_4 = H$; b. $R_1 = R_2 = R_4 = H$, $R_3 = OMe$;
c. $R_1 = R_2 = H$, $R_3 = R_4 = OMe$; d. $R_1 = Br$, $R_2 = R_3 = R_4 = H$;
e. $R_1 = Cl$, $R_2 = R_3 = R_4 = H$; f. $R_1 = R_3 = Cl$, $R_2 = R_4 = H$;
g. $R_1 = R_4 = Cl$, $R_2 = R_3 = H$; h. $R_1 = Cl$, $R_2 = R_3 = H$, $R_4 = OMe$;
i. $R_1 = R_3 = H$, $R_2 = R_4 = OMe$; j. $R_1 = R_3 = R_4 = H$, $R_2 = Cl$;
k. $R_1 = R_3 = R_4 = H$, $R_2 = NO_2$

Scheme 1. Reagents and conditions: (i) (a) MTPPB (1.2 equiv), *tert*-BuOK (2.3 equiv), THF, rt, 1 h; (b) 2-bromoacetophenone (**2a**) (1.1 equiv), 2-bromo-4′-methoxyacetophenone (**2b**) (1.1 equiv) , 2-bromo-4′chloroacetophenone (**2c**) (1.1 equiv), reflux, 1 h; (ii) *tert*-BuOK (1.2 equiv), THF, reflux, 30 min.

Table 1
Treatment of **3b** (2.68 g, 10 mmol) with various bases (1.2 equiv) and solvents (15 mL) to examine the yield of **4b**

Entry	Base	Solvent[a]	Temp (°C)	Time (hr)	Yield (%)
1	*n*-BuLi	THF	−78 °C to rt	2	Ref. 9
2	LDA	THF	−78 °C to rt	2	—[d]
3	LDA	THF-HMPA[b]	0 °C to rt	2	50[e]
4	NaOEt	EtOH	rt	3	Trace
5	NaOEt	THF	rt	4	47
6	*t*-BuOK	THF	rt	1.5[c]	89
7	*t*-BuOK	THF	Reflux	0.5[c]	86
8	*t*-BuOK	CH_2Cl_2	rt	1.5[c]	86

[a] Solvents were dried by the standard procedures before use.
[b] 15 mL THF and 7.5 mL HMPA were used.
[c] Reaction time was determined by checking the consumption of starting material with TLC.
[d] Even after prolonged reaction time of 4 h, almost no desired product was detected by TLC, but starting material mixed with messy products was observed.
[e] In the mixed solvents, the percentage yield increases and decreases the high polar unidentified by-products.

in this cyclization reaction (entry 8). Therefore, the use of potassium *tert*-butoxide as the base and anhydrous THF as solvent provided the optimum conditions for this type of carbanion-olefin cyclization. The results of the optimization are compiled in Table 1.

Based on the above results, compounds **3a–k** were subjected to the carbanion-olefin intramolecular cyclization using potassium *tert*-butoxide as base in refluxing THF for 0.5–1 h to afford **4a–k** in 33–86% yields. The selected spectral data of **4a–k** are summarized in Table 2.

Spectroscopic analysis showed that 5-*exo*-*trig* products were not observed during this reaction. The stereospecificity of the cyclization and the correct connectivity were confirmed by the acquired spectral data.[8] In addition, the elemental analytical data which were measured are consistent with the structure of **4a–k**. The proposed mechanism for the carbanion-olefin intramolecular cyclization of **3** is shown in Scheme 2. The proton near the carbonyl group of **3**, which is more acidic than others, is abstracted by potassium *tert*-butoxide to generate a carbanion. The resultant carbanion attacks the olefinic carbon to undergo 6-*endo*-*trig* reaction to form a benzylic carbanion. Subsequently, the carbanion abstracts a proton from *tert*-butyl alcohol generated in situ to yield the title compounds.

In order to minimize the synthetic steps, to reduce the reaction wastes, to shorten workup processes, and to increase the efficiency of the reaction, the synthesis of 2-aroyl-3,4-dihydro-2*H*-benzopyrans (**4a–k**) was achieved through a sequence of a Wittig reaction, O-alkylation, and carbanion-olefin intramolecular cyclization from salicylaldehydes (**1a–h**) in a three-step one-pot reaction (Scheme 3).[11]

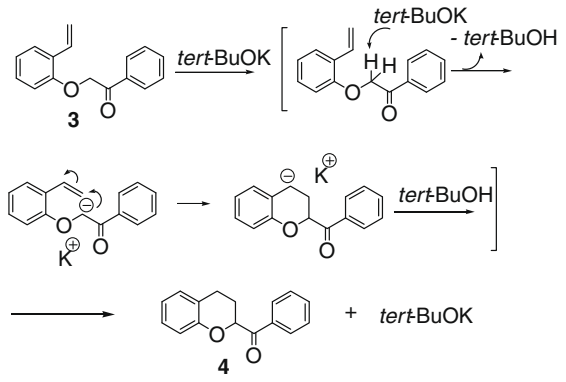
The percentage yields of 2-aroyl-3,4-dihydro-2*H*-benzopyrans (**4a–k**) which were obtained from salicyl-aldehydes (**1a–h**) in a three-step one-pot reaction are 47% for **4a**, 66% for **4b**, 64% for **4c**, 64% for **4d**, 62% for **4e**, 67% for **4f**, 58% for **4g**, 62% for **4h**, 41% for **4i**, 48% for **4j**, and 26% for **4k**, respectively.

In conclusion, we have established a novel carbanion-olefin 6-*endo*-*trig* cyclization from the reaction of 1-aryl-2-(2-vinylphenoxy)ethanones (**3a–k**) with potassium *tert*-butoxide. Based on this cyclization, a new series of substituted 2-aroyl-3,4-dihydro-2*H*-benzopyrans was efficiently synthesized either from the cyclization of the intermediates **3a–k** in a two-step reaction or from the starting materials **1a–h** through a sequence of a Wittig reaction, O-alkylation, and cyclization in a one-pot reaction. Although the

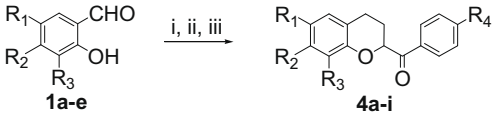
Table 2
The selected physical and spectral data of **4a–k**

Compd	Yield* (%)	MP (°C)	IR (cm^{-1})	^1H and ^{13}C NMR			
				H-2 (δ) (Hz)	C-2	C-3	C-4
4a	67	69–70	1693	5.38 (8.4, 3.2)	77.1	23.5	24.4
4b	86	91–93	1695	5.56 (6.8, 4.0)	77.1	22.8	24.2
4c	82	112–113	1685	5.49 (7.2, 3.6)	77.0	22.9	24.3
4d	76	90–92	1691	5.42 (7.6, 3.6)	76.8	23.1	23.9
4e	79	87–88	1689	5.43 (8.4, 3.2)	76.9	23.2	24.0
4f	80	85–86	1682	5.54 (6.8, 4.0)	77.5	22.9	23.3
4g	72	109–110	1692	5.32 (8.0, 3.6)	77.1	23.2	23.8
4h	82	128–130	1683	5.37 (8.0, 3.6)	76.9	23.3	24.2
4i	55	107–108	1682	5.32 (8.4, 3.2)	77.2	23.0	24.9
4j	61	110–111	1693	5.44 (7.2, 3.6)	77.1	22.9	24.1
4k	33	117–118	1695	5.60 (6.6, 4.4)	76.8	23.1	23.4

* General procedure: Under the protection of N_2, to **3a–k** (10 mmol) dissolved in THF (15 mL) was added potassium *tert*-butoxide (1.35 g, 12 mmol). The reaction mixture was heated to the reflux for 0.5–1 h until the consumption of starting material. Work-up as general procedure, and purified by column chromatography (EA/*n*-hexane = 1:10) to yield **4a–k**.



Scheme 2. The proposed mechanism of intramolecular carbanion-olefin cyclization of **3**.



Scheme 3. Synthesis of 2-aroyl-3,4-dihydro-2*H*-benzopyrans (**4ai**) from salicylicaldehydes (**1a–e**) in a three-step one pot reaction. Reagents and conditions: (i) (a) MTPPB (1.2 equiv), *tert*-BuOK (2.3 equiv), THF, rt, 1 h; (ii) (b) 2-bromoacetophenone (**2a**) (1.1 equiv), 2-bromo-4′-methoxyacetophenone (**2b**) (1.1 equiv), 2-bromo-4′-chloro-acetophenone (**2c**) (1.1 equiv), reflux, 1 h; (iii) *tert*-BuOK (1.2 equiv), THF, reflux, 30 min.

one-pot reaction could not improve the total yields compared to that of the two-step reaction, it provides a unique and concise route to handle and leads to less workup procedures. Besides, the reduction of environmental pollutants is also advantage. Thus, we have provided a concise and green chemistry for the synthesis of title compounds either in two steps or in a one-pot reaction in good total yields, respectively. Further applications and the development of this type of reaction for other heterocyclic compounds are currently in progress in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.132.

References and notes

1. (a) Harding, K. E.; Tiner, T. H.. In *Comprehensive Organic Synthesis*; Semmelhack, M. F., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p 363; (b) Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 33–62. and 63–116; (c) Ali Dondas, H.; Grigg, R.; Hadjisoteriou, M.; Markandu, J.; Kennewell, P.; Thornton-Pett, M. *Tetrahedron* **2001**, *57*, 1119–1128.
2. (a) Heck, R. F. *Accounts Chem. Res.* **1979**, *12*, 146–151; (b) Link, J. T. *Org. React.* **2002**, *60*, 157–534; (c) Laschat, S.; Narjes, F.; Overman, L. E. *Tetrahedron* **1994**, *50*, 347–358; (d) Grigg, R.; Fretwell, P.; Meerholtz, C.; Sridharan, V. *Tetrahedron* **1994**, *50*, 359–370; (e) Hudlicky, T.; Olivo, H. F. *J. Amer. Chem. Soc.* **1992**, *114*, 9694–9696; (f) Sundberg, R. J.; Cherney, R. J. *J. Org. Chem.* **1990**, *55*, 6028–6037.
3. (a) Mealy, M. J.; Bailey, W. F. *J. Organomet. Chem.* **2002**, *646*, 59–67; (b) Kamyar, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, *15*, 2025–2046; (c) Coldham, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, *7*, 1343–1364.
4. (a) Malacria, M. *Chem. Rev.* **1996**, *96*, 289–306. and literatures cited therein; (b) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2004**, *60*, 6239–6278; (c) Majumdar, K. C.; Ray, K.; Debnath, P.; Maji, P. K.; Kundu, N. *Tetrahedron Lett.* **2008**, *49*, 5597–5600.
5. Ichikawa, J.; Miyazaki, H.; Sakoda, K.; Wada, Y. *J. Fluorine Chem.* **2004**, *125*, 585–593.
6. (a) Sono, M.; Hashimoto, A.; Nakashima, K.; Tori, M. *Tetrahedron Lett.* **2000**, *41*, 5115–5118; (b) Sono, M.; Nakashiba, Y.; Nakashima, K.; Tori, M. *J. Org. Chem.* **2000**, *65*, 3099–3106.
7. (a) Wataha, J. C.; Hanks, C. T. *J. Oral Rehabil.* **1996**, *23*, 309–320; (b) Liu, T. Z.; Lee, S. D.; Bhatnagar, R. S. *Toxicol. Lett.* **1979**, *4*, 469–473; (c) Moore, W.; Hysell, D.; Hall, L.; Campbell, K.; Stara, J. *Environ. Health Persp.* **1975**, *10*, 63–71; (d) Nyarko, E.; Hara, T.; Grab, D. J.; Habib, A.; Kim, Y.; Nikolskaia, O.; Fukuma, T.; Tabata, M. *Chem. Biol. Interact.* **2004**, *148*, 19–25.
8. Payard, M.; Tronche, P.; Bastide, J.; Bastide, P.; Chavernac, G. *European J. Med. Chem.* **1981**, *16*, 453–470.
9. The procedure for the preparation of compounds **3a–k**, and **4a–k** together with their physical and spectral data which were obtained are given in Supplementary data.
10. *1-(2-Methoxy-6-vinylphenoxy)-2-phenylhexan-2-ol* (2.22 g, 68%) was obtained as colorless liquid, R_f = 0.48 (ethyl acetate/*n*-hexane = 1:7), IR (neat) ν_{max}: 3497, 3062, 3026, 2955, 2869, 1576, 1473, 1299, 1266, 1212, 1069, 1028, 909, 795, 747, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.83 (t, J = 7.0 Hz, 3H, $(CH_2)_2CH_2CH_3$), 1.00–1.45 (m, 4H, $CH_2(CH_2)_2CH_3$), 1.75–2.04 (m, 2H, $CH_2(CH_2)_2CH_3$), 3.79 (s, 3H, OCH_3), 4.05 (d, J = 9.6 Hz, 1H, OCH_aH_bC), 4.05 (br s, 1H, OH), 4.14 (d, J = 9.4 Hz, 1H, OCH_aH_bC), 5.23 (dd, J = 11.2, 1.2 Hz, 1H, $ArCH{=}CH_aH_b$), 5.66 (dd, J = 17.8, 1.2 Hz, 1H, $ArCH{=}CH_aH_b$), 6.74 (dd, J = 8.0, 1.6 Hz, 1H, ArH), 6.82 (dd, J = 17.8, 11.2 Hz, 1H, $ArCH{=}CH_2$), 6.96 (t, J = 8.0 Hz, 1H, ArH), 7.05 (dd, J = 8.0, 1.6 Hz, 1H, ArH), 7.18–7.26 (m, 1H, ArH), 7.30–7.38 (m, 2H, ArH), 7.49–7.54 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 13.9, 23.0, 25.2, 38.6, 55.7, 76.3, 81.4, 111.3, 115.5, 118.1, 124.1, 125.5, 126.5, 127.9, 131.1, 131.9, 143.8, 145.6, 152.1; EI-MS (70 eV) *m/z* (rel intensity, %) 308 (M^+-H_2O, 3), 251 (19), 164 (100), 150 (98), 135 (28), 121 (29), 107 (23), 91 (29).
11. General procedure for the preparation of 2-aroyl-3,4-dihydro-2*H*-benzopyranes (**4a–k**) from salicylaldehydes (**1a–h**) in one pot: under nitrogen, a suspension of MTPPB (4.29 g, 12 mmol) in anhydrous THF (15 mL) was treated with potassium *tert*-butoxide (1.35 g, 12 mmol) in portions. After stirring for 10 min at room temperature, to the resultant reaction mixture was added a mixture of 2-hydroxybenzaldehydes (**1a–h**) (10 mmol) and potassium *tert*-butoxide (1.23 g, 11 mmol) in THF (15 mL). The given mixture stirred at room temperature for 1 h was heated to the reflux, and then was added a solution of 2-bromoacetophenones (**2a–c**) (33 mmol) in THF (15 mL) in drops. To the resultant mixture continually stirred under reflux for 1 h was added another portion of potassium *tert*-butoxide (1.35 g, 12 mmol). The reaction mixture was kept at reflux for 0.5–1 h until the desired **4** did not increase apparently as denoted by the TLC analysis. Finally, the reaction was quenched with saturated NH_4Cl solution. Most of the THF was removed in vacuo, and the resultant mixture was extracted with EtOAc (20 mL × 4). The organic layers were combined, washed with brine, and dried with anhydrous $MgSO_4$. After filtration, the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:10) to give pure **4a** (1.11 g, 47%), **4b** (1.77 g, 66%), **4c** (1.92 g, 64%), **4d** (2.03 g, 64%), **4e** (1.69 g, 62%), **4f** (2.05 g, 67%), **4g** (1.79 g, 58%), **4h** (1.88 g, 62%), **4i** (1.21 g, 41%), **4j** (1.30 g, 48%), and **4k** (0.74 g, 33%), respectively. Selected physical and spectra data of **4b**: it was obtained as a colorless crystal, mp 91–93 °C; R_f 0.49 (ethyl acetate/*n*-hexane = 1:4); IR (KBr) ν_{max}: 3062, 2931, 2836, 1695 (C=O), 1579, 1478, 1339, 1217, 1091, 991, 903, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.18–2.27 (m, 1H, Ha-3), 2.29–2.36 (m, 1H, Hb-3), 2.69–2.76 (m, 1H, Ha-4), 2.79–2.87 (m, 1H, Hb-4), 5.56 (dd, J = 6.8, 4.0 Hz, 1H, H-2), 6.65 (dd, J = 7.6, 1.2 Hz, 1H, ArH), 6.73, (dd, J = 7.6, 1.2 Hz, 1H, ArH), 6.81(t, J = 7.6 Hz, 1H, ArH), 7.43–7.47 (m, 2H, ArH), 7.56 (tt, J = 7.6, 1.2 Hz, 1H, ArH), 8.01–8.03 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 24.2, 55.9, 77.1, 109.7, 120.1, 121.3, 122.1, 128.6, 128.8, 133.4, 134.5, 143.4, 148.3, 196.9; EIMS (70 eV) *m/z* (rel intensity, %) 268 (M+, 26), 163 (100), 105 (31); Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.11; H, 5.76.