Facile transformation of benzyl ethers, alcohols, amides and amines to substituted indans

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The elimination of HX from $ArMe_2CX$ (X = OH, OMe, NHCOMe, NH_2) in sulfuric acid–liquid hydrocarbon leads easily to indan formation.

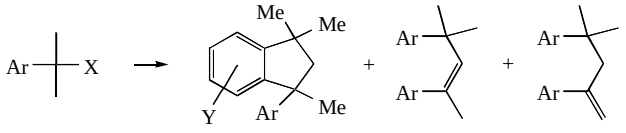
The dimerization of substituted styrene under acidic conditions affords the corresponding substituted indans.[1–3] Since elimination from α,α-dimethylbenzyl derivatives should be facile one might expect the formation of indans *via* intermediate α-methylstyrene.

It appeared that α,α-dimethylbenzyl alcohol, ether, amide and amine treated with sulfuric acid do indeed form the indan **1**, chain dimers **2** and **3** and by-products of benzyl cation degradation (Scheme 1).† The distribution of products depends on the solvent used and the concentration of the substrate.

In the biphasic system liquid *n*-alkane–sulfuric acid indans **1** are produced in high yields (Table 1) at moderate temperature (70 °C).

The benzyl alcohols and ether, regardless of the substituent in the aromatic ring, reacted readily and selectively (Table 1, entries 1, 4, 7 and 9) while amides (entries 2, 5 and 10) reacted more slowly, still affording high yields. The system sulfuric acid–hexane proved not to be effective for the elimination of ammonia from the corresponding amine (entries 3, 6 and 11), but at elevated temperature the elimination proceeds in a dodecane medium (entries 8 and 12). It is noteworthy that amide elimination is scarcely known,[4] whereas direct amine elimination under acidic conditions was not reported.

We found that unsubstituted dimethylbenzyl substrates form the only cyclization product, 1-phenyl- **1a** (Scheme 1, Ar = Ph, Y = H), and the 3,5-dichlorocompounds form only 1-(3,5-dichlorophenyl)-1,3,3-trimethyl-5,7-dichloroindan **1b** (Ar = 3,5-dichlorophenyl, Y = 3,5-dichloro) while the 3-chloro-α,α-dimethyl alcohol, amide and amine afford two possible isomers 1-(3-chlorophenyl)-1,3,3-trimethyl-7-chloroindan **1c** (Ar = = $3\text{-}ClC_6H_4$, Y = 7-Cl) and 1-(3-chlorophenyl)-1,3,3-trimethyl-5-chloroindan **1d** (Ar = $3\text{-}ClC_6H_4$, Y = 5-Cl), the ratio of the two isomers lying within the limits **1c**:**1d** = 1.7–2.



X = OH, OMe, NHCOMe, NH_2
Y = H, Cl

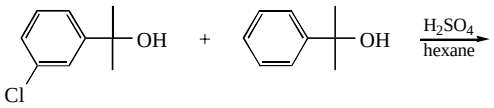
Scheme 1

Table 1 The formation of indan **1** from α,α-dimethylbenzyl alcohol, acetamides and amines (Scheme 1) in hexane–sulfuric acid (5 mmol substrate, 1 ml H_2SO_4, 20 ml hexane).

Entry	Ar	*T*/°C	Time/h	X	Yield (%)
1	Ph	70	1	OH	93
2	Ph	70	2.5	NHCOMe	94
3	Ph	70	10	NH_2	0
4	$3\text{-}ClC_6H_4$	70	1	OH	100
5	$3\text{-}ClC_6H_4$	70	3	NHCOMe	97
6	$3\text{-}ClC_6H_4$	70	10	NH_2	0
7	$3\text{-}ClC_6H_4$	70	1	OMe	100
8	$3\text{-}ClC_6H_4$	170[a]	3	NH_2	30
9	$3,5\text{-}Cl_2C_6H_3$	70	1	OH	80
10	$3,5\text{-}Cl_2C_6H_3$	70	3	NHCOMe	75
11	$3,5\text{-}Cl_2C_6H_3$	70	10	NH_2	0
12	$3,5\text{-}Cl_2C_6H_3$	170[a]	3	NH_2	57
13	$3\text{-}ClC_6H_4$	70	3	$NHCOMe\cdot H_2SO_4$	85[b]
14	$3\text{-}ClC_6H_4$	70	3	$NHCOMe\cdot H_2SO_4$	0[c]

[a] *n*-Dodecane. [b] No hexane added. [c] No H_2SO_4 added.

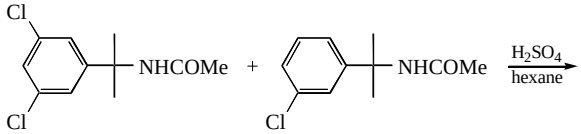
In order to obtain possible cross-cyclization products we studied the fate of two different substrate mixtures in the elimination–cyclization process (Schemes 2 and 3, yields given based on cross-cyclization product). We found that cross-cyclization products are formed if both substrates contain the same functional group. The cyclization of alcohols (Scheme 2) leads to a mixture of dimers **1a**,**c**,**d** along with three cross-products **1e** (Scheme 1 , Y = 7-Cl, Ar = Ph), **1f** (Y = H, Ar = = 3-chlorophenyl) and **1g** (Y = 5-Cl, Ar = Ph).



1a + **1c** + **1d** + **1e** + **1f** + **1g**
37% 8% 20% 7% 5% 13%

Scheme 2

The cross-dimerization of amides leads to similar results (Scheme 3), the cross products **1h** (Scheme 1, Y = 3,5-dichloro, Ar = 3-chlorophenyl), **1i** (Y = 3-Cl, Ar = 3,5-dichlorophenyl) being minor products.



1b + **1c** + **1d** + **1h** + **1i**
34% 15% 24% 11% 6%

Scheme 3

† For **1a**: ^{1}H NMR ($CDCl_3$) δ: 1.03 [s, 3H, C(3)–Me], 1.35 [s, 3H, C(3)–Me], 1.69 [s, 3H, C(1)–Me], 2.19 [d, 1H, C(2)–H, *J* 13.02 Hz], 2.42 [d, 1H, C(2)–H, *J* 13.02 Hz], 7.1–7.29 (m, 9H, Ar); MS, *m*/*z*: 236 (M^+).

For **1b**: ^{1}H NMR ($CDCl_3$) δ: 1.22 [s, 3H, C(3)–Me], 1.35 [s, 3H, C(3)–Me], 1.82 [s, 3H, C(1)–Me], 2.20 [d, 1H, C(2)–H, *J* 13.62 Hz], 2.29 [d, 1H, C(2)–H, *J* 13.62 Hz], 7.0–7.23 (m, 5H, Ar); MS, *m*/*z*: 372 (M^+).

For **1c**: ^{1}H NMR ($CDCl_3$) δ: 1.19 [s, 3H, C(3)–Me], 1.34 [s, 3H, C(3)–Me], 1.85 [s, 3H, C(1)–Me], 2.19 [d, 1H, C(2)–H, *J* 13.2 Hz], 2.30 [d, 1H, C(2)–H, *J* 13.2 Hz], 6.9–7.3 (m, 7H, Ar); MS, *m*/*z*: 304 (M^+).

For **1d**: ^{1}H NMR ($CDCl_3$) δ: 1.04 [s, 3H, C(3)–Me], 1.33 [s, 3H, C(3)–Me], 1.64 [s, 3H, C(1)–Me], 2.19 [d, 1H, C(2)–H, *J* 13.2 Hz], 2.39 [d, 1H, C(2)–H, *J* 13.2 Hz], 6.9–7.3 (m, 7H, Ar); MS, *m*/*z*: 304 (M^+).

For **2**: ^{1}H NMR δ: 1.51 (s, 6H, CMe_2), 1.56 (s, 3H, Me), 6.13 (s, 1H, =C–H), 7.10–7.44 (m, 10H, Ph).

For **3**: ^{1}H NMR δ: 1.21 (s, 6H, CMe_2), 2.82 (s, 2H, CH_2), 4.78 (s, 1H, =C–H), 5.13 (s, 1H, =C–H), 7.10–7.44 (m, 10H, Ph).

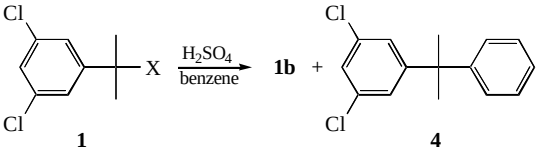
Table 2 The formation of indan **1** and 2,2-diarylpropane **4** from α,α-dimethylbenzyl alcohols, acetamides and amines (Scheme 2) in benzene–sulfuric acid (5 mmol of substrate, 1 ml H_2SO_4, 10 ml benzene, reflux).

Entry	Ar	Time/h	X	Yield **1** (%)	Yield **4** (%)
1	Ph	1	OH	80	0
2	Ph	2.5	NHCOMe	90	0
3	Ph	10	NH_2	0	0
4	3-ClC_6H_4	1	OH	90	0
5	3-ClC_6H_4	3	NHCOMe	97	0
6	3-ClC_6H_4	10	NH_2	0	0
7	3,5-$Cl_2C_6H_3$	1	OH	60	25
8	3,5-$Cl_2C_6H_3$	3	NHCOMe	50	30
9	3,5-$Cl_2C_6H_3$	10	NH_2	0	0
10[a]	3-ClC_6H_4	5	NHCOMe·H_2SO_4	0	0

[a]No H_2SO_4.

Cross-dimerization of α-methylstyrene with *N*-(α,α-dimethyl-3,5-dichlorobenzyl)acetamide does not proceed, and only indans **1a** (46%) and **1b** (48%) are formed.

In order to determine the phase in which cyclization occurs we performed experiments in which an excess of one of the liquid phases was avoided. We therefore obtained the sulfate of 3-chloro-α,α-dimethylbenzylamide $ClC_6H_4CMe_2NHCOMe·H_2SO_4$ [mp 148 °C; ^{1}H NMR (DMSO) δ: 1.50 (s, 6H, CMe_2), 1.81 (s, 3H, COMe), 7.17–7.30 (m, 4H, Ar), 8.13 (s, 1H, NH), 8.47 (s, 2H, H_2SO_4)]. On heating this salt with sulfuric acid (Table 1, entry 13) **1c** and **1d** were formed in 88% yield, but on heating with hexane (entry 14) no product was found. Hence, we believe that the cyclization takes place in the H_2SO_4 medium and possibly proceeds *via* carbenium ion formation. The formation of indans showed that the benzyl carbenium ions have a lifetime long enough to encounter a molecule of styrene in the sulfuric acid phase, and the cation produced undergoes intramolecular alkylation to give the indan ring. In order to confirm that mechanism the elimination–cyclization reactions were performed with benzene as the hydrocarbon phase (Table 2). In most cases the reaction proceeds in a similar fashion to hexane–sulfuric acid conditions (entries 1–6) but with 3,5-dichlorophenyldimethylcarbinol (entry 7) and *N*-(α,α-dimethyl-3,5-dichlorobenzyl)acetamide (entry 8) the dimerization process is accompanied by the alkylation of benzene[5] with formation of 2,2-diarylpropane **4** (Scheme 4).



1 **4**

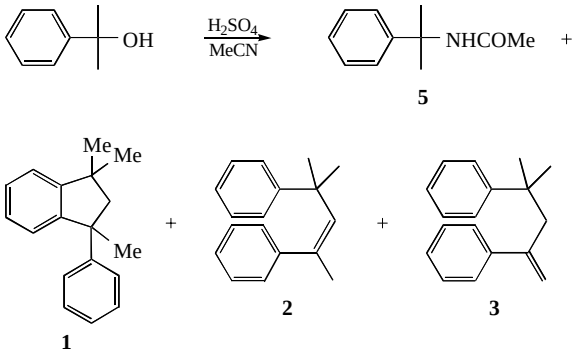
Scheme 4

Since a possible method of carbenium ion degradation is elimination promoted by base, we performed the reactions of benzyl alcohols with sulfuric acid in a homogeneous solution in acetonitrile (Table 3). We found that, depending on the conditions, the indan dimer might be the favourable product or alternatively chain dimer **2** and **3** and amide **5** become predominant (Scheme 5).

The formation of chain dimer proved to be kinetically controlled since the treatment of chain dimer **2** and **3** with sulfuric acid in hexane affords quantitatively **1**.

Table 3 The formation of **1**–**3** and **5** from α,α-dimethylbenzyl alcohols (Scheme 5) in acetonitrile medium at ambient temperature (5 mmol alcohol, acetonitrile, 1 ml H_2SO_4, 24 h).

Entry	Ar	Concentration of alcohol/M	Yield **1** (%)	Yield **2** (%)	Yield **3** (%)	Yield **5** (%)
1	Ph	1	71	9	5	6
2	Ph	0.1	—	65	30	—
3	3-ClC_6H_4	1	26	27	15	30
4	3-ClC_6H_4	0.1	—	—	—	88



Scheme 5

Thus, in the sulfuric acid–alkane system the elimination proceeds selectively to afford the indan skeleton, and this might be useful for the synthesis of indan derivatives.

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