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Ortho-Selective Side-Chain Nitration of α-Bromoacyl-polymethylbenzenes and its Application to the Syntheses of Indan-1-one and Inden-1-one Derivatives

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Key Words: α-Bromoacylpolymethylbenzene; Ortho-selective Side-chain Nitration; Intramolecular S_N Reaction; Indan-1-one; Inden-1-one

Abstract: α-Bromoacylpolymethylbenzenes **2a-m** react with fuming nitric acid in acetic anhydride to give 2-(nitromethyl)-(α-bromoacyl)polymethylbenzenes **3a-m** in good isolated yields. Compounds **3a-j** undergo the intramolecular nucleophilic substitution/cyclization in the presence of 1 equiv. of base either in benzene or *N,N*-dimethylformamide (DMF) to provide the corresponding substituted 3-nitroindan-1-ones **4a-j** in quantitative yields as mixtures of diastereomers (*cis* and *trans*). The *cis/trans* ratios of 4 vary with the steric factor and the nature of solvent: *cis* < *trans* in benzene, whereas *cis* > *trans* in DMF. On the contrary, 3-unsubstituted 2-nitromethyl compounds **3k-m** afford 3,2-benzoxazepin-5(4*H*)-ones **7k-m** under the same reaction condition. On the other hand, the reactions of **3a-j** in the presence of 2 equiv. of base give the substituted inden-1-ones **5** in satisfactory isolated yields.

Introduction

Aliphatic nitro compounds constitute a group of versatile intermediates to be utilized as the building blocks in organic syntheses. In general, striking characteristics in the reactions of these materials mainly consist of the following two aspects: the carbon-carbon bond formation under mild reaction conditions, and the conversion of the nitro group into other functionalities. The first aspect is derived from the electron-withdrawing character of the nitro group through the adjacent carbon-nitrogen bond, while the second one from the function of its nitrogen atom as the electron-acceptor.[2]

The regioselective side-chain functionalization directed by the acyl group[3] has formerly been investigated extensively, but only from the theoretical interest in the past.[4] In this respect, previously we have first reported that acylpolymethylbenzenes are nitrated selectively at the methyl group *ortho* to the acyl group to give 2-(nitromethyl)-acylbenzenes, by use of a mixture of fuming nitric acid in acetic anhydride.[5] The resulting arylnitromethanes readily generate the reactive carbanions by the action of mild bases[6] and can subsequently be converted into various functionalities.[7] Second, we have applied the side-chain nitration method to the convenient syntheses of substituted phthalic acid derivatives from the corresponding benzoic acids.[5] Third, we have shown the side-chain nitration of the alkenoylpolymethylbenzenes followed by the intramolecular Michael addition reaction with base catalysts to give 4-nitro-1-tetralone derivatives.[8]

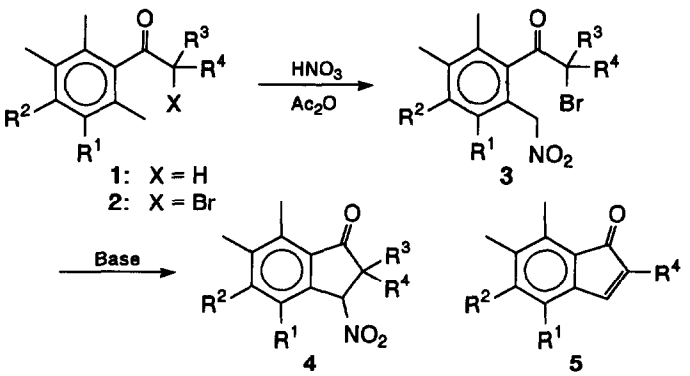
These findings led us to the present study involving the syntheses of indan-1-ones[9] and inden-1-ones.[9f,10] Structures of these materials are often found in synthons of natural products and their related biologically active counterparts,[9e,11] and have thus far been prepared by means of Friedel-Crafts alkylation/acylation reactions.[12] These previously existing procedures are, however, inappropriate to the syntheses of polyfunctionalized indan/inden-1-one derivatives, since reaction conditions required are often very severe, and therefore, inevitably induce the rearrangement of substituents in aromatic rings.[13]

In this paper, we wish to report the side-chain nitration-based significant solution for it, and some related discoveries, too.

Results and Discussion

We present the extention of the regioselective side-chain nitration method towards the construction of 3-nitroindan-1-ones **4** and inden-1-ones **5** from methyl-substituted-α-bromoacylbenzenes **2**, for the former of which no report has been found to our knowledge. According to our previous observations,[5,8,14] the nitration

Scheme 1



	R^1	R^2	R^3	R^4
a	CH_3	CH_3	H	H
b	CH_3	CH_3	H	CH_3
c	CH_3	CH_3	CH_3	CH_3
d	CH_3	CH_3	H	CH_2CH_3
e	CH_3	CH_3	H	$CH_2CH_2CH_3$
f	CH_3	CH_3	H	$CH(CH_3)_2$
g	CH_3	CH_3	H	$C(CH_3)_3$
h	CH_3	CH_3	H	$CH(CH_2)_4$
i	CH_3	CH_3	$-(CH_2)_5-$	
j	CH_3	CH_3	H	C_6H_5
k	H	CH_3	H	CH_3
l	H	OCH_3	H	CH_3
m	H	CH_3	CH_3	CH_3

of α-bromoacylbenzenes having the methyl substituents either at 2- or 5-position afford the 2-(nitromethyl)-α-bromoacylbenzenes **3**. Compounds **3** have bromoalkyl groups nearby the nitromethyl group, therefore, the intramolecular nucleophilic substitution reactions between both groups occur on treatment of **3** with bases. For these reasons, in the present study, the nitration of acylpentamethylbenzenes **3** having a variety of α-bromoacyl groups has been undertaken to confirm the directing effect of α-bromoacyl groups in the primary nitration. Then, the intramolecular nucleophilic substitution of the resulting nitro compounds **3** is investigated in the presence of bases to give compounds **4** and **5**. The entire reaction sequence is outlined in Scheme 1.

Nitration of α-bromoacylbenzenes. The nitration of various α-bromoacylpentamethylbenzenes **2a-j** is carried out using a mixture of fuming nitric acid in acetic anhydride. For example, 2,3,4,5,6-pentamethyl-1-(α-bromopropionyl)benzene (**2b**) is allowed to react with 2 equiv. of fuming nitric acid in acetic anhydride at 0 - 5 °C for 2 h. The crude product obtained after the work-up by hydrolysis (see Experimental Section) is analyzed by HPLC on silica gel, using hexane/ethyl acetate (8v/2v) as an eluent. The example HPLC chart for crude **3b** is shown as Fig. 1.

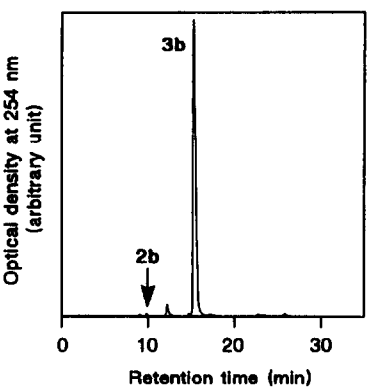
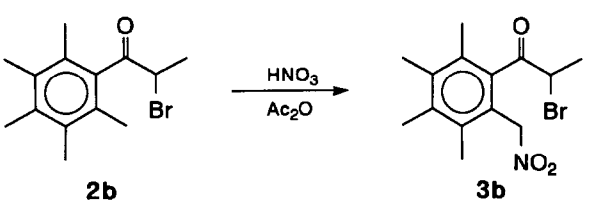


Fig. 1. The example HPLC chart for the crude product (**3b**) obtained in the nitration of **2b** by use of fuming nitric acid/acetic anhydride mixture.

The above HPLC chart exhibits that the nitration proceeds specifically to give an almost single compound. Recrystallization of the crude material from cyclohexane gives 2-(nitromethyl)-3,4,5,6-tetramethyl-1-(α-bromopropionyl)benzene (**3b**) in 77% yield (Scheme 2).

Scheme 2



2b **3b**

In similar procedures to those described above, the nitration of a variety of α-bromoacylbenzenes **3a-j** is carried out using the fuming nitric acid-acetic anhydride system to afford the corresponding 2-(nitromethyl)-α-bromoacylbenzenes (**3a-j**) in satisfactory isolated yields. Results of the side-chain nitration and representative

physical data of products are summarized in Tables 1 and 2. The sites of side-chain nitration are easily determined by the decrement of methyl proton signal intensities (at 2- and 6-positions) in their ^{1}H NMR spectra; these signals appear at higher magnetic fields compared with other methyl proton signals and therefore easily distinguished, due to the anisotropic effect of the sterically twisted carbonyl function from the plane of the benzene ring.[3b,5,8] The methylene proton signals of 2-nitromethyl groups are observed as the two sets of doublets having the large geminal coupling constants (J = 14 - 16 Hz) in the region of 4.95 - 5.60 ppm (δ scale).[15] This indicates the restriction of the free C-C bond rotation adjacent to the methylene moiety of nitromethyl groups, due to the steric hindrance effected by the nearby α-bromoacyl groups.

Table 1. Analytical Data of Compounds 3.

Compd	Yield (%)	mp(°C)	Formula	Crystal Form (Recryst.Solv.)	Found(%)(Calcd(%)) C	H	N
3a	76	148-149	$C_{13}H_{16}NO_3Br$	white plates (EtOH)	49.73 (49.70)	5.43 (5.13)	4.70 (4.46)
3b	77	130-131	$C_{14}H_{18}NO_3Br$	white prisms (cyclohexane)	51.44 (51.23)	5.74 (5.53)	4.32 (4.27)
3c	54	102-103	$C_{15}H_{20}NO_3Br$	white needles (MeOH)	52.43 (52.64)	6.07 (5.89)	4.11 (4.09)
3d	70	119-120	$C_{15}H_{20}NO_3Br$	white needles (*n*-hexane)	52.52 (52.64)	5.95 (5.89)	4.33 (4.09)
3e	64	72-73	$C_{16}H_{22}NO_3Br$	white prisms (90% MeOH)	53.68 (53.94)	6.33 (6.22)	4.01 (3.93)
3f	70	106-107	$C_{16}H_{22}NO_3Br$	white prisms (MeOH)	53.58 (53.94)	6.34 (6.22)	3.81 (3.93)
3g	70	124-125	$C_{17}H_{24}NO_3Br$	white prisms (90% MeOH)	55.01 (55.14)	6.52 (6.53)	3.71 (3.78)
3h	73	117-118	$C_{18}H_{24}NO_3Br$	white prisms (MeOH)	56.32 (56.55)	6.56 (6.33)	3.59 (3 66)
3i	59	113-114	$C_{18}H_{24}NO_3Br$	white prisms (MeOH)	56.79 (56.55)	6.49 (6.33)	3.79 (3.66)
3j	63	135-136	$C_{19}H_{20}NO_3Br$	white prisms (EtOH)	58.55 (58.47)	5.32 (5.17)	3.63 (3.59)
3k	66[a]	93-94	$C_{13}H_{16}NO_3Br$	white prisms (*n*-hexane)	49.67 (49 70)	5.12 (5.13)	4.37 (4.46)
3l	87	111-112	$C_{13}H_{16}NO_4Br$	white prisms (*n*-hexane)	47.00 (47.29)	5.14 (4.88)	4.38 (4.24)
3m	61[b]	59-60	$C_{14}H_{18}NO_3Br$	white prisms (90% MeOH)	51.38 (51.23)	5.49 (5.53)	4.22 (4.27)

[a]Compound **6k** is obtained in 18% yield [b]Compound **6m** is obtained in 22% yield

Table 2. Spectral Data of Compounds 3.

Compd	^{1}H NMR ($CDCl_3$) δ_{ppm}			IR (KBr)	M^+ (m/z)
	ring CH_3	CH_2NO_2	others	$\nu_{cm^{-1}}$	
3a	2.22 (s, 3H) 2.26 (s, 3H) 2.27 (s, 3H) 2.28 (s, 3H)	5.46 (s, 2H)	4.41 (s, 2H)	1713 (C=O) 1560 (NO_2) 1363 (NO_2)	266[a,b,c]
3b	2.20 (s, 3H) 2.23 (s, 3H) 2.26 (s, 3H) 2.29 (s, 3H)	5.41 (d, 1H, J = 17 Hz) 5.52 (d, 1H, J = 17 Hz)	1.89 (d, 3H, J = 7 Hz) 4.84 (q, 1H, J = 7 Hz)	1699 (C=O) 1554 (NO_2) 1370 (NO_2)	327[c]
3c	2.14 (s, 3H) 2.19 (s, 3H) 2.25 (s, 3H) 2.28 (s, 3H)	5.54 (d, 1H, J = 17 Hz) 5.62 (d, 1H, J = 17 Hz)	1.86 (s, 3H) 2.05 (s, 3H)	1702 (C=O) 1548 (NO_2) 1364 (NO_2)	341[c]
3d	2.20 (s, 6H) 2.26 (s, 3H) 2.29 (s, 3H)	5.43 (d, 1H, J = 17 Hz) 5.53 (d, 1H, J = 17 Hz)	1.14 (t, 3H, J = 7 Hz) 2.08-2.20 (m, 2H) 4.67 (dd, 1H, J = 5 & 9 Hz)	1696 (C=O) 1550 (NO_2) 1369 (NO_2)	341[c]
3e	2.22 (s, 3H) 2.23 (s, 3H) 2.26 (s, 3H) 2.29 (s, 3H)	5.42 (d, 1H, J = 16 Hz) 5.53 (d, 1H, J = 16 Hz)	0.99 (t, 3H, J = 7 Hz) 1.40-1.77 (m, 1H) 2.08 (q, 2H, J = 7 Hz) 4.74 (t, 1H, J = 7 Hz)	1686 (C=O) 1555 (NO_2) 1368 (NO_2)	356[a,d]
3f	2.22 (s, 3H) 2.26 (s, 6H) 2.29 (s, 3H)	5.41 (d, 1H, J = 17 Hz) 5.51 (d, 1H, J = 17 Hz)	1.13 (d, 3H, J = 5 Hz) 1.16 (d, 3H, J = 5 Hz) 2.33-2.41 (m, 1H) 4.71 (d, 1H, J = 6 Hz)	1694 (C=O) 1552 (NO_2) 1368 (NO_2)	309[a,e,c]
3g	2.22 (s, 3H) 2.24 (s, 3H) 2.28 (s, 3H) 2.30 (s, 3H)	5.37 (d, 1H, J = 16 Hz) 5.55 (d, 1H, J = 16 Hz)	1.28 (s, 9H) 4.71 (s, 1H)	1696 (C=O) 1553 (NO_2) 1368 (NO_2)	323[a,e,c]
3h	2.22 (s, 3H) 2.26 (s, 6H) 2.29 (s, 3H)	5.40 (d, 1H, J = 16 Hz) 5.53 (d, 1H, J = 16 Hz)	1.30-2.02 (m, 8H) 2.55-2.69 (m, 1H) 4.80 (d, 1H, J = 7 Hz)	1699 (C=O) 1555 (NO_2) 1370 (NO_2)	382[a,d]
3i	2.19 (s, 6H) 2.25 (s, 3H) 2.28 (s, 3H)	5.60 (s, 2H)	1.14-2.43 (m, 10H)	1698 (C=O) 1555 (NO_2) 1368 (NO_2)	381[c]
3j	2.13 (s, 6H) 2.24 (s, 3H) 2.27 (s, 3H)	5.20 (br. s, 2H)	5.73 (s, 1H) 7.34-7.36 (m, 3H) 7.49-7.51 (m, 2H)	1702 (C=O) 1550 (NO_2) 1362 (NO_2)	343[a,e]
3k	2.22 (s, 3H) 2.24 (s, 3H) 2.36 (s, 3H)	5.30 (d, 1H, J = 15 Hz) 5.38 (d, 1H, J = 15 Hz)	1.90 (d, 3H, J = 7 Hz) 4.87 (q, 1H, J = 7 Hz) 7.16 (s, 1H)	1695 (C=O) 1554 (NO_2) 1374 (NO_2)	267[a,e]

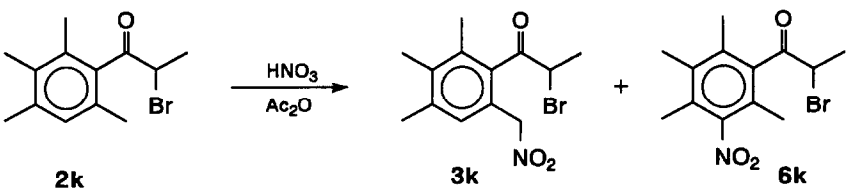
Table 2. (continued)

Compd	^{1}H NMR ($CDCl_3$) δ_{ppm}			IR (KBr)	M^+ (m/z)
	ring CH_3	CH_2NO_2	others	$\nu_{cm^{-1}}$	
3l	2.18 (s, 3H) 2.24 (s, 3H)	5.34 (d, 1H, J = 15 Hz) 5.38 (d, 1H, J = 15 Hz)	1.90 (d, 3H, J = 7 Hz) 3.88 (s, 3H) 4.88 (q, 1H, J = 7 Hz) 6.81 (s, 1H)	1688 (C=O) 1552 (NO_2) 1374 (NO_2)	329[c]
3m	2.04 (s, 3H) 2.18 (s, 3H) 2.21 (s, 3H) 2.34 (s, 3H)	5.39 (d, 1H, J = 15 Hz) 5.52 (d, 1H, J = 15 Hz)	1.90 (s, 3H) 7.15 (s, 1H)	1703 (C=O) 1578 (NO_2) 1369 (NO_2)	281[a,e]

[a] M^+ was not observed. [b] m/z = M^+ - 46 (NO_2) -1. [c] Isotopic peak by ^{81}Br was also observed. [d] m/z = M^+ + 1. [e] m/z = M^+ - 46 (NO_2).

On the other hand, the nitration of compounds **2k-m**, having one unsubstituted position (*meta*) in benzene rings, also give 2-(nitromethyl) compounds (**3k-m**) as the major product along with small amounts of the conventional ring-nitrated isomers.[14] For example, the nitration of 2,4,5,6-tetramethyl-(α-bromopropionyl)-benzene (**2k**) with fuming nitric acid in acetic anhydride affords the crude material of which HPLC chart is shown as Fig. 2. The chromatographic separation of the crude material obtained above gives 2-(nitromethyl)-4,5,6-trimethyl-1-(α-bromopropionyl)benzene (**3k**) and 3-nitro-4,5,6-trimethyl-1-(α-bromopropionyl)benzene (**6k**), in the isolated yields of 66% and 18%, respectively (Scheme 3). The nitration of compounds **2l-m** also give the 2-nitromethyl compounds **3l-m**, accompanied by conventional ring-nitrated isomers **6l-m**.

Scheme 3



2k **3k** **6k**

These results indicate that the nitronium ion preferentially attacks the methyl-substituted 5-positions of these substrates rather than the unsubstituted 3-position. They are in accordance with the reaction mechanism giving the side-chain nitrated product at the methyl group *ortho* to the acyl group.[4,14,16] They can also be explained by the HOMO electron densities, which are calculated in 2,4,5,6-tetramethyl-1-(α-bromoacetyl)-benzene, show their maximum at the ring carbon of 5-position.[17]

Intramolecular S_N reaction of 3. Compounds **3** at once possess the nitromethyl group as the nucleophile (carbanion) precursor, and the bromoalkyl group as the electrophilic center. Therefore, they readily undergo the intramolecular cyclization on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or triethylamine (TEA) in benzene or *N,N*-dimethylformamide (DMF) to give the 2-substituted 4,5,6,7-tetramethylindan-1-ones (**4a-j**). For example, 2-(nitromethyl)-3,4,5,6-tetramethyl-1-(α-bromopropionyl)benzene (**3b**) reacts in the presence of 1 equiv. of DBU in benzene at 25 °C for 5 h to afford a mixture (in quantitative yield) of diastereomers of

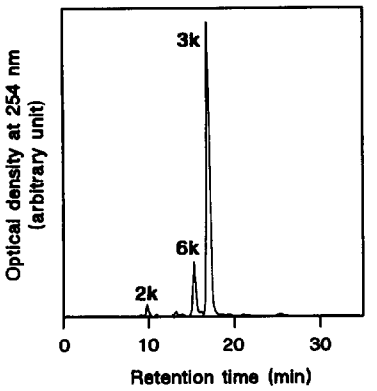
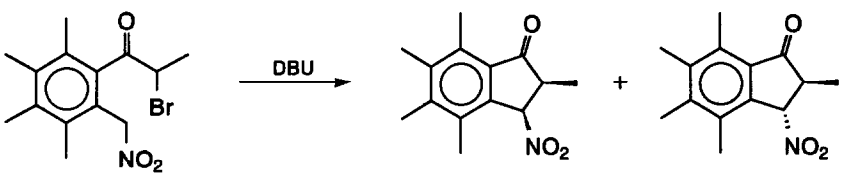


Fig. 2. The example HPLC chart for the crude product (**3k**) obtained in the nitration of **2k** by use of fuming nitric acid/acetic anhydride mixture.

2,4,5,6,7-pentamethylindan-1-one (**4b**), which is separated into *cis*-**4b** and *trans*-**4b** in 35% and 45% yields, respectively (Scheme 4).

Scheme 4



3b *cis*-**4b** *trans*-**4b**

Reactions of **3a-j** are carried out in similar procedures to that described above. The isolated yields and physical data of products **4a-j** are summarized in Tables 3 and 4, respectively. The steric conformation of the cyclized products are determined by their characteristic ^{1}H NMR chemical shifts for the methine (C<u>H</u>R^4) or the substituent (R^4) protons. For example, the multiplet (δ scale; 2.99 - 3.04 ppm) assigned as the methine proton (C<u>H</u>CH$_3$) of *trans*-**4b** is shielded over the corresponding proton signal (3.03 - 3.07 ppm) in *cis*-**4b**, as a consequence of the anisotropic effect by the nitro group located in the same side of the five-membered ring. The methine protons assigned as the C<u>H</u>NO$_2$ of compounds **4** are observed in the region of 5.76 - 6.36 ppm. The signals assigned as the 7-methyl protons appear at lower fields (in the region of 2.63 - 2.67 ppm) than those of the corresponding protons of compounds **3**, indicating the increase in the coplanarity of the methyl group with the carbonyl group effected by the cyclization.

The ratios of diastereomers in the cyclization products vary considerably with reaction solvents. The *cis*/*trans* ratios of **4** are listed in Table 5, together with reaction solvents and bases in use.

Table 3. Analytical Data of Compounds 4.

Compd	Yield (%)	mp(°C)	Formula	Crystal Form (Recryst.Solv.)	Found(%)(Calcd(%)) C	H	N
4a	88	136-137	$C_{13}H_{15}NO_3$	white needles (cyclohexane)	66.67 (66.94)	6.65 (6.48)	6.27 (6.00)
cis-**4b**	35	122-123	$C_{14}H_{17}NO_3$	white powder (80% MeOH)	67.87 (68.00)	6.99 (6.93)	5.36 (5.66)
trans-**4b**	45	141-142	$C_{14}H_{17}NO_3$	white needles (80% MeOH)	67.84 (68.00)	7.03 (6.93)	5.37 (5.66)
4c	88	131-132	$C_{15}H_{19}NO_3$	white prisms (*n*-hexane)	69.20 (68.94)	7.54 (7.33)	5.35 (5.36)
cis-**4d**	13	89-90	$C_{15}H_{19}NO_3$	yellowish needles (*n*-hexane)	69.22 (68.94)	7.61 (7.33)	5.60 (5.36)
trans-**4d**	52	180-181	$C_{15}H_{19}NO_3$	white needles (*n*-hexane)	68.77 (68.94)	7.56 (7.33)	5.65 (5.36)
cis-**4e**	13	87-88	$C_{16}H_{21}NO_3$	yellowish needles (80% MeOH)	69.60 (69.79)	7.61 (7.69)	4.94 (5.09)
trans-**4e**	67	177-178	$C_{16}H_{21}NO_3$	white wool-like (EtOH)	69.75 (69.79)	7.52 (7.69)	5.00 (5.09)
cis-**4f**	42	117-118	$C_{16}H_{21}NO_3$	white plates (90% MeOH)	70.09 (69.79)	7.74 (7.69)	4.89 (5.09)
trans-**4f**	30	198-199	$C_{16}H_{21}NO_3$	white wool-like (EtOH)	69.93 (69.79)	7.95 (7.69)	4.86 (5.09)
trans-**4g**	100[a]	154-155	$C_{17}H_{23}NO_3$	white needles (*n*-hexane)	70.27 (70.56)	7.84 (8.01)	4.64 (4.84)
cis-**4h**	38	123-124	$C_{18}H_{23}NO_3$	white needles (EtOH)	71.87 (71.73)	7.74 (7.69)	4.64 (4.65)
trans-**4h**	46	230-231	$C_{18}H_{23}NO_3$	white wool-like (EtOH)	71.54 (71.73)	7.72 (7.69)	4.51 (4.65)
4i	100	133-134	$C_{18}H_{23}NO_3$	white needles (90% MeOH)	71.77 (71.73)	7.84 (7.69)	4.39 (4.65)
trans-**4j**	48[b,c]	162-163	$C_{19}H_{19}NO_3$	yellowish needles (MeOH)	73.48 (73.77)	6.45 (6.19)	4.54 (4.53)

[a] *Cis*-**4g** is not formed. [b] The reaction is carried out with 0.5 equiv. of Na_2CO_3 in 80% aq. acetone at 0 °C for 24 h. [c] Trace amount of *cis*-**4j** is isolated.

Table 4. Spectral Data of Compounds 4.

Compd	^{1}H NMR ($CDCl_3$) δ_{ppm}			IR (KBr)	M^+ (m/z)
	ring CH_3	CHR^4	others	$\nu_{cm^{-1}}$	
4a	2.28 (s, 3H) 2.31 (s, 6H) 2.66 (s, 3H)	3.07-3.11 (m, 2H)	6.19 (dd, 1H, J = 7 & 3 Hz)	1708 (C=O) 1541 (NO_2) 1367 (NO_2)	187[a,b]
cis-**4b**	2.25 (s, 3H) 2.29 (s, 3H) 2.32 (s, 3H) 2.66 (s, 3H)	3.03-3.07 (m, 1H)	1.44 (d, 3H, J = 8 Hz) 5.76 (d, 1H, J = 2 Hz)	1712 (C=O) 1550 (NO_2) 1358 (NO_2)	247
trans-**4b**	2.26 (s, 3H) 2.29 (s, 3H) 2.31 (s, 3H) 2.66 (s, 3H)	2.99-3.04 (m, 1H)	1.29 (d, 3H, J = 7 Hz) 6.27 (d, 1H, J = 7 Hz)	1704 (C=O) 1540 (NO_2) 1360 (NO_2)	247
4c	2.24 (s, 3H) 2.29 (s, 3H) 2.31 (s, 3H) 2.65 (s, 3H)		1.25 (s, 3H) 1.32 (s, 3H) 5.86 (s, 1H)	1714 (C=O) 1557 (NO_2) 1362 (NO_2)	261
cis-**4d**	2.26 (s, 3H) 2.29 (s, 3H) 2.31 (s, 3H) 2.66 (s, 3H)	2.90-2.96 (m, 1H)	1.08 (t, 3H, J = 8 Hz) 1.62-1.73 (m, 1H) 1.97-2.05 (m, 1H) 5.85 (d, 1H, J = 2 Hz)	1712 (C=O) 1542 (NO_2) 1363 (NO_2)	215[a,b]
trans-**4d**	2.28 (s, 3H) 2.30 (s, 3H) 2.33 (s, 3H) 2.65 (s, 3H)	2.74-2.82 (m, 1H)	1.16 (t, 3H, J = 7 Hz) 1.33-1.44 (m, 1H) 2.12-2.22 (m, 1H) 6.36 (d, 1H, J = 7 Hz)	1712 (C=O) 1541 (NO_2) 1355 (NO_2)	215[a,b]
cis-**4e**	2.26 (s, 3H) 2.28 (s, 3H) 2.31 (s, 3H) 2.54 (s, 3H)	2.96-3.00 (m, 1H)	0.97 (t, 3H, J = 7 Hz) 1.44-1.65 (m, 3H) 1.88-1.98 (m, 1H) 5.85 (d, 1H, J = 2 Hz)	1707 (C=O) 1551 (NO_2) 1364 (NO_2)	275
trans-**4e**	2.28 (s, 3H) 2.30 (s, 3H) 2.33 (s, 3H) 2.65 (s, 3H)	2.82-2.90 (m, 1H)	0.99 (t, 3H, J = 7 Hz) 1.25-1.40 (m, 1H) 1.48-1.65 (m, 2H) 2.02-2.15 (m, 1H) 6.33 (d, 1H, J = 7 Hz)	1713 (C=O) 1543 (NO_2) 1360 (NO_2)	229[a,b]
cis-**4f**	2.27 (s, 3H) 2.28 (s, 3H) 2.31 (s, 3H) 2.66 (s, 3H)	2.93 (dd, 1H, J = 2 & 4 Hz)	0.79 (d, 3H, J = 7 Hz) 1.15 (d, 3H, J = 7 Hz) 2.37-2.64 (m, 1H) 5.92 (d, 1H, J = 2 Hz)	1703 (C=O) 1562 (NO_2) 1360 (NO_2)	229[a,b]
trans-**4f**	2.26 (s, 3H) 2.28 (s, 3H) 2.36 (s, 3H) 2.63 (s, 3H)	2.56 (dd, 1H, J = 6 & 9 Hz)	1.05 (d, 3H, J = 6 Hz) 1.35 (d, 3H, J = 6 Hz) 2.07-2.20 (m, 1H) 6.31 (d, 1H, J = 6 Hz)	1710 (C=O) 1541 (NO_2) 1358 (NO_2)	229[a,b]

Table 4. (continued)

Compd	^{1}H NMR ($CDCl_3$) δ_{ppm}			IR (KBr)	M^+ (m/z)
	ring CH_3	CHR^4	others	$\nu_{cm^{-1}}$	
trans-**4g**	2.28 (s, 6H) 2.30 (s, 3H) 2.64 (s, 3H)	2.76 (d, 1H, J = 2 Hz)	1.06 (s, 9H) 5.99 (d, 1H, J = 2 Hz)	1701 (C=O) 1555 (NO_2) 1368 (NO_2)	243[a,b]
cis-**4h**	2.27 (s, 3H) 2.28 (s, 3H) 2.31 (s, 3H) 2.65 (s, 3H)	3.02 (dd, 1H, J = 1 & 7 Hz)	1.06-1.20 (m, 1H) 1.51-1.75 (m, 7H) 1.85-1.96 (m, 1H) 5.87 (d, 1H, J = 1 Hz)	1709 (C=O) 1553 (NO_2) 1362 (NO_2)	301
trans-**4h**	2.27 (s, 3H) 2.28 (s, 3H) 2.35 (s, 3H) 2.64 (s, 3H)	2.68-2.74 (m, 1H)	1.31-1.68 (m, 7H) 1.81-1.92 (m, 1H) 2.00-2.18 (m, 1H) 6.29 (d, 1H, J = 6 Hz)	1711 (C=O) 1543 (NO_2) 1360 (NO_2)	255[a,b]
4i	2.28 (s, 3H) 2.29 (s, 6H) 2.64 (s, 3H)		1.34-2.05 (m, 10H) 6.07 (s, 1H)	1715 (C=O) 1555 (NO_2) 1358 (NO_2)	301
trans-**4j**	2.32 (s, 6H) 2.35 (s, 3H) 2.67 (s, 3H)	4.21 (d, 1H, J = 2 Hz)	6.16 (d, 1H, J = 2 Hz) 7.06-7.10 (m, 2H) 7.31-7.36 (m, 3H)	1718 (C=O) 1543 (NO_2) 1359 (NO_2)	262[a,c]

[a] M^+ was not observed. [b] m/z = M^+ - 46 (NO_2). [c] m/z = M^+ - 46 (NO_2) - 1

Table 5. Cis/Trans Ratios of Products 4.[a]

Compd	R^4	DBU				TEA			
		benzene		DMF		benzene		DMF	
		%conv.	*cis/trans*	%conv.	*cis/trans*	%conv.	*cis/trans*	%conv.	*cis/trans*
4b	Me	92	44/56	100	81/19	90	14/86	98	80/20
4d	Et	92	19/81	100	64/36	85	3/97	100	60/40
4e	*n*-Pr	97	18/82	89	59/41	89	3/97	98	59/41
4f	*i*-Pr	94	56/44	100	82/18	28	13/87	100	82/18
4g	*t*-Bu	99	0/100	99	0/100	0	------	99	0/100
4h	*c*-Pn[b]	93	45/55	100	78/22	28	9/91	100	73/27

[a] Reaction condition: 5 h at room temperature. *Cis/trans* ratios are determined by ^{1}H NMR spectra [b] Cyclopentyl.

Whenever the secondary bromides are to be attacked by the nitromethyl carbanions, the ratios of *cis*-isomers show smaller values in benzene than in DMF. The exception is the *tert*-butyl group-containing material (**4g**), where no *cis*-isomer is detected. In addition, the conversion of the reaction itself often decreases in relation to the bulkiness of substituents. These tendencies can be seen when TEA is used instead of DBU, and the reaction is carried out in benzene. It is noteworthy that the cyclization reaction of **3g** hardly occurs when catalyzed by TEA in benzene. Thus, the reaction in benzene may proceed by way of the S_N2-like mechanism, since the steric hindrance of substituents seems to play important roles in determining both the reactivity and the ratios of isomers. The substituent effects observed on the *cis/trans* ratios can be attributed to the steric hindrance between the substituents R^4's and the nitro groups in the transition state.

When DMF is used as the reaction solvent, where in general *cis*-isomers emerge as the major products, the nucleophilic substitution reaction proceeds smoothly even when R^4 = *t*-Bu. However, in this case, *trans*-isomer is formed predominantly. Bégué and Charpentier-Morize[18] reported that α-halocarbonyl compounds underwent the substitution on the carbon α to the carbonyl group *via* the carbocationic intermediates under solvolytic conditions. Therefore, when DMF (a polar aprotic solvent) is used, the reaction mechanism might favor the S_N1 type, rather than the S_N2 type.

On the other hand, the reaction of compounds **3k-m**, possessing unsubstituted sites on benzene ring, exhibit the completely different features from those described to the fully ring-substituted **3**. For example, compound **3m** reacts with 1 equiv. of TEA in benzene to undergo the intramolecular *O*-alkylation of the nitronate anion by the carbon α to the carbonyl group to afford 4,4,6,7,8-pentamethyl-3,2-benzoxazepin-5(4*H*)-one 2-oxide (**7m**). When this compound is allowed to stand for a few days at room temperature, it is converted into 3,4-dihydro-3,3,5,6,7-pentamethylisocoumarin-4-one 1-oxime (**8m**), as shown in Scheme 5. Oxime **8m** is easily hydrolyzed to give the corresponding lactone **9m**. Compounds **3k** and **3l** also afford products **7k** and **7l** on treatment with TEA in benzene, respectively.

Scheme 5

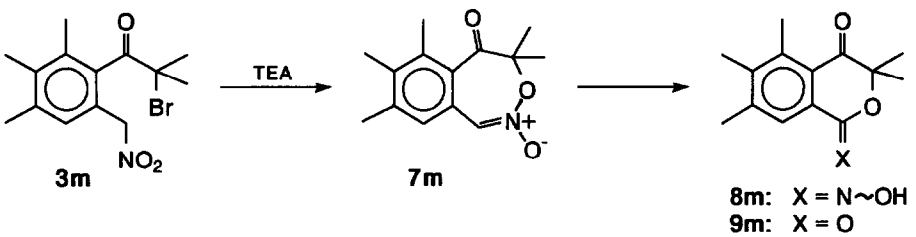


Table 6. Analytical Data of Compounds 5.

Compd	Yield (%)	mp(°C)	Formula	Crystal Form (Recryst.Solv.)	Found(%)(Calcd(%)) C	H	N
5a	59	139-141	$C_{13}H_{14}O$	orange prisms (cyclohexane)	83.66 (83.83)	7.73 (7.58)	-------
5b	100	139-140	$C_{14}H_{16}O$	orange needles (MeOH)	83.75 (83.96)	8.16 (8.05)	-------
5d	100	88-89	$C_{15}H_{18}O$	orange needles (MeOH)	84.32 (84.07)	8.73 (8.47)	-------
5e	100	87-88	$C_{16}H_{20}O$	orange needles (90% MeOH)	84.22 (84.16)	8.97 (8.83)	-------
5f	78	59-60	$C_{16}H_{20}O$	yellow plates (MeOH)	84.37 (84.16)	9.11 (8.83)	-------
5g	100	131-132	$C_{17}H_{22}O$	orange needles (MeOH)	84.53 (84.25)	9.16 (9.15)	-------
5h	100	111-112	$C_{18}H_{22}O$	orange needles (MeOH)	84.77 (84.99)	9.01 (8.72)	-------
5j	100	141-142	$C_{19}H_{18}O$	red needles (MeOH)	87.11 (86.99)	7.00 (6.92)	-------

Reactivity difference between 3-substituted (**3a-j**) and 3-unsubstituted compounds (**3k-m**) in the cyclization reaction can be interpreted by our working hypotheses shown as Fig. 3.

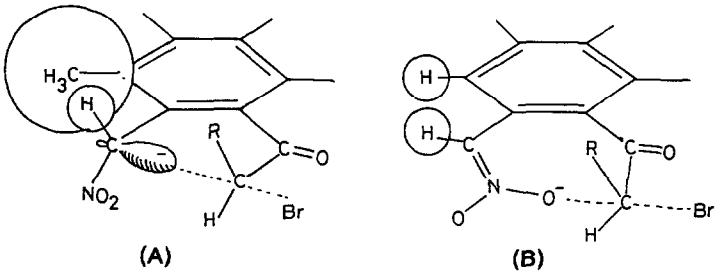


Fig. 3. Expected Transition States of the Cyclization of Compounds 3.
(A) for 3-substituted compounds (**3a-j**).
(B) for 3-unsubstituted compounds (**3k-m**).

The *intermolecular* alkylation of the anion derived from phenylnitromethanes is known to undergo *O*-substitution rather than *C*-substitution when bromo leaving group is used.[19] Therefore, in our present *intramolecular* cyclization system, the formation of the 7-membered ring-containing (or *O*-alkylated) products **7** is considered to be feasible (pattern (B)). However, when adjacent methyl group exists in the benzene ring, pattern (A) becomes feasible in order to minimize the steric interaction between C-H and C-CH_3 expected from pattern (B), giving the 5-membered ring-containing (or *C*-alkylated) products **4**.

Rearrangement of **7** to **8** is considered to proceed by way of the tricyclic intermediates (or their equivalents), which are formed by the attack of the ring oxygen to the immonium carbon. Possibility of the nitrile *N*-oxide intermediates by ring-opening mechanism is avoided due to the absence of furoxanes, which inevitably form by the quick dimerization of nitrile *N*-oxides.[20]

When 2 equiv. of base is used in the reaction of **3a-j** in benzene, the cyclization followed by the elimination of nitrous acid moiety give 4,5,6,7-tetramethylinden-1-one derivatives (**5a-j**) in good isolated yields. The isolated yields and physical data of products **5a-j** are listed in Tables 6 and 7, respectively.

Indenone derivatives attract huge amount of theoretical interest as the annulenones of anti-aromaticity against the Hückel rule.[21] However, these materials in general have difficulties in preparation due to their thermal instability, which limits the reaction conditions themselves. We successfully prepare 2-substituted 4,5,6,7-tetramethylinden-1-ones from compounds **3** applying mild reaction conditions instead.

As described above, fuming nitric acid/acetic anhydride system readily brings about the ring-nitration whenever unsubstituted position exists in the benzene ring. Therefore, in order to obtain the side-chain nitration products in satisfactory isolated yields, acylpolymethylbenzenes possessing methyl substituents at 2-, 4-, and 5-position are to be used as substrates. Our methods, though leaving some problems behind, would provide the tacit basis in preparing several types of generally useful synthons. Further exploitations are now in progress in our laboratory.

Table 7. Spectral Data of Compounds 5.

Compd	^{1}H NMR ($CDCl_3$) δ_{ppm}		IR (KBr)	M^+ (m/z)
	ring CH_3	others	$\nu_{cm^{-1}}$	
5a	2.16 (s, 3H) 2.18 (s, 3H) 2.19 (s, 3H) 2.48 (s, 3H)	5.73 (d, 1H, J = 6 Hz) 7.63 (d, 1H, J = 6 Hz)	1695 (C=O)	186
5b	2.12 (s, 3H) 2.13 (s, 3H) 2.14 (s, 3H) 2.45 (s, 3H)	1.82 (d, 3H, J = 2 Hz) 7.18 (d, 1H, J = 2 Hz)	1690 (C=O)	200
5d	2.11 (s, 3H) 2.14 (s, 6H) 2.44 (s, 3H)	1.13 (t, 3H, J = 7 Hz) 2.24 (q, 2H, J = 7 Hz) 7.14 (s, 1H)	1690 (C=O)	214
5e	2.12 (s, 3H) 2.15 (s, 6H) 2.45 (s, 3H)	0.95 (t, 3H, J = 7 Hz) 1.48-1.61 (m, 2H) 2.20 (t, 2H, J = 7 Hz) 7.16 (s, 1H)	1686 (C=O)	228
5f	2.13 (s, 3H) 2.16 (s, 6H) 2.46 (s, 3H)	1.14 (d, 6H, J = 7 Hz) 2.66-2.71 (m, 1H) 7.13 (d, 1H, J = 1 Hz)	1690 (C=O)	228
5g	2.13 (s, 3H) 2.16 (s, 6H) 2.45 (s, 3H)	1.25 (s, 9H) 7.14 (s, 1H)	1692 (C=O)	242
5h	2.13 (s, 3H) 2.16 (s, 6H) 2.46 (s, 3H)	1.42-2.01 (m, 8H) 2.71-2.82 (m, 1H) 7.12 (d, 1H, J = 2 Hz)	1686 (C=O)	254
5j	2.18 (s, 3H) 2.20 (s, 3H) 2.45 (s, 3H) 2.52 (s, 3H)	7.30-7.42 (m, 3H) 7.33 (s, 1H) 7.77-7.81 (m, 2H)	1696 (C=O)	262

Experimental Section

General information

All melting points are uncorrected. Infrared (IR) spectra were measured with a Shimadzu IR-430 grating infrared spectrophotometer and a JASCO FT/IR-8000 Fourier transform infrared spectrometer. ^{1}H NMR spectral measurements were carried out with a JEOL JNM-GX200 Fourier transform NMR spectrometer (270 MHz). All signals are expressed as ppm downfield from tetramethylsilane (TMS) used as an internal standard (δ value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Mass spectra (EI mode) were taken with a JEOL JMS-DX300 mass spectrometer. HPLC analyses were carried out on a JASCO-TRI ROTAR-IV high-performance liquid chromatograph using a Megapak SIL column (JASCO silica, l = 40 cm, ϕ = 5 mm) as the column and *n*-hexane/ethyl acetate (8v/2v) as an eluent.

Product distributions based on HPLC were calculated from the relative peak area with respect to the internal standard (naphthalene or dibenzofuran) on a System Instruments Chromatocorder 11 instrument after calibration for each authentic sample. Column chromatography and thin layer chromatography (TLC) were all performed using silica gel as an adsorbent. Combined organic extracts were dried over anhyd. Na_2SO_4 or $MgSO_4$ prior to filtration and concentration *in vacuo*. *N,N*-Dimethylformamide (DMF) was distilled from calcium hydride under reduced pressure prior to use.

Preparation of Starting Materials (1). Acylpolymethylbenzenes **1a-m** were prepared from the corresponding polymethylbenzenes and acid chlorides according to the well-known procedures[22] in satisfactory isolated yields. The physical data of compounds **1a-m** are as follows.

Acetylpentamethylbenzene (1a). mp 82-83 °C (lit.,[23] mp 84 °C).

Propionylpentamethylbenzene (1b). mp 84-85 °C (lit.,[22b] mp 84-85 °C).

Isopropionylpentamethylbenzene (1c). mp 46-47 °C (lit.,[22b] mp 49-50 °C).

Butyrylpentamethylbenzene (1d). mp 79-80 °C (lit.,[22b] mp 79 °C).

Valeroylpentamethylbenzene (1e). mp 45-46 °C (90% MeOH). ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, *J* = 7 Hz), 1.40 (sextet, 2H, *J* = 7 Hz), 1.70 (quintet, 2H, *J* = 7 Hz), 2.09 (s, 6H), 2.18 (s, 6H), 2.23 (s, 3H), 2.67 (t, 2H, *J* = 7 Hz). IR (KBr) ν 2953, 1698 cm^{-1}. MS (EI) m/z (rel. intensities) 232 (M^+, 26), 189 (3), 175 (100) , 147 (68). Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.52; H, 10.15.

Isovaleroylpentamethylbenzene (1f). mp 71-72 °C (MeOH). ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 6H, *J* = 7 Hz), 2.10 (s, 6H), 2.18 (s, 6H), 2.23 (s, 3H), 2.29-2.34 (m, 1H), 2.57 (d, 2H, *J* = 6 Hz). IR (KBr) ν 2950, 1693 cm^{-1}. MS (EI) m/z (rel. intensities) 232 (M^+, 14), 175 (100), 147 (18). Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.94; H, 10.24.

(β,β-Dimethylbutyryl)pentamethylbenzene (1g). mp 138-139 °C (MeOH). ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 9H), 2.11 (s, 6H), 2.17 (s, 6H), 2.21 (s, 3H), 2.59 (s, 2H). IR (KBr) ν 2951, 1696 cm^{-1}. MS (EI) m/z (rel. intensities) 246 (M^+, 42), 201 (10), 189 (15), 175 (100). Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.54; H, 10.38.

(Cyclopentylacetyl)pentamethylbenzene (1h). mp 72-73 °C (90% MeOH). ^{1}H NMR ($CDCl_3$) δ 1.08-2.01 (m, 8H), 2.10 (s, 6H), 2.18 (s, 6H), 2.22 (s, 3H), 2.33-2.49 (m, 1H), 2.72 (d, 2H, *J* = 7 Hz). IR (KBr) ν 2951, 1698 cm^{-1}. MS (EI) m/z (rel. intensities) 258 (M^+, 33), 200 (12), 189 (24), 175 (100). Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.57; H, 10.23.

Cyclohexylcarbonylpentamethylbenzene (1i). mp 122-123 °C (90% MeOH). ^{1}H NMR ($CDCl_3$) δ 1.17-1.96 (m, 10H), 2.09 (s, 6H), 2.18 (s, 6H), 2.23 (s, 3H), 2.61 (tt, 1H, *J* = 3 Hz, 12 Hz). IR (KBr) ν 2930, 1686 cm^{-1}. MS (EI) m/z (rel. intensities) 258 (M^+, 24), 199 (9), 175 (100), 154 (26). Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.46; H, 10.15.

(Phenylacetyl)pentamethylbenzene (1j). mp 133-134 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 6H), 2.18 (s, 6H), 2.23 (s, 3H), 3.97 (s, 2H), 7.21-7.33 (m, 5H). IR (KBr) ν 2860, 1705 cm^{-1}. MS (EI) m/z (rel. intensities) 266 (M^+, 4), 175 (100), 147 (100), 117 (20). Anal. Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.32. Found: C, 85.69; H, 8.32.

1-Propionyl-2,4,5,6-tetramethylbenzene (1k). mp 54-55 °C (80% MeOH). ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3H, *J* = 7 Hz), 2.10 (s, 3H), 2.13 (s, 6H), 2.25 (s, 3H), 2.69 (q, 2H, *J* = 7 Hz), 6.84 (s, 1H). IR (KBr) ν 2980, 1695 cm^{-1}. MS (EI) m/z (rel. intensities) 190 (M^+, 16), 161 (100), 133 (28). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.84; H, 9.22.

1-Propionyl-4-methoxy-2,5,6-trimethylbenzene (1l). mp 56-57 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ 1.18 (t, 3H, J = 7 Hz), 2.10 (s, 6H), 2.18 (s, 3H), 2.69 (q, 2H, J = 7 Hz), 3.80 (s, 3H), 6.53 (s, 1H). IR (KBr) ν 2973, 1698 cm^{-1}. MS (EI) m/z (rel. intensities) 206 (M^+, 24), 177 (90), 105 (22). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.37; H, 8.76.

1-Isobutyryl-2,4,5,6-tetramethylbenzene (1m). bp 156-157 °C/11 mmHg. ^{1}H NMR ($CDCl_3$) δ 1.17 (d, 6H, J = 7 Hz), 2.11 (s, 3H), 2.13 (s, 3H), 2.15 (s, 3H), 2.25 (s, 3H), 2.89-3.00 (m, 1H), 6.85 (s, 1H). IR (KBr) ν 2990, 1698 cm^{-1}. MS (EI) m/z (rel. intensities) 204 (M^+, 6), 161 (100), 133 (27), 117 (8). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 81.98; H, 9.48.

Typical Procedure for the Preparation of α-Bromoacylpolymethylbenzenes (2). Preparation of 2,3,4,5,6-Pentamethyl-1-(α-bromoacetyl)-benzene (2a). To a solution of **1a** (5.00 g, 26.2 mmol) in acetic acid (30 mL) was added a solution of bromine (4.20 g, 26.2 mmol) in acetic acid (30 mL) with stirring at room temperature in the dark over 30 min. After the addition was complete, the reaction mixture was further stirred for 1 h at room temperature, and was poured onto ice-water (500 mL), then stirred for 2 h. The resulting solid was filtered, washed with water, and dried to give crude **2a** (6.74 g, 96%, mp 85-98 °C), which was recrystallized from MeOH to give pure **2a** (3.93 g, 56% yield, mp 106-108 °C). Compounds **2b-m** were also prepared from the corresponding acylpolymethylbenzenes using the similar procedure to that described above, in quantitative yields except **2l** (in an isolated yield of 55%). The physical data of compounds **2a-m** are as follows.

2,3,4,5,6-Pentamethyl-1-(α-bromoacetyl)benzene (2a): mp 108-109 °C (white needles from MeOH). ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 6H), 2.19 (s, 6H), 2.24 (s, 3H), 4.27 (s, 2H). IR (KBr) ν 2910, 1715 cm^{-1}. MS (EI) m/z (rel. intensities) 270 (M^+ + 2, 17), 268 (M^+, 18), 189 (6), 175 (100), 161 (7). Anal. Calcd for $C_{13}H_{17}OBr$: C, 58.01; H, 6.37. Found: C, 58.09; H, 6.52.

2,3,4,5,6-Pentamethyl-1-(α-bromopropionyl)benzene (2b): mp 93-95 °C (white needles from *n*-hexane). ^{1}H NMR ($CDCl_3$) δ 1.87 (d, 3H, J = 7 Hz), 2.15 (s, 6H), 2.19 (s, 6H), 2.24 (s, 3H), 4.80 (q, 1H, J = 7 Hz). IR (KBr) ν 2960, 1694 cm^{-1}. MS (EI) m/z (rel. intensities) 284 (M^+ + 2, 37), 282 (M^+, 37), 203 (7), 175 (100). Anal. Calcd for $C_{14}H_{19}OBr$: C, 59.37; H, 6.76. Found: C, 59.26; H, 6.91.

2,3,4,5,6-Pentamethyl-1-(α-bromoisobutyryl)benzene (2c): mp 105-106 °C (white plates from MeOH). ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 6H), 2.17 (s, 6H), 2.18 (s, 6H), 2.23 (s, 3H). IR (KBr) ν 2900, 1690 cm^{-1}. MS (EI) m/z (rel. intensities) 298 (M^+ + 2, 16), 296 (M^+, 16), 217 (9), 175 (100). Anal. Calcd for $C_{15}H_{21}OBr$: C, 60.61; H, 7.12. Found: C, 60.98; H, 7.49.

2,3,4,5,6-Pentamethyl-1-(α-bromobutyryl)benzene (2d): mp 107-108 °C (white needles from *n*-hexane). ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J = 7 Hz), 2.01-2.14 (m, 2H), 2.16 (s, 6H), 2.19 (s, 6H), 2.24 (s, 3H), 4.63 (dd, 1H, J = 4 Hz, 9 Hz). IR (KBr) ν 2950, 1696 cm^{-1}. MS (EI) m/z (rel. intensities) 298 (M^+ + 2, 10), 296 (M^+, 10), 175 (100), 147 (13). Anal. Calcd for $C_{15}H_{21}OBr$: C, 60.61; H, 7.12. Found: C, 60.86; H, 7.21.

2,3,4,5,6-Pentamethyl-1-(α-bromovaleroyl)benzene (2e): mp 80-81 °C (white plates from 90% MeOH). ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, J = 7 Hz), 1.39-1.58 (m, 1H), 1.62-1.78 (m, 1H), 1.99-2.10 (m, 2H), 2.17 (s, 6H), 2.19 (s, 6H), 2.24 (s, 3H), 4.70 (dd, 1H, J = 6 Hz, 9 Hz). MS (EI) m/z (rel. intensities) 312 (M^+ + 2, 4), 310 (M^+, 4), 231 (3), 201 (5), 187 (15), 175 (100). Anal. Calcd for $C_{16}H_{23}OBr$: C, 61.74; H, 7.45. Found: C, 61.37; H, 7.62.

2,3,4,5,6-Pentamethyl-1-(α-bromoisovaleroyl)benzene (2f): mp 104-105 °C (white prisms from MeOH). ^{1}H NMR ($CDCl_3$) δ 1.10 (d, 3H, J = 5 Hz), 1.13 (d, 3H, J = 5 Hz), 2.17 (s, 6H), 2.18-2.44

(m, 1H), 2.19 (s, 6H), 2.24 (s, 3H), 4.72 (d, 1H, J = 4 Hz). IR (KBr) ν 2960, 1683 cm^{-1}. MS (EI) m/z (rel. intensities) 312 (M^+ + 2, 3), 310 (M^+, 3), 175 (100), 147 (18). Anal. Calcd for $C_{16}H_{23}OBr$: C, 61.74; H, 7.45. Found: C, 62.03; H, 7.66.

2,3,4,5,6-Pentamethyl-1-(α-bromo-β,β-dimethylbutyryl)benzene (2g): mp 101-102 °C (white plates from 90% MeOH). ^1H NMR ($CDCl_3$) δ 1.27 (s, 9H), 2.19 (s, 6H), 2.21 (s, 6H), 2.24 (s, 3H), 4.68 (s, 1H). IR (KBr) ν 2961, 1694 cm^{-1}. MS (EI) m/z (rel. intensities) 326 (M^+ + 2, 41), 324 (M^+, 41), 279 (3), 239 (6), 215 (15). Anal. Calcd for $C_{17}H_{25}OBr$: C, 62.77; H, 7.75. Found: C, 62.70; H, 7.76.

2,3,4,5,6-Pentamethyl-1-(α-bromo-α-cyclopentylacetyl)benzene (2h): mp 112-113 °C (white prisms from MeOH). ^1H NMR ($CDCl_3$) δ 1.38-1.97 (m, 8H), 2.18 (s, 6H), 2.19 (s, 6H), 2.24 (s, 3H), 2.47-2.61 (m, 1H), 4.82 (d, 1H, J = 7 Hz). IR (KBr) ν 2981, 2869, 1686 cm^{-1}. MS (EI) m/z (rel. intensities) 338 (M^+ + 2, 10), 336 (M^+, 10), 256 (5), 228 (8), 189 (6), 175 (100). Anal. Calcd for $C_{18}H_{25}OBr$: C, 64.10; H, 7.47. Found: C, 63.93; H, 7.61.

2,3,4,5,6-Pentamethyl-1-(1-bromo-1-cyclohexylcarbonyl)benzene (2i): mp 162-163 °C (white prisms from *n*-hexane). ^1H NMR ($CDCl_3$) δ 1.68-1.88 (m, 7H), 2.18 (s, 12H), 2.24 (s, 3H), 2.22-2.26 (m, 3H). IR (KBr) ν 2936, 2863, 1686 cm^{-1}. MS (EI) m/z (rel. intensities) 338 (M^+ + 2, 51), 336 (M^+, 51), 281 (8), 256 (33), 231 (16). Anal. Calcd for $C_{18}H_{25}OBr$: C, 64.10; H, 7.47. Found: C, 63.73; H, 7.60.

2,3,4,5,6-Pentamethyl-1-(1-bromo-1-phenylacetyl)benzene (2j): mp 122-123 °C (white needles from cyclohexane). ^1H NMR ($CDCl_3$) δ 1.40-2.50 (br. s, 6H), 2.14 (s, 6H), 2.20 (s, 3H), 5.68 (s, 1H), 7.30-7.33 (m, 3H), 7.45-7.49 (m, 2H). IR (KBr) ν 2910, 1710 cm^{-1}. MS (EI) m/z (rel. intensities) 237 (3), 207 (4), 175 (100, M^+ - CHBrPh), 147 (11), 131 (3). Anal. Calcd for $C_{19}H_{21}OBr$: C, 66.09; H, 6.13. Found: C, 66.46; H, 6.26.

2,4,5,6-Tetramethyl-1-(α-bromopropionyl)benzene (2k): mp 35-36 °C (white needles from 90% MeOH). ^1H NMR ($CDCl_3$) δ 1.88 (d, 3H, J = 7 Hz), 2.15 (s, 3H), 2.18 (s, 3H), 2.23 (s, 3H), 2.27 (s, 3H), 4.83 (q, 1H, J = 7 Hz), 6.89 (s, 1H). IR (KBr) ν 2980, 1698 cm^{-1}. MS (EI) m/z (rel. intensities) 270 (M^+ + 2, 6), 268 (M^+, 6), 203 (21), 189 (8), 175 (16). Anal. Calcd for $C_{13}H_{17}OBr$: C, 58.01; H, 6.37. Found: C, 57.82; H, 6.21.

2,5,6-Trimethyl-4-methoxy-1-(α-bromopropionyl)benzene (2l): mp 76-78 °C (white prisms from *n*-hexane). ^1H NMR ($CDCl_3$) δ 1.87 (d, 3H, J = 7 Hz), 2.11 (s, 3H), 2.17 (s, 3H), 2.27 (s, 3H), 3.82 (s, 3H), 4.84 (q, 1H, J = 7 Hz), 6.56 (s, 1H). IR (KBr) ν 2910, 1688 cm^{-1}. MS (EI) m/z (rel. intensities) 286 (M^+ + 2, 10), 284 (M^+, 10), 203 (3), 189 (2), 177 (100). Anal. Calcd for $C_{13}H_{17}O_2Br$: C, 54.75; H, 6.01. Found: C, 54.49; H, 6.33.

2,4,5,6-Tetramethyl-1-(α-bromoisobutyryl)benzene (2m): mp 48-49 °C (white prisms from 90% MeOH). ^1H NMR ($CDCl_3$) δ 1.96 (s, 6H), 2.14 (s, 3H), 2.18 (s, 3H), 2.23 (s, 3H), 2.26 (s, 3H), 6.83 (s, 1H). IR (KBr) ν 2920, 1700 cm^{-1}. MS (EI) m/z (rel. intensities) 283 (M^+ + 2, 9), 281 (M^+, 9), 202 (6), 174 (8), 160 (100). Anal. Calcd for $C_{14}H_{19}OBr$: C, 59.37; H, 6.76. Found: C, 59.61; H, 6.57.

Typical Procedures for the Side-Chain Nitration of α-Bromoacylpolymethylbenzenes (2). (A) Nitration of 2,3,4,5,6-Pentamethyl-1-(α-bromoacetyl)benzene (2a). To a solution of **2a** (2.00 g, 7.4 mmol) in acetic anhydride (30 mL) was added a solution of fuming nitric acid (0.94 g, 14.9 mmol) in acetic anhydride (10 mL) with stirring at 0 °C over 15 min. After the reaction mixture was further stirred for 2 h at 0 °C, it was poured onto ice-water (500 mL), and then stirred overnight. The resulting solids were filtered, washed successively with water, aq. sodium carbonate and water, and then dried *in vacuo* to give crude **3a** as a

yellow solid (2.12 g, 91% yield, mp 140-144 °C). Purity of this sample was checked by HPLC at this point. The crude product was recrystallized from ethanol to give pure **3a** (1.75 g, 76% yield, mp 148-149 °C). Nitration of **2b-j** was also carried out using the similar procedure to that described above. Analytical and physical data of products **3a-j** are listed in Tables 1 and 2, respectively.

(B) Nitration of 2,4,5,6-Tetramethyl-1-(α-bromopropionyl)benzene (2k). To a solution of **2k** (5.00 g, 18.6 mmol) in acetic anhydride (80 mL) was added fuming nitric acid (2.96 g, 46.5 mmol) in acetic anhydride (20 mL) with stirring at 0 °C, and the mixture was further stirred for 2 h at 0 °C. The reaction mixture was poured onto ice-water (500 mL), and then stirred overnight. The aqueous mixture was decanted and the residual oil was extracted with Et_2O (100 mL), washed with water, dried over $MgSO_4$, and then Et_2O was evaporated under reduced pressure. The residual yellow solid (5.70 g) was chromatographed on silica gel using *n*-hexane/ethyl acetate (8v/2v) as an eluent to give **3k** (3.83 g, 66% yield, mp 91-93 °C) and **6k** (1.01 g, 18% yield, mp 82-86 °C). Compounds **3k** and **6k** were recrystallized from *n*-hexane and 90% aq. MeOH to give pure **3k** and **6k**, respectively. Nitration of **2l** and **2m** were also carried out using a similar procedure to that described above. Analytical and physical data of products **3k-m** are listed in Tables 1 and 2, respectively. The physical data of compounds **6k** and **6m** are as follows:

3-Nitro-4,5,6-trimethyl-1-(α-bromopropionyl)benzene (6k): mp 90-91 °C (white needles from 90% MeOH). ^1H NMR ($CDCl_3$) δ 1.90 (d, 3H, J = 7 Hz), 2.16 (s, 3H), 2.21 (s, 3H), 2.22 (s, 3H), 2.23 (s, 3H), 4.77 (q, 1H, J = 7 Hz). IR (KBr) ν 1705, 1524, 1372 cm^{-1}. MS (EI) m/z (rel. intensities) 312 (M^+, 2), 206 (100), 189 (20), 160 (26). Anal. Calcd for $C_{13}H_{16}NO_3Br$: C, 49.70; H, 5.13; N, 4.46. Found: C, 49.36; H, 5.04; N, 4.26.

3-Nitro-4,5,6-trimethyl-1-(α-bromoisobutyryl)benzene (6m): mp 101-102 °C (white prisms from 90% MeOH). ^1H NMR ($CDCl_3$) δ 1.97 (s, 3H), 1.98 (s, 3H), 2.17 (s, 3H), 2.20 (s, 3H), 2.23 (s, 6H). IR (KBr) ν 1696, 1538, 1369 cm^{-1}. MS (EI) m/z (rel. intensities) 328 (M^+ + 2, 4), 326 (M^+, 4), 247 (6), 219 (4), 206 (100), 188 (51). Anal. Calcd for $C_{14}H_{18}NO_3Br$: C, 51.23; H, 5.53; N, 4.27. Found: C, 50.94; H, 5.50; N, 4.09.

Typical Procedure for the Preparation of Polysubstituted 3-Nitroindan-1-ones (4). Preparation of 2,4,5,6,7-Pentamethyl-3-nitroindan-1-one (4b). To a solution of **3b** (0.50 g, 1.52 mmol) in benzene (15 mL) was added DBU (0.23 g, 1.52 mmol) in benzene (5 mL) at room temperature over 15 min. The mixture was stirred for 5 h at room temperature, and then quenched with ice-water (100 mL). The organic layer was washed with water, dried over anhyd. $MgSO_4$, and then evaporated *in vacuo* to afford crude **4b** (0.39 g, quant.) as a mixture of diastereomers. The crude **4b** was chromatographed on silica gel using *n*-hexane/ethyl acetate (8v/2v) as an eluent to give *cis*-**4b** (0.13 g, 35% yield, mp 114-119 °C) and *trans*-**4b** (0.17 g, 45% yield, mp 117-129 °C). These isomers were each recrystallized from 80% MeOH to give pure compounds, respectively. Similarly, other 3-nitroindan-1-ones (**4a-j**) were prepared. Analytical and physical data of products **4a-j** are summarized in Tables 3 and 4, respectively. Product distribution (*cis/trans*) is summarized in Table 5.

Typical Procedure for the Intramolecular S_N Reaction of 3k-m. Preparation of 4,4,6,7,8-Pentamethyl-3,2-benzoxazepin-5(4*H*)-one 2-Oxide (7m). To a solution of **3m** (1.00 g, 3.05 mmol) in benzene (50 mL) was added TEA (0.31 g, 3.05 mmol) in benzene (30 mL) at room temperature over 15 min. After stirring for 5 h at room temperature, the reaction mixture was poured onto acidic ice-water (300 mL) and extracted with Et_2O. The combined organic extracts were washed with water, dried over anhyd. $MgSO_4$, and

then evaporated to afford crude **7m** as a yellow solid (0.67 g). The crude product was washed with *n*-hexane/ethyl acetate (8v/2v) solution to give pure **7m** (0.44 g, 59% yield, mp 100-102 °C) as a white powder. Similarly, compounds **7k** and **7l** were obtained from **3k** and **3l**, respectively.

Compound **7m** was allowed to stand for a few days at room temperature to undergo the conversion into 3,4-dihydro-3,3,5,6,7-pentamethylisocoumarin-4-one 1-oxime (**8m**; 84% yield). Similarly, compound **7k** was found to convert into **8k**. Hydrolysis of compound **8m** with *conc.* HCl in acetone for 2 h under reflux led to the corresponding lactone **9m** (90% yield). The physical data of compounds **7k-m**, **8k**, **8m**, and **9m** are as follows. Due to the difficulty in dealing with these materials, analytically identified were two compounds (**7l** and **9m**). Rest of them were identified through spectral comparisons (**7k**, **7m** vs. **7l**; **8m** vs. **8k**) and derivatizations (**7k** ➡ **8k**; **7m** ➡ **8m** ➡ **9m**).

4,6,7,8-Tetramethyl-3,2-benzoxazepin-5(4*H*)-one 2-Oxide (7k): 54% yield. mp 105-108 °C (white solid). ^{1}H NMR ($CDCl_3$) δ 1,60 (d, 3H, *J* = 7 Hz), 2.25 (s, 3H), 2.31 (s, 3H), 2.34 (s, 3H), 5.35 (q, 1H, *J* = 7 Hz), 6.88 (s, 1H), 6.94 (s, 1H). IR (KBr) ν 3061, 2919, 1688, 1630, 1356, 1240 cm^{-1}. MS (EI) m/z (rel. intensities) 233 (*M*$^+$, 20), 181 (11), 172 (12), 144 (13), 134 (12).

4,6,7-Trimethyl-8-methoxy-3,2-benzoxazepin-5(4*H*)-one 2-Oxide (7l): 100% yield. mp 148-149 °C (white crystal from *n*-hexane/ethyl acetate (8v/2v)). ^{1}H NMR ($CDCl_3$) δ 1.61 (d, 3H, *J* = 7 Hz), 2.20 (s, 3H), 2.31 (s, 3H), 3.88 (s, 3H), 5.32 (q, 1H, *J* = 7 Hz), 6.50 (s, 1H), 6.97 (s, 1H). IR (KBr) ν 2920, 1678, 1620, 1580, 1350, 1240 cm^{-1}. MS (EI) m/z (rel. intensities) 249 (*M*$^+$, 67), 204 (100), 190 (22), 176 (38), 158 (37). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.44; H, 6.41; N, 5.64.

4,4,6,7,8-Pentamethyl-3,2-benzoxazepin-5(4*H*)-one 2-Oxide (7m): 59% yield. mp 100-102 °C (white powder). ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 6H), 2.24 (s, 3H), 2.28 (s, 3H), 2.33 (s, 3H), 6.86 (s, 1H), 7.04 (s, 1H). IR (KBr) ν 3050, 2940, 1696, 1608, 1352, 1240 cm^{-1}. MS (EI) m/z (rel. intensities) 247 (*M*$^+$, 76), 231 (13), 217 (10), 201 (15), 188 (31), 171 (90).

3,4-Dihydro-3,5,6,7-tetramethylisocoumarin-4-one 1-Oxime (8k): 54% yield. mp 205-206 °C (white wool-like crystal from cyclohexane). ^{1}H NMR ($CDCl_3$) δ 1.55 (d, 1H, *J* = 7 Hz), 2.21 (s, 3H), 2.35 (s, 3H), 2.56 (s, 3H), 4.72 (q, 1H, *J* = 7 Hz), 6.10 (s, 1H), 6.90 (s, 1H). IR (KBr) ν 3449, 2936, 1696, 1599, 1377, 1238, 968 cm^{-1}. MS (EI) m/z (rel. intensities) 233 (*M*$^+$, 28), 131 (55), 100 (35).

3,4-Dihydro-3,3,5,6,7-pentamethylisocoumarin-4-one 1-Oxime (8m): 84% yield. mp 140-142 °C (white crystal from cyclohexane). ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 6H), 2.28 (s, 3H), 2.38 (s, 3H), 2.59 (s, 3H), 7.37 (s, 1H), 7.74 (s, 1H). IR (KBr) ν 3430, 2990, 1688, 1589, 1380, 1220, 979 cm^{-1}. MS (EI) m/z (rel. intensities) 247 (*M*$^+$, 15), 232 (48), 217 (3), 189 (17).

3,4-Dihydro-3,3,5,6,7-pentamethylisocoumarin-4-one (9m): 90% yield. mp 82-83 °C (white crystal from *n*-hexane). ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 6H), 2.34 (s, 3H), 2.45 (s, 3H), 2.63 (s, 3H), 7.95 (s, 1H). IR (KBr) ν 2990, 1722, 1693 cm^{-1}. MS (EI) m/z (rel. intensities) 232 (*M*$^+$, 53), 217 (5), 191 (4), 174 (100). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.41; H, 6.90. Found: C, 72.54; H, 6.95.

Typical Procedure for the Preparation of Polysubstituted inden-1-ones (5). Preparation of 4,5,6,7-Tetramethylinden-1-one (5a). To a solution of **3a** (0.50 g, 1.59 mmol) in benzene (40 mL) was added DBU (0.48 g, 3,18 mmol) in benzene (20 mL) at room temperature over 20 min. After stirring for 24 h, the reaction mixture was poured onto acidic ice-water (100 mL) and extracted with Et_2O (100 mL). The ether layer was washed with water, dried over anhyd. $MgSO_4$, and then evaporated to give crude **5a** as an orange solid (0.32 g). The crude **5a** was chromatographed on silica gel with benzene to give pure **5a** (0.17 g, 59%

yield, mp 129-139 °C) as an orange powder. Recrystallization of **5a** from cyclohexane gave the analytical sample. Other polysubstituted inden-1-ones (**5b-i**) were also prepared using similar procedures to that described above. Analytical and physical data are shown in Tables 6 and 7, respectively.

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