A Convenient Synthetic Route to 4-Aryl-1,4-dihydro-3(2*H*)-isoquinolinones

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The title compounds are synthesized by Friedel-Crafts cyclization of *N*-benzyl-α-chloroacetamides, derived from the dichlorocarbene adducts of benzaldehyde *N*-benzylimines.

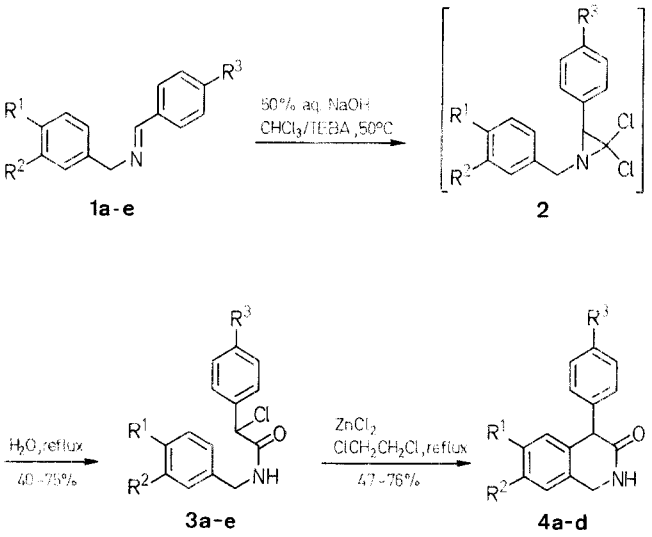
In the course of our investigation we needed several 4-aryl-1,4-dihydro-3(2*H*)-isoquinolinones (4-aryl-3-oxo-1,2,3,4-tetrahydroisoquinolines, **4**). Compounds of this type can be easily transformed[1] into 4-aryltetrahydroisoquinolines, some of which possess antidepressant activity[1] and are structural analogues of the alkaloid cherylline.[2]

It is known that dichlorocarbene, generated under anhydrous[3] or phase transfer-catalyzed (PTC)[3,4,5] conditions, adds readily to imines giving 2,2-dichloroaziridine derivatives. On the other hand, 2,2-dichloroaziridines rearrange into α-chloroimidoyl chlorides, which can be hydrolyzed to give substituted 2-chloroacetamides.[4,6,7,8]

The easily available benzyaldehyde *N*-benzylimines **1a–e** were treated with dichlorocarbene, generated *in situ* in the two-phase system chloroform/50% aqueous sodium hydroxyde in the presence of triethylbenzylammonium chloride (TEBA) under vigorously stirring at 50 °C for 30 min. After work-up, the crude 2,2-dichloroaziridines of type **2**, without isolation, were transformed into the *N*-benzyl-α-chloroarylacetamides **3a–e** in good yields by heating in water (Table). Longer reaction time led to the formation of complex reaction mixtures and lower yields of **3a–e**.

It has been reported[4] that imines, derived from unsubstituted benzaldehydes and aliphatic amines, give complex mixtures when treated with dichlorocarbene generated under PTC conditions. Only in the case of 4-nitrobenzaldehyde *N*-alkylimines, 2,2-dichloroaziridines and/or products of their rearrangement and hydrolysis can be isolated.[4] In contrast to Lit.[4], the *N*-benzyl-α-chloroarylacetamides **3a–d** were isolated in satisfactory yields under the conditions employed.

Friedel-Crafts cyclization of compounds **3a–d** to afford the 4-aryl-1,4-dihydro-3(2*H*)-isoquinolinones **4a–d** was achieved with zinc chloride in boiling dichloroethane in good yields (Table). Under similar conditions, cyclization of **3e** to **4e** failed. Stronger Lewis acids such as aluminium chloride led to cleavage of the methylenedioxy group of **3e**. An analogous cyclization of unsubstituted *N*-benzyl-α-hydroxyphenylacetamide to a compound of the type **4** has been reported.[9,10]



TEBA = benzyltriethylammonium chloride

1–4	R^1	R^2	R^3
a	H	H	H
b	H	H	Cl
c	$-O-CH_2-O-$		H
d	$-O-CH_2-O-$		Cl
e	$-O-CH_2-O-$		NO_2

The advantages of the two-step procedure described here are the easy availability of the variously substituted starting materials and the low cost of the reagents. The method may be applied to the synthesis of 4-aryl-1,4-dihydro-3(2*H*)-isoquinolines **4** having electron-donating or weakly electron-withdrawing groups (Table).

N-Benzyl-α-chloroarylacetamides 3a–e;

Aqueous 50% sodium hydroxide (6 ml) is added to vigorously stirred solution of the benzaldehyde *N*-benzylimine **1a–e** (10 mmol) and triethylbenzylammonium chloride (1 mmol) in chloroform (20 ml). Stirring is continued for 30 min at 50 °C and the mixture then poured into ice/water (20 ml). The layers are separated and the aqueous phase is extracted with dichloromethane (3 × 5 ml)). The combined extracts are washed with water (10 ml) and the solvent is removed at reduced pressure. The residue is mixed with water (20 ml) and heated under reflux for 30 min with stirring. After cooling to room temperature, the mixture is extracted with dichloromethane (3 × 5 ml) and the extract is dried with sodium sulfate. The solvent is removed under reduced pressure and the residue is purified by column chromatography on silica gel (10X by weight) using benzene as eluent (Table).

Table. *N*-Benzyl-α-chloroarylacetamides **3a–e** and 4-Aryl-1,4-dihydro-3(2*H*)-isoquinolinones **4a–d** Prepared

Product	Yield[a] (%)	m.p. (°C)[b] (solvent)	Molecular Formula[c]	MS (CI)[d] m/e $(M+1)^+$	IR (KBr)[e] ν (cm^{-1})	^{1}H-NMR (solvent/TMS)[f] δ (ppm)
3a	53	94.5–96.5 (benzene/hexane)	$C_{15}H_{14}ClNO$ (259.7)	260, 262	1536, 1648, 3066, 3336	($CDCl_3$): 4.43 (d, 2H, J = 5.6 Hz, CH_2N); 5.36 (s, 1H, CHCl); 7.27 (br s, $5H_{arom}$); 7.20 (br s, 1H, NH); 7.33 (br s, $5H_{arom}$)
3b	40	102–104 (benzene/hexane)	$C_{15}H_{13}Cl_2NO$ (294.2)	295, 297, 299	1558, 1652, 3068, 3248	($CDCl_3$): 4.43 (d, 2H, J = 5.6 Hz, CH_2N); 5.32 (s, 1H, CHCl); 7.0–7.5 (m, $9H_{arom}$ + NH)
3c	50	98–100 (benzene)	$C_{16}H_{14}ClNO_3$ (303.7)	304, 306	1540, 1640, 3060, 3280	($CDCl_3$): 4.30 (d, 2H, J = 6 Hz, CH_2N); 5.33 (s, 1H, CHCl); 5.86 (s, 2H, OCH_2O); 6.73 (s, $3H_{arom}$); 7.2 (br s, 1H, NH); 7.38 (br s, $5H_{arom}$)
3d	50	128–130 (benzene)	$C_{16}H_{13}Cl_2NO_3$ (338.2)	339, 341, 343	1550, 1656, 3066, 3290	($CDCl_3$): 4.38 (d, 2H, J = 6 Hz, CH_2N); 5.36 (s, 1H, CHCl); 5.95 (s, 2H, OCH_2O); 6.73 (s, $3H_{arom}$); 7.1 (br s, 1H, NH); 7.37 (s, $4H_{arom}$)
3e	75	154–155 (benzene)	$C_{16}H_{13}ClN_2O_5$ (348.7)	349, 351	1548, 1598, 1658, 3080, 3300	($CDCl_3$): 4.32 (d, 2H, J = 6 Hz, CH_2N); 5.48 (s, 1H, CHCl); 5.90 (s, 2H, OCH_2O); 6.70 (s, $3H_{arom}$); 7.65 (d, $2H_{arom}$, J = 9 Hz); 7.80 (br s, 1H, NH); 8.18 (d, $2H_{arom}$, J = 9 Hz)
4a	76[g]	199–201[h] (benzene)	$C_{15}H_{13}NO$ (223.3)	224	1625, 3060, 3260	(DMSO-d_6): 4.40 (s, 2H, H-1); 4.70 (s, 1H, H-4); 7.0–7.5 (m, $9H_{arom}$); 8.23 (br s, 1H, NH)
4b	74[i]	181–183 (benzene)	$C_{15}H_{12}ClNO$ (257.7)	258, 260	1658, 3060, 3186	($CDCl_3$): 4.43 (s, 2H, H-1); 4.73 (s, 1H, H-4); 6.8–7.5 (m, $8H_{arom}$); 7.73 (br s, 1H, NH)
4c	47[j]	212–214 (benzene)	$C_{16}H_{13}NO_3$ (267.2)	268	1650, 3040, 3180	(DMSO-d_6): 4.30 (s, 2H, H-1); 4.60 (s, 1H, H-4); 5.96, 6.00 (s, 2H, OCH_2O); 6.68 (s, $1H_{arom}$); 6.90 (s, $1H_{arom}$); 7.0–7.5 (m, $5H_{arom}$); 8.13 (br s, 1H, NH)
4d	62[j]	214–216 (benzene)	$C_{16}H_{12}ClNO_3$ (301.7)	302, 304	1660, 3046, 3182	(DMSO-d_6): 4.30 (s, 2H, H-1); 4.63 (s, 1H, H-4); 5.96 (br s, 2H, OCH_2O); 6.65 (s, $1H_{arom}$); 6.93 (s, $1H_{arom}$); 7.0–7.5 (m, $4H_{arom}$); 8.22 (br s, 1H, NH)

[a] Yield of isolated pure product.
[b] Uncorrected, measured with a micro heating table Beotius.
[c] Satisfactory microanalyses obtained: C ± 0.33, H ± 0.25, N ± 0.28.
[d] Recorded on a JEOL JMS-D300 spectrometer, with isobutane as reagent gas.
[e] Recorded on a Unicam SP. 200G Infrared spectrophotometer.
[f] Obtained on a Tesla BS-467 spectrometer at 60 MHz.
[g] Reaction time: 34 h.
[h] Lit[9] m.p. 207–208°C (benzene).
[i] Reaction time: 50 h.
[j] Reaction time: 10 h.

4-Aryl-1,4-dihydro-3(2*H*)-isoquinolinones 4a–d; General Procedure:
A mixture of the *N*-benzyl-α-chloroarylacetamide **3a–d** (2 mmol) and zinc chloride (6 mmol) in dry dichloroethane (20 ml) is heated under reflux with stirring for 10–50 h. The mixture is then cooled, washed with water (2 × 5 ml), and dried with sodium sulfate, and the solvent removed at reduced pressure. The residue is purified by column chromatography on silica gel (10x by weight) using benzene as eluent, and recrystallized from benzene (Table).

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