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Efficient synthesis of halo indanones via chlorosulfonic acid mediated Friedel–Crafts cyclization of aryl propionic acids and their use in alkylation reactions

Anil K. Sharma, Amutha V. Subramani and Christopher B. Gorman*

Department of Chemistry, North Carolina State University, Box 8204, Raleigh, NC 27695-8204, USA

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Abstract—Several halo indanones were synthesized from benzyl Meldrum's acid derivatives in two steps. Although several Lewis acids are effective for the Friedel–Crafts ring-closing reaction on more electron-rich arenes, in the case of the electron-deficient arenes this chemistry is not efficient. Here it is reported that chlorosulfonic acid (used as solvent) is an efficient reagent for cyclization of electron-withdrawing arenes. These molecules are potentially useful for subsequent alkylation reactions. The selective alkylation of 5,7-dibromo indanone is demonstrated using Pd-catalyzed Grignard coupling to provide monoalkylated indanone in good yield.

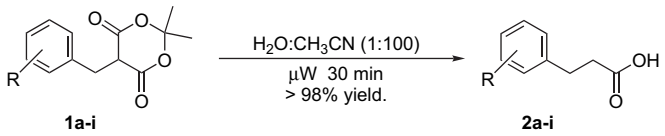
1. Introduction

Indanones are important substrates in the synthesis of many biologically active compounds including indacrinone,[1a–c] indanoyl isoleucine conjugates,[1d] indanocines[1e] and other medicinally important products.[1f–k] The most typical approach to the synthesis of indanone derivatives is via intramolecular Friedel–Crafts acylation.[2] A variety of Lewis acids catalyze this reaction including $AlCl_3$,[3] $TiCl_4$,[4] polyphosphoric acid,[5] methanesulfonic acid,[6] HF,[7] P_2O_5,[8] trifluoroacetic anhydride[9] and perfluorinated sulfonic acid resin (Nafion-H).[10] Acylation of substrates in which the aromatic ring bears electron-withdrawing substituents is generally inefficient, however. High temperatures and excess of reagents coupled with low overall yields significantly reduces the viability of this reaction.[11] Thus, it is of interest to develop conditions for the preparation of electron-deficient indanones. For example, bromo indanones are attractive intermediates in that they are amenable to subsequent metal-mediated coupling reactions.

Here, we describe a procedure that is efficient for the preparation of halo indanones. To access alkylated indanones, halo indanones are potentially useful precursors. To this end, we illustrate the selective alkylation of 5,7-dibromo indanone using Pd/Grignard coupling chemistry. Two key observations are made. First, formation of the precursor carboxylic acids via microwave irradiation of benzyl Meldrum's acid derivatives is found to be essentially quantitative. Second, chlorosulfonic acid is found to be an ideal reagent for the intramolecular acylation of electron-deficient arenes.

2. Results and discussion

Our route began with the Meldrum's acid derivatives (**1**, Scheme 1). These were prepared from benzaldehyde and Meldrum's acid via aldol condensation/reduction using triethylammonium formate following the procedure described by Tóth and Kövér.[12] These authors also reported that, at elevated temperature, the aldehyde/Meldrum's acid reaction



a: R=3,5-Br_2; **b**: R=3,5-Cl_2; **c**: R=3,5-F_2
d: R=4-CF_3; **e**: R=4-Br ; **f**: R=3-Br
g: R=4-CN; **h**: R=3,5-$(MeO)_2$; **i**: R=4-*t*-bu

Scheme 1. Synthesis of carboxylic acids from Meldrum's acid derivatives.

* Corresponding author. Tel.: +1 919 515 4252; fax: +1 919 515 8920; e-mail: chris_gorman@ncsu.edu

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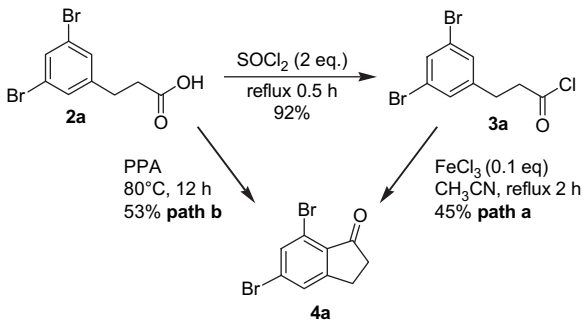
product further underwent hydrolysis and decarboxylation to afford the carboxylic acids (**2**) directly. However, we found that higher overall yields and product purity could be obtained by isolation of the Meldrum's acid derivative followed by hydrolysis and decarboxylation under microwave irradiation (Scheme 1). The reaction was completed in 30 min. The carboxylic acids were isolated by removing acetonitrile under reduced pressure. Previously Helavi et al. demonstrated a microwave-mediated hydrolysis/decarboxylation of Meldrum's acids in two steps using a poly-(4-vinyl pyridine) catalyst.[13] Here, only one step is required and no catalyst is employed.

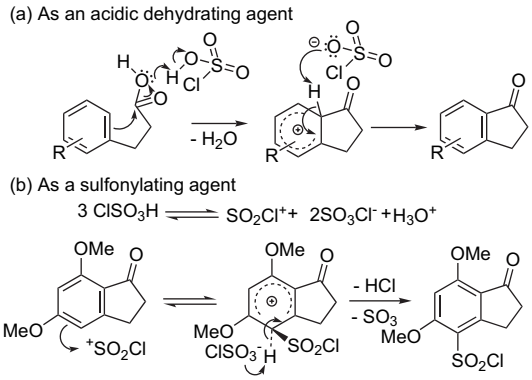
The second synthetic challenge was to cyclize the resulting carboxylic acids to form the indanones. In general, Friedel–Crafts acylation works well on arenes provided they are not very electron deficient. For example, Fillion and Fishlock[14] described the synthesis of indanones using $Sc(OTf)_3$ as the Lewis acid. This methodology worked well with electron-rich arenes, but failed to give either chloro indanone isomer from the deactivated *m*-chloro substrate. If the benzylic position of the Meldrum's acid derivative was substituted with an activating, spiropentyl group, yields increased. However, a mixture of the two indanone regioisomers was obtained.[14] In more recent work, this group cyclized the more activated 5,5-di(3-fluorobenzyl) Meldrum's acid in 93% yield, but again as a mixture of regioisomers.[15] 4,7-Dibromoindan-1-one[16] has also been synthesized from 3-(2,5-dibromo-phenyl)-propanoic acid using polyphosphoric acid but only in 51% yield. In another report, 7-bromoindan-1-one[17] was synthesized via a Friedel–Crafts acylation reaction with a low overall yield. Thus, alternative reaction conditions were explored to determine if the efficiency of the synthesis of halogen-substituted indanones was possible.

An example of the synthetic difficulties in the preparation of electron-deficient indanones is illustrated in Scheme 2. When 3-(3,5-dibromo-phenyl)-propionic acid was first converted into acid chloride using thionyl chloride as the chlorinating agent and then cyclized using $FeCl_3$ as the Lewis acid (path a), only a 45% yield of 5,7-dibromo-indan-1-one was isolated. When the same substrate was subjected to intramolecular cyclization using polyphosphoric acid (path b),[16] the product was formed only in 53% yield after heating for 12 h at 80 °C. Further, a tedious aqueous work-up was necessary to remove the polyphosphoric acid.



Scheme 2. Intramolecular cyclization of 3-(3,5-dibromo-phenyl)-propionic acid under two different conditions.

It was thought that an alternative, more acidic reagent might improve the efficiency of this chemistry. After surveying several reagents, chlorosulfonic acid was found as the generally most efficient reagent. Chlorosulfonic acid (CSA)[18] has been used as a dehydrating agent in the cyclization of phenoxypropanoic acid[19] and arylthioglycolic acids.[20] Anilinomethylenemalonates, anilinofumarates and anilinomaleates are similarly cyclized in the presence of CSA or oleum to yield quinolinecarboxylic acids and their derivatives.[21] However, there is no report of using chlorosulfonic acid for the cyclization of aryl propanoic acids with electron-withdrawing substituents. Here, we document the utility and drawbacks of CSA to prepare indanones via Friedel–Crafts acylation. The role of CSA is mechanistically illustrated in Scheme 3a.

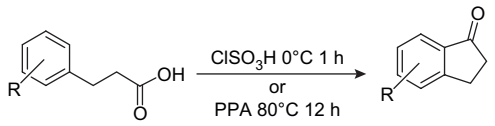


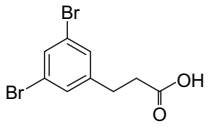
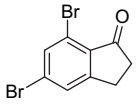
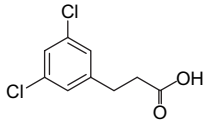
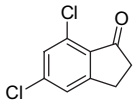
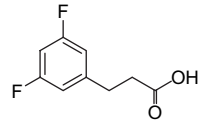
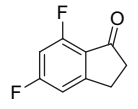
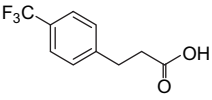
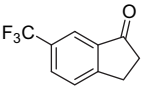
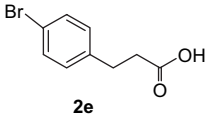
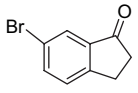
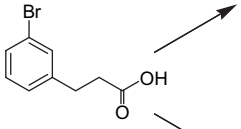
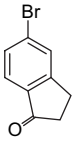
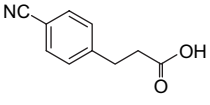
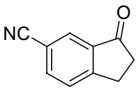
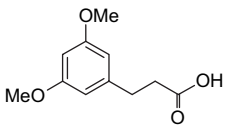
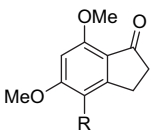
Scheme 3. Mechanisms for CSA-based dehydration and sulfonation.

CSA was used for the cyclization of 3-(3,5-dibromo-phenyl)-propionic acid and the corresponding indanone was formed in 99% yield (Table 1, entry 1). Thin-layer chromatography of the reaction mixture showed complete consumption of starting material after 1 h without the formation of any side product. Simple work-up using ice-cold water and extraction with dichloromethane furnished the indanone as the pure compound without chromatographic purification. To determine how generally this reagent could be used in the synthesis of indanones, several additional substrates were studied. The results are given in Table 1. Indeed, for many halogenated substrates (Table 1, entries 1–3, 5 and 6), CSA was the reagent of choice. When 5,7-dibromo benzyl Meldrum's acid was reacted with chlorosulfonic acid no indanone was produced.

6-Trifluoromethyl indanone (Table 1, entry 4) was obtained in only 23% yield. However, the only published synthesis of this compound[22] is from the closing of the 2-bromo-(4-trifluoromethyl) propionic acid via transmetalation of the halogen with butyl lithium[23] and thus requires more effort to achieve than the route reported here. There was no reaction of chlorosulfonic acid with 3-(4-cyano-phenyl)-propionic acid (Table 1, entry 7), indicating a lack of complete generality of this reagent for electron-deficient arenes. In the case of electron-rich arene substrates (Table 1, entries 8 and 9), sulfonylation or chlorosulfonylation of the arene ring competed with cyclization. This result is not surprising as CSA is a reagent of choice for the sulfonation or chlorosulfonation of a wide range of organic compounds (Scheme 3b).[18] However, there was no sulfonylation in the cyclization of 3-(4-*tert*-butyl-phenyl)-propionic acid (Table 1, entry 9). Except for a few examples (Table 1, entries 3, 6 and 8), use of PPA afforded moderate yields of indanones.

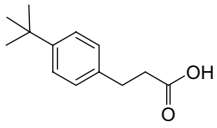
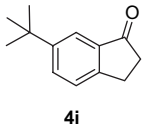
Table 1. Synthesis of indanones via chlorosulfonic acid and PPA mediated intramolecular cyclization of aryl propionic acids



	Reactant	Product	Yield (%)	
			with CSA	with PPA
1	 **2a**	 **4a**	99	53
2	 **2b**	 **4b**	99	26
3	 **2c**	 **4c**	99	84
4	 **2d**	 **4d**	23	Traces
5	 **2e**	 **4e**	98	56
6	 **2f**	 **4fi**  **4fii**	20 79	42 56
7	 **2g**	 **4g**	No reaction	No reaction
8	 **2h**	 **4h**	15[a]	97[b]

(*continued*)

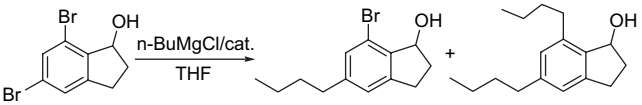
Table 1. (*continued*)

	Reactant	Product	Yield (%)	
			with CSA	with PPA
9	 **2i**	 **4i**	66	46

[a] R=SO_2Cl.
[b] R=H.

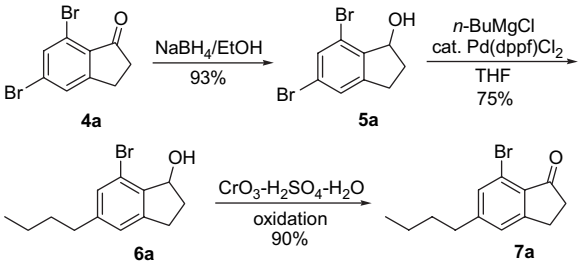
Alkylation of an aryl bromide group on 5,7-dibromoindan-1-one (**4a**) was then investigated. We plan to exploit this chemistry in the synthesis of some novel monomers and polymers in future work. 5,7-Dibromoindan-1-one (**4a**) was specifically chosen to determine both the efficiency and regioselectivity of alkylation. The compound **4a** was reduced with $NaBH_4$ in the presence of ethanol to provide indanol **5a** in 93% yield. This compound was then reacted with *n*-butylmagnesium bromide in the presence of several different metal catalysts to provide the desired indanol **6a** (Table 2). It was found that the bidentate phosphine–nickel complexes (e.g., $Ni(dppp)Cl_2$) were much less active and selective than $Pd(dppb)Cl_2$ and $Pd(dppf)_2$. Using catalytic $Pd(dppf)Cl_2$ and 3.5 equiv of Grignard reagent resulted in successful incorporation of the alkyl substituent at the 5-position of **5a** in 75% yield. Only a trace amount of dialkylated product was formed when the reaction mixture was stirred for 8 h at room temperature. Subsequent Jones oxidation of **6a** gave the desired indanone **7a** in 90% yield (Scheme 4).

Table 2. Selective alkylation of 5,7-dibromo-indan-1-ol using different metal catalysts



5a **6a** **6a'**

Catalyst	*n*-BuMgCl (equiv)	Reaction Conditions		Yield (%)	
		Temperature (°C)	Time (h)	**6a**	**6a′**
$Ni(PPh_3)_2Br_2$	6	25	72	<5	<2
$Ni(PPh_3)_2Br_2$	6	50	72	Trace	Trace
$Ni(dppp)Cl_2$	6	25	24	<10	<5
$Pd(dppb)Cl_2$	6	70	20	12	28
$Pd(dppb)Cl_2$	3.5	60	15	47	5
$Pd(dppf)Cl_2$	3.5	50	15	45	Trace
$Pd(dppf)Cl_2$	3.5	25	8	75	Trace



4a **5a** **6a** **7a**

Scheme 4. Synthesis of 7-bromo-5-butyl-indan-1-one via selective alkylation/re-oxidation.

3. Conclusions

In summary, we synthesized several halogen-substituted indanones from benzyl Meldrum's acid derivatives in two steps with high overall yields. We also studied the selective behavior of chlorosulfonic acid toward the cyclization of aryl propionic acids with different substituents. The dual behavior of chlorosulfonic acid was also observed in cyclization and sulfonylation of 3-(3,5-dimethoxy-phenyl)-propionic acid. Thus the formation of carboxylic acids from benzyl Meldrum's acid derivatives under neutral condition and intramolecular cyclization using chlorosulfonic acid make it an attractive choice for the synthesis of halogen-substituted indanones. The easy operation, short reaction time, ready availability, and low cost of reagents (both acetonitrile and chlorosulfonic acid) are another attractive features of this methodology. One of the dihalo-substituted indanones was further subjected to palladium-catalyzed Grignard coupling to furnish exclusively the monoalkylated indanone in good yield.

4. Experimental

4.1. General methods

All reactions were carried out in flame-dried glassware under a dry nitrogen atmosphere. TEAF (triethylammonium formate) was prepared freshly by dropwise addition of triethyl amine to formic acid at 0 °C. Commercial grade acetonitrile and chlorosulfonic acid were used in original form without further purification. The catalysts $Ni(PPh_3)_2Br_2$ and Ni(dppp)Cl_2 were purchased from Acros, Pd(dppb)Cl_2[24] and Pd(dppf)Cl_2[25] were prepared according to the literature methods.

^{1}H NMR spectra were referenced to residual ^{1}H shift in $CDCl_3$ (7.24 ppm). $CDCl_3$ (77.0 ppm) was used as the internal reference for ^{13}C NMR. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, br s=broad singlet.

Reactions were monitored by thin-layer chromatography (TLC) on commercial silica precoated plates with a particle size of 60 Å. Developed plates were viewed by UV lamp (254 nm). Flash chromatography was performed using 230–400 mesh silica gel. Microwave heating was performed by a microwave reactor of model The Discover instrument by CEM Corp., Matthews, NC, operating at a power of 300 W. Temperature was measured via an internal IR-sensor. Specified reaction times refer to total heating time. Ramp times are specified for each individual solvent and temperature. All reactions were performed in sealed vessels.

4.2. Procedure for the synthesis of Meldrum's acid derivatives

All Meldrum's acid derivatives were prepared according to the method reported by Tóth and Kövér.[12] Spectral data for compound **1h** matches that previously reported.[14]

4.2.1. 5-(3,5-Dibromo-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (1a). Yield: 85%; mp: 117–119 °C; IR: 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.62 (s, 3H), 1.72 (s, 3H), 3.3 (d, 2H, J=4.8 Hz), 3.70 (t, 1H, J=5.2 Hz), 7.38 (m, 2H), 7.48 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 26.8, 28.4, 30.8, 47.8, 105.4, 122.8, 131.6, 132.8, 141.2, 164.6; Mass calculated for (M^+) $C_{13}H_{12}Br_2O_4$: 389.9102, found (HRMS-EI): 389.9098.

4.2.2. 5-(3,5-Dichloro-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (1b). Yield: 71%; mp: 113–115 °C; IR: 1746 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.61 (s, 3H), 1.72 (s, 3H), 3.33 (d, 2H, J=5.0 Hz), 3.68 (t, 1H, J=5 Hz), 7.18 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 27.0, 28.4, 31.0, 47.8, 105.4, 127.5, 128.4, 134.9, 140.6, 164.6; Mass calculated for (M^+) $C_{13}H_{12}Cl_2O_4$: 302.0113, found (HRMS-EI): 302.0102.

4.2.3. 5-(3,5-Difluoro-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (1c). Yield: 67%; mp: 107–109 °C; IR: 1746 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.59 (s, 3H), 1.71 (s, 3H), 3.38 (d, 2H, J=4.8 Hz), 3.69 (t, 1H, J=5 Hz), 6.62 (m, 1H), 6.83 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 26.9, 28.4, 31.3, 47.7, 102.7, 105.3, 112.6, 112.8, 140.9, 161.2, 164.6; Mass calculated for (M^+) $C_{13}H_{12}F_2O_4$: 270.0704, found (HRMS-EI): 270.0694.

4.2.4. 2,2-Dimethyl-5-(4-trifluoromethyl-benzyl)-[1,3]dioxane-4,6-dione (1d). Yield: 77%; mp: 142–144 °C; IR: 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.55 (s, 3H), 1.69 (s, 3H), 3.47 (d, 2H, J=5 Hz), 3.71 (t, 1H, J=5 Hz), 7.41 (m, 2H), 7.47 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 27.0, 28.4, 31.5, 47.9, 105.3, 125.4, 125.5, 130.2, 141.2, 164.8; Mass calculated for (M^+) $C_{14}H_{13}F_3O_4$: 302.0766, found (HRMS-EI): 302.0766.

4.2.5. 5-(4-Bromo-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (1e). Yield: 63%; mp: 143–145 °C; IR: 1737 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.53 (s, 3H), 1.69 (s, 3H), 3.36 (d, 2H, J=5 Hz), 3.68 (t, 1H, J=5 Hz), 7.16 (m, 2H), 7.36 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 27.1, 28.4, 31.3, 47.9, 105.2, 121.2, 131.6, 136.1, 165.0; Mass calculated for (M^+) $C_{13}H_{13}BrO_4$: 311.9997, found (HRMS-EI): 311.9987.

4.2.6. 5-(3-Bromo-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (1f). Yield: 75%; mp: 97–99 °C; IR: 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.55 (s, 3H), 1.70 (s, 3H), 3.37 (d, 2H, J=5 Hz), 3.68 (t, 1H, J=5 Hz), 7.10 (t, 1H, J=8 Hz), 7.21 (d, 1H, J=8 Hz), 7.32 (d, 1H, J=8 Hz), 7.43 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 27.1, 28.4, 31.4, 48.0, 105.3, 122.5, 128.5, 130.1, 130.4, 132.7, 139.6, 164.9; Mass calculated for (M^+) $C_{13}H_{13}BrO_4$: 311.9997, found (HRMS-EI): 311.9985.

4.2.7. 4-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl-methyl)-benzonitrile (1g). Yield: 71%; mp: 140–142 °C; IR: 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.59 (s, 3H), 1.71 (s, 3H), 3.46 (d, 2H, J=5 Hz), 3.75 (t, 1H, J=5 Hz), 7.39 (m, 2H), 7.52 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 26.9, 28.3, 31.6, 47.6, 105.3, 111.0, 118.6, 130.7, 132.2, 142.6, 164.7; Mass calculated for (M^+) $C_{14}H_{13}NO_4$: 259.0845, found (HRMS-EI): 259.0852.

4.2.8. 5-(4-*tert*-Butyl-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (1i). Yield: 75%; mp: 114–116 °C; IR: 1751 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.22 (s, 9H), 1.39 (s, 3H),

1.66 (s, 3H), 3.39 (d, 2H, J=4.9 Hz), 3.69 (t, 1H, J=5 Hz), 7.20 (m, 2H), 7.26 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 27.2, 28.4, 31.3, 31.7, 34.4, 48.2, 105.2, 125.5, 129.4, 134.2, 150.1, 165.4; Mass calculated for (M^+) $C_{17}H_{22}O_4$: 290.1518, found (HRMS-EI): 290.1506.

4.3. General procedure for the preparation of carboxylic acids

To 1 mmol of benzyl Meldrum's acid derivative was added 25 mL of acetonitrile followed by 0.25 mL of water. The solution was subjected to microwave irradiation at 120 °C for 30 min (150 psi, 300 W, run time 5 min, hold time 30 min). After the designated time the solution was cooled to room temperature. Acetonitrile was removed under reduced pressure and carboxylic acid was directly used for the next step of indanone synthesis.

Compounds **2c**,[11d] **2d**,[26] **2e**,[11b] **2f**,[11a] **2g**,[26] **2h**,[27] and **2i**[26] match the previously reported spectra.

4.3.1. 3-(3,5-Dibromo-phenyl)-propionic acid (2a). Yield: 100%; mp: 61–63 °C; IR: 1707 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.61 (t, 2H, J=7 Hz), 2.84 (t, 2H, J=7 Hz), 7.24 (m, 2H), 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 29.8, 34.8, 123.0, 130.2, 132.2, 144.0, 177.9; Mass calculated for (M^+) $C_9H_8Br_2O_2$: 305.8891, found (HRMS-EI): 305.8888.

4.3.2. 3-(3,5-Dichloro-phenyl)-propionic acid (2b). Yield: 100%; appearance: viscous liquid; IR: 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.62 (t, 2H, J=7.5 Hz), 2.84 (t, 2H, J=7.5 Hz), 7.04 (m, 2H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 29.9, 34.8, 126.7, 127.0, 135.1, 143.3, 178.3; Mass calculated for (M^+) $C_9H_8Cl_2O_2$: 217.9901, found (HRMS-EI): 217.9898.

4.4. General procedure for the synthesis of indanones

4.4.1. Using chlorosulfonic acid. To 1 mmol of the carboxylic acid was added 3.0 mL of chlorosulfonic acid. The solution was stirred for 1 h at 0 °C. At the end of reaction, the mixture was quenched in 5 mL of ice-cold water and extracted with 2×5 mL of dichloromethane. The combined organic layers were washed with 5 mL of $NaHCO_3$ solution and dried over Na_2SO_4. Dichloromethane was removed under reduced pressure to furnish indanones. All analytical data were obtained without any further purification.

4.4.2. Using polyphosphoric acid. All indanones were prepared according to the method reported by Metz.[28]

Compounds **4c**,[11d] **4e**,[11b] **4fi**,[17] **4fii**,[11a] **4h**[14,27] (R=H) and **4i**[29] match the previously reported spectra.

4.4.3. 5,7-Dibromo-indan-1-one (4a). Yield: 99%; mp: 147–149 °C; IR: 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.67 (t, 2H, J=7 Hz), 3.02 (t, 2H, J=7 Hz), 7.53 (s, 1H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.7, 36.9, 120.2, 129.0, 129.4, 133.3, 135.1, 158.7, 202.6; Mass calculated for (M^+) $C_9H_6Br_2O$: 287.8785, found (HRMS-EI): 287.8783.

4.4.4. 5,7-Dichloro-indan-1-one (4b). Yield: 99%; mp: 97–99 °C; IR: 1708 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.67 (t, 2H, J=5.8 Hz), 3.02 (t, 2H, J=5.8 Hz), 7.25 (s, 1H), 7.30 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 25.0, 36.9, 125.4, 129.2, 131.5, 132.7, 140.9, 158.3, 202.2; Mass calculated for (M^+) $C_9H_6Cl_2O$: 199.9796, found (HRMS-EI): 199.9802.

4.4.5. 6-Trifluoromethyl-indan-1-one (4d). Yield: 23%; mp: 124–126 °C; IR: 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.70 (t, 2H, J=5.8 Hz), 3.16 (t, 2H, J=5.8 Hz), 7.56 (d, 1H, J=7.8 Hz), 7.77 (d, 1H, J=7.8 Hz), 7.95 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 25.9, 36.3, 121.0, 127.4, 131.0, 137.5, 158.2, 205.5; Mass calculated for (M^+) $C_{10}H_7F_3O$: 200.0449, found (HRMS-EI): 200.0447.

4.4.6. 4-Chlorosulfanyl-5,7-dimethoxy-indan-1-one (4h, R=SO_2Cl). Yield: 15%; mp: 174–176 °C (dec); IR: 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.62 (t, 2H, J=7 Hz), 3.41 (t, 2H, J=7 Hz), 4.00 (s, 3H), 4.09 (s, 3H), 6.39 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 27.0, 36.3, 56.7, 57.4, 94.5, 119.6, 122.1, 159.7, 164.3, 165.1, 201.4; Mass calculated for (M^+) $C_{11}H_{11}ClO_5S$: 290.0016, found (HRMS-EI): 290.0002.

4.4.7. 5,7-Dibromo-indan-1-ol (5a). Sodium borohydride (0.352 g, 9.26 mmol) was added for15 min to a cooled (0 °C) solution of ethyl alcohol (50 mL), containing **4a** (0.895 g, 3.09 mmol). After addition of $NaBH_4$, ice bath was removed and the reaction mixture was stirred for 1 h and the solution was then acidified with 2 N hydrochloric acid. The solution was extracted with diethyl ether (4×50 mL) and the organic layer was dried with sodium sulfate. After evaporation, the crude product **5a** was purified by column chromatography using ethyl acetate/hexane (1:6) as eluent. Yield: 93%; appearance: viscous liquid; IR: 3334 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.07 (m, 1H), 2.26 (s, 1H), 2.33 (m, 1H), 2.81 (m, 1H), 3.15 (m, 1H), 5.22 (d, 1H, J=6.5 Hz), 7.28 (s, 1H), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 30.9, 33.5, 76.0, 120.3, 122.9, 127.3, 132.3, 143.1, 148.0; Mass calculated for (M^+) $C_9H_8Br_2O$: 289.8942, found (HRMS-EI): 288.8870.

4.4.8. 7-Bromo-5-butyl-indan-1-ol (6a). To a solution of **5a** (1.45 g, 4.96 mmol) and Pd(dppf)Cl_2 (0.357 g, 0.496 mmol) in 50 mL of THF, was added dropwise, *n*-butylmagnesium chloride (2.025 g,, 17.38 mmol, 20 wt % solution in THF/toluene) at 0 °C. After complete addition of Grignard reagent, ice bath was removed, and solution was stirred for 8 h at room temperature. The mixture was then quenched with ice-cold 1 N hydrochloric acid (50 mL). Ether (100 mL) was then added and the organic phase was separated, washed with water (50 mL), and dried with sodium sulfate. After evaporation, the crude product **6a** was purified by column chromatography using ethyl acetate/hexane (1:6) as eluent. Yield: 75%; appearance: viscous liquid; IR: 3369 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, J=7.5 Hz), 1.28 (m, 2H), 1.51 (m, 2H), 2.04 (m, 1H), 2.32 (m, 1H), 2.50 (t, 2H, J=8 Hz), 2.77 (m, 1H), 3.12 (m, 1H), 5.23 (d, 1H, J=6.5 Hz), 6.94 (s, 1H), 7.12 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.9, 22.2, 30.8, 33.5, 35.2, 76.4, 119.5, 124.2, 129.9, 141.3, 145.8, 146.3; Mass calculated for (M^+) $C_{13}H_{17}BrO$: 268.0463, found (HRMS-EI): 268.0463.

4.4.9. 7-Bromo-5-butyl-indan-1-one (7a). To a solution of **6a** (1 g, 3.74 mmol) in 10 mL acetone at 0 °C, was added

Jones reagent dropwise until the color of solution became orange. The reaction mixture was stirred for 30 min at 0 °C and subsequently monitored by TLC. After completion of reaction as monitored by TLC (EtOAc/hexane, 6:1), 10 mL of water was added, followed by the addition of 10 mL of diethyl ether. The organic layer was separated, whereas the aqueous layer was further extracted with 3×10 mL portions of diethyl ether. After evaporation, the crude product **7a** was purified by column chromatography using ethyl acetate/hexane (1:6) as eluent. Yield: 90%; mp: 67–69 °C; IR: 1717 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, J=7.2 Hz), 1.31 (m, 2H), 1.53 (m, 2H), 2.58 (t, 2H, J=7.6 Hz), 2.66 (t, 2H, J=6.2 Hz), 2.99 (t, 2H, J=6.2 Hz), 7.14 (s, 1H), 7.28 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.8, 22.2, 24.7, 33.0, 35.4, 37.0, 119.1, 125.5, 132.0, 132.6, 151.5, 158.0, 203.3; Mass calculated for (M^+) $C_{13}H_{15}BrO$: 266.0306, found (HRMS-EI): 266.0307.

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Supplementary data

^1H and ^{13}C spectra for all products. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.065.

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