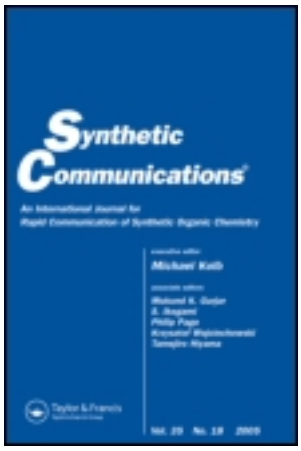

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# A Convenient Preparation of *N*-Alkyl and *N*-Arylamines by Smiles Rearrangement—Synthesis of Analogues of Diclofenac

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## ABSTRACT

Smiles rearrangement of substituted aryloxyacetamides in which oxygen and nitrogen are separated by $COCH_2$ group has been successful even when the aryloxy ring carries weak or no electron withdrawing group. Earlier reports of such reactions involved either strong electron withdrawing groups or a special catalyst. The diphenylamines thus obtained gave analogues of diclofenac in only one case.

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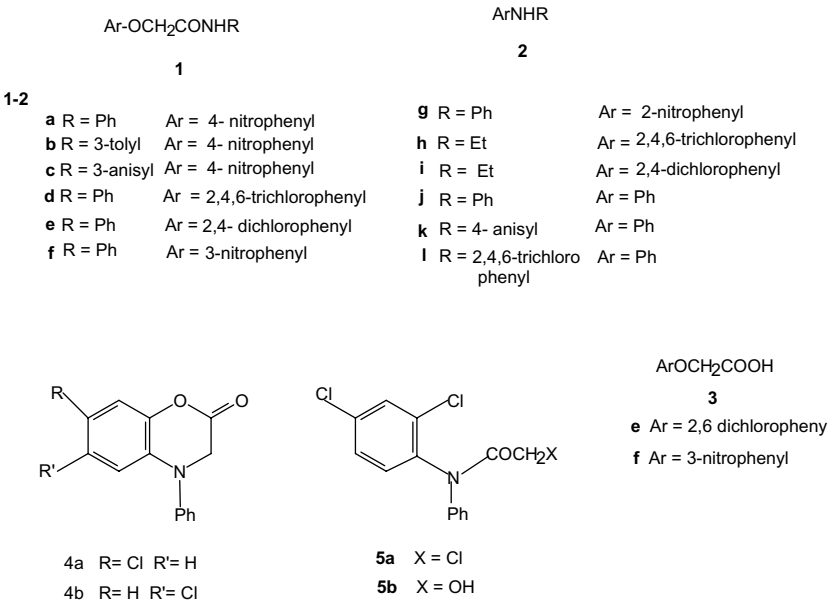
Diaryl amines are frequently difficult to prepare, especially if the two aryl rings are different. One method for their preparation involves Smiles rearrangement.[1,2a] The rearrangement of *o*-aminophenyl aryl ethers has been reviewed.[2a]

Rearrangements are reported when the aryl rings carried strong electron withdrawing substituents like nitro and three or more fluorine atoms.[2a] The first example of Smiles rearrangement with a single halogen atom as the activating group was carried out in this series of compounds using excess $NaNH_2$ in refluxing benzene.[2b]

For aryloxyacetamides where oxygen and nitrogen are separated by $CH_2$-CO group, the Smiles rearrangement has been successful in NaH/DMF at 50°C only when aryloxy ring contains strong electron withdrawing groups such as $NO_2$.[4] The only report[4] when phenoxy ring carries two or three chlorines needs a special catalyst viz TDA.

The reaction is facilitated if the oxygen and nitrogen of the aryloxyacetamides are separated by $CMe_2$-CO group[3,5] since formation of spirocyclic intermediate is aided by the presence of methyl groups. When the reaction is carried out with NaH/DMF[3] the reaction was successful only when the aryloxy ring contains strong electron withdrawing groups such as $NO_2$, $COC_6H_5$ or $CF_3$. However in this class of compounds reactions are successful even when the aryloxy ring contains no activating groups provided the reaction are carried out in NaH in the carcinogenic HMPA or NaH/DMF in presence of DMPU.[5] The present study reports the Smiles rearrangement of aryloxyacetamides in which the oxygen and nitrogen are separated by a $CH_2$-CO group. Smiles reaction of the amide **1a** has been reported[6] using NaOEt/EtOH at reflux. Under these conditions it gave a product characterized (m.p., spectral data) as the desired amine **2a** in 95% yield. Similar reactions were then carried out on the amides **1b–d** to afford the expected amines **2b–d** in 87,67, and 80% yields respectively. Reaction of the dichloroamide **1e**, under these conditions, gave a product m.p.138–139°C (82% yield) characterized as the acid **3e**. It has been reported[6] that rearrangement using $^{-}OH$ of less activated amides **1f** afforded the hydrolysis product **3f** whereas that of the more activated amides **1a** or **1g** under these conditions gave the rearranged products **2a** or **2g**.

In order to avoid such type of hydrolytic cleavage, it was decided to carry out further reactions in NaH/DMF.[3] Reaction of the amide **1d** afforded the product **2d** m.p. 42–43°C (characterized by the usual means) in 76% yield. Similar reaction on **1e**, **1h**, and **1i** provided the amines **2e**, **2h**, and **2i** in 52, 50, and 47% yields. Reaction of **1e** at 125°C gave the rearranged product **2e** in 40% yield and another compound m.p. 154–155°C (14%) which could have either structure **4a** or **4b**. In order



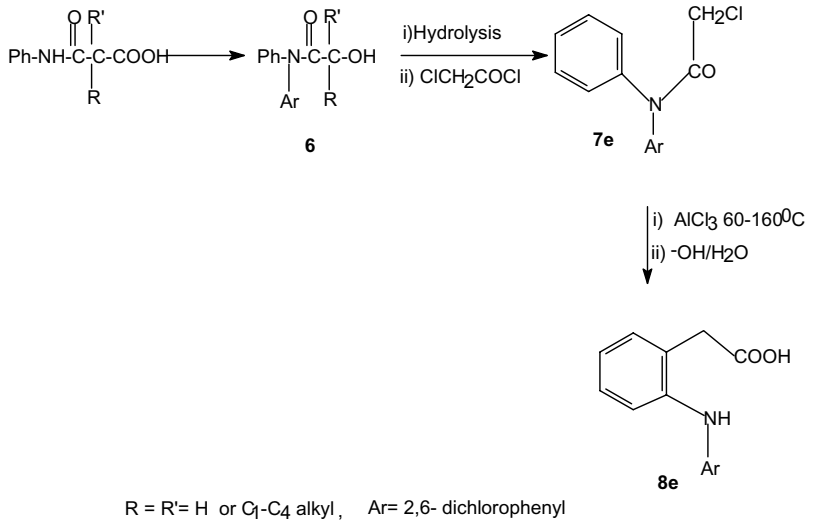

to decide between structure **4a** and **4b**, the amine **2e** was converted to the chloride **5a** (reaction with chloroacetyl chloride, 93% yield) and then to alcohol **5b** (hydrolysis with $Na_2CO_3$, yield 61% based on **5a** consumed). In the hydrolysis reaction, the amine **2e** characterized by direct comparison (TLC, IR, NMR) was isolated in 16% yield. Attempted cyclization of **5b** using NaH/DMF at room temperature gave two products one of which (28%) was identified as the amine **2e**. The other compound had m.p. 103–104°C very different from that (m.p. 154–155°C) isolated in the reaction of **1e** with NaH/DMF at high temperature. This initially led to the conclusion that compound m.p. 103–104°C was **4b** and compound m.p. 154–55°C was **4a**. However examination of its properties (TLC, Spectra) established that compound m.p. 103–104°C has structure **1e** and its formation involved a Smiles rearrangement occurring in 47% yield. Since Smiles rearrangement had been obtained starting from dichlorophenyl ethers **1e**, **1i**, **5b** it became of interest to see whether the rearrangement could be obtained in the unsubstituted phenyl ethers. Reaction of **1j** and **1k** with NaH/DMF at room temperature resulted in recovery of starting material. Reaction at 110°C gave the rearranged products **2j** and **2k** in 14 (65% based on **1j** consumed) and 35% yield respectively. This supported the idea that nucleophilicity of nitrogen is one of the factors[1,2] that governs the Smiles rearrangement. In keeping

with this the phenyl ether **1l**, where the nitrogen has very low nucleophilicity failed to give the rearranged product.

The rearrangement of **1j–k** represent the first examples of Smiles rearrangement in which oxygen and nitrogen are separated by $CH_2CO$ group and the phenoxy ring carries no substitutents.

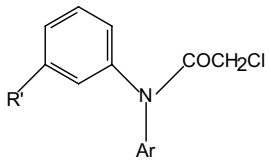
Diclofenac **8e** is perhaps the most widely used nonsteroidal antiinflammatory agent being the eighth largest selling drug overall.[7] Interestingly only one patent[8] uses a Smiles rearrangement for its synthesis (Sch. 1). The method reports[8] that R and R′ could be alkyl or hydrogen .The patent does not clarify if the reaction to give alcohol **6** during rearrangement is possible when both R and R′ are hydrogen. If this is possible then the direct conversion of **6** to **7e** (by $SOCl_2$) would make the process even more convenient.

Having obtained the amines **2a–e**, it was planned to convert these to compound **7a–e** which could then be converted to analogues of diclofenac **8e**. To check the validity of this reasoning diphenyl amine was converted via the chloroamide **7f** to the cyclized product **9f** which on hydrolysis provided the desired acid **8f** m.p. 114°C (Lit.[18] m.p. 114–116°C). The identity of **9f** and **8f** was confirmed by their spectral properties. Similarly the amine **2d** was transformed via **7d** and **9d** to **8d**. Since the conversion of **2e** to **8e** is reported, this was not carried out.




*Scheme 1.*

Interestingly cyclizations of the chloroamides **7a–c** (prepared from the amines **2a–c**) did not afford the desired cyclic products **9a–c** under a variety of conditions. The failure of cyclization of **7c** was a great surprise as it had a suitably placed methoxy group to aid the cyclization. The reaction of **7c** provided the compound **7g** in which demethylation had occurred. The identity of **7g** was conformed by its spectral properties.

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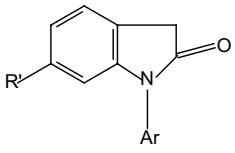


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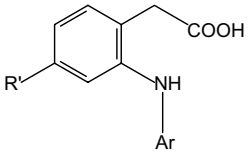


**8**

**7-9**

| | | | | | |
|---|---|---|---|---|---|
| **a** | Ar= 4-nitrophenyl | R'= H | **e** | Ar= 2,4-dichlorophenyl | R'= H |
| **b** | Ar= 4-nitrophenyl | R'=$CH_3$ | **f** | Ar= Ph | R'= H |
| **c** | Ar= 4-nitrophenyl | R'=$OCH_3$ | **g** | Ar= 4-nitrophenyl | R'= OH |
| **d** | Ar= 2,4,6-trichloro phenyl | R'= H | | | |

## EXPERIMENTAL

All melting points and boiling points are uncorrected. The yields of all the compounds reported are of crystallized or distilled pure compounds. All solvents were distilled and dried. Elemental analysis were obtained using Hosli's rapid carbon hydrogen analyzer. IR spectra were recorded on Perkin-Elmer FT-IR Model (1615). NMR spectra were recorded on Jeol FX 90Q (90 MHz) instrument in $CDCl_3$, values are given in $\delta$.

### General Procedure for the Preparation of Aryloxyacetamide

A mixture of aryloxyacetic acid (1 equiv.) and excess thionyl chloride was refluxed in an oil bath for 8–10 h. Excess thionyl chloride was removed under vacuum. To a cooled solution of the above acid chloride in dry benzene (20 mL), primary amine (2 equiv.) was added drop by drop keeping the temperature between 0–5°C. After addition, reaction was

refluxed for 2–4 h. After addition of few drops of conc. HCl and water, the aqueous layer was extracted with ether ($3 \times 40$ mL). The organic layer was washed with brine and then with water. Organic layer was dried over $Na_2SO_4$. Removal of ether by distillation afforded the product which was further purified by passage through silica gel column. The yields, m.p., IR, and analysis are given below.

**1a.** Yield: 93%, m.p. 169–170°C (Lit.[6] m.p. 170–71°C). IR (nujol): 3386, 1681, 1595, 1542, 1511, 1336, 870 $cm^{-1}$. $^1H$ NMR: $\delta = 4.83$ (s, 2H, $OCH_2$-), 7.2 (d, 2H, $J = 8$ Hz, ArH), 7.37 (d, 2H, $J = 9$ Hz, ArH), 7.43 (t, 1H, $J = 8$ Hz, ArH), 7.71 (m, 2H, ArH), 8.25 (d, 2H, $J = 9$ Hz, ArH), 9.71 (bs, 1H, NH). Anal. calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.41. Found: C, 61.85; H, 4.21.

**1b.** Yield: 95%, m.p. 93–94°C. IR (nujol): 3284, 1680, 1593, 1554, 1339, 846 $cm^{-1}$. $^1H$ NMR: $\delta = 2.37$ (s, 3H, $ArCH_3$), 4.88 (s, 2H, $OCH_2$), 6.98 (bd, 1H, $J = 9$ Hz, ArH), 7.28 (m, 5H, ArH), 8.28 (d, 2H, $J = 9$ Hz, ArH), 9.8 (bs, 1H, NH). Anal. calcd. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.89. Found: C, 63.15; H, 5.06.

**1c.** Yield: 88%, m.p. 114°C. IR (nujol): 3268, 1673, 1609, 1592, 1550, 1343, 858 $cm^{-1}$. $^1H$ NMR: $\delta = 3.94$ (s, 3H, $OCH_3$), 4.83 (s, 2H, $OCH_2$), 7.0 (bd, 1H, $J = 9$ Hz, ArH), 7.4 (bs, 1H, NH), 7.51 (m, 5H, ArH), 8.6 (d, 2H, $J = 9$ Hz, ArH). Anal. calcd. for $C_{15}H_{14}N_2O_5$: C, 59.60; 4.63. Found: C, 59.45; H, 4.86.

**1d.** Yield: 80%, m.p. 109–110°C (Lit.[9] m.p. 108–110°C). IR (nujol): 3392, 1694, 1597, 859, 763, 696 $cm^{-1}$. $^1H$ NMR: $\delta = 4.66$ (s, 2H, -$OCH_2$CO-), 7.11–7.60 (m, 5H, -NPh), 7.7 (s, 1H, ArH), 7.8 (s, 1H, ArH), 8.8 (bs, 1H, -NH). Anal. calcd. for $C_{14}H_{10}Cl_3NO_2$: C, 50.83; H, 3.02. Found: C, 50.54; H, 2.96.

**1e.** Yield: 82%, m.p. 103–104°C (Lit.[10] m.p. 105–106°C). IR (nujol): 3381, 1689, 1602, 901, 867, 755, 689 $cm^{-1}$. $^1H$ NMR: $\delta = 4.66$ (s, 2H, –$CH_2$CO), 6.94 (d, 1H, $J = 8$ Hz, ArH), 7.07–7.91 (m, 7H, ArH), 8.66 (bs, 1H, –NH). Anal. calcd. for $C_{14}H_{11}Cl_2NO_2$: C, 56.75; H, 3.72. Found: C, 56.94; H, 3.74.

**1h.** Yield: 84%, m.p. 98–99°C. IR (nujol): 3404, 1662, 1536, 856 $cm^{-1}$. $^1H$ NMR: $\delta = 1.24$ (t, 3H, $J = 6.5$ Hz, -$CH_3$), 3.48 (quin, 2H, $J = 6.5$ Hz, NH-$CH_2$), 4.57 (s, 2H, $OCH_2CO$), 7.31 and 7.4 (s, 1H each, ArH). Anal. calcd. for $C_{10}H_{10}Cl_3NO_2$: C, 42.48; H, 3.54. Found: C, 42.51; H, 3.47.

**1i.** Yield: 88%, m.p. 102–103°C. IR (nujol): 3287, 1663, 1563, 935, 867 $cm^{-1}$. $^1H$ NMR: $\delta = 1.23$ (t, 3H, $J = 6.5$ Hz, -$CH_3$), 3.43 (quin, 2H, $J = 6.5$ Hz, NH-$CH_2$), 4.54 (s, 2H, $OCH_2CO$), 6.80, (bs, 1H, NH), 6.88 (d, 1H, $J = 9$ Hz, ArH), 7.31 (bd, 1H, $J = 9$ Hz, ArH), 7.51 (bs, 1H, ArH). Anal. calcd. for $C_{10}H_{11}Cl_2NO_2$: C, 48.38; H, 4.43. Found: C, 48.35; H, 4.58.

**1j.** Yield: 90%, m.p. 98–99°C (Lit.[11] m.p. 101°C). IR (nujol): 3185, 1659, 1598, 1494, 764, 689 $cm^{-1}$. $^1H$ NMR: $\delta = 4.63$ (s, 2H, $OCH_2CO$), 6.88–7.86 (m, 10H, ArH), 8.37 (bs, 1H, NH). Anal. calcd. for $C_{14}H_{13}NO_2$: C, 74.00; H, 5.72. Found: C, 73.89; H, 5.55.

**1k.** Yield: 80%, m.p. 131°C (Lit.[11] m.p. 130°C). IR (nujol): 3254, 3198, 1664, 1615, 1494, 831, 753, 690 $cm^{-1}$. $^1H$ NMR: $\delta = 3.83$ (s, 3H, $OCH_3$), 4.66 (s, 2H, O-$CH_2CO$), 6.94 (d, 2H, $J = 8$ Hz, ArH), 7.1 (t, 1H, $J = 8$ Hz, ArH), 7.2 (d, 2H, $J = 8$ Hz, ArH), 7.4 (d, 2H, $J = 8$ Hz, ArH), 7.57 (t, 2H, $J = 8$ Hz, ArH), 8.37 (bs, 1H, -NH). Anal. calcd. for $C_{15}H_{15}NO_3$: C, 70.04; H, 5.84. Found: C, 70.13; H, 5.99.

**1l.** Yield: 78%, m.p. 162°C. IR (nujol): 3188, 1688, 1600, 1522, 875, 857, 770, 750, 688 $cm^{-1}$. $^1H$ NMR: $\delta = 4.74$ (s, 2H, -$OCH_2CO$), 7.12 (m, 3H, ArH), 7.36 (m, 2H, ArH), 7.46 (s, 2H, ArH), 8.14 (bs, 1H, -NH). Anal. calcd. for $C_{14}H_{10}Cl_3NO_2$: C, 50.83; H, 3.02. Found: C, 51.01; H, 3.26.

## General Procedure for the Preparation of Amines Using Smiles Rearrangement

I. A mixture of the amide (10 mmol) and alcoholic sodium ethoxide (20 mmol, 1 N) was refluxed for 30 min. The orange red reaction mixture was diluted with an equal volume of water and the precipitate of amine was filtered off, washed with water and recrystallized.

**2a.** Yield: 95%, m.p. 131°C (Lit.[6] m.p. 131–132°C). IR (nujol): 3336, 1603, 1584, 1540, 1524, 1376, 1303, 843, 749, 702, 690 $cm^{-1}$. $^1H$ NMR: $\delta = 6.8$ (bs, 1H, NH), 7.46 (d, 2H, $J = 9$ Hz, ArH), 7.8 (m, 5H, ArH), 8.77 (d, 2H, $J = 9$ Hz, ArH). Anal. calcd. for $C_{12}H_{10}N_2O_2$: C, 67.29; H, 4.67. Found: C, 67.17; H, 4.88.

**2b.** Yield: 67%, m.p. 123–124°C (Lit.[12] m.p. 125°C). IR (nujol): 3320, 1581, 1540, 1498, 1323, 840 $cm^{-1}$. $^1H$ NMR: $\delta = 2.22$ (s, 3H, $ArCH_3$), 6.48 (bs, 1H, NH), 7.2 (m, 6H, ArH), 8.37 (d, 2H, $J = 9$ Hz, ArH). Anal. calcd. for $C_{13}H_{12}N_2O_2$: C, 68.42; H, 5.26. Found: C, 68.55; H, 5.54.

**2c.** Yield: 87%, m.p. 112–113°C. IR (nujol): 3344, 1602, 1579, 1495, 1376, 1331, 842 $cm^{-1}$. $^1H$ NMR: $\delta = 3.88$ (s, 3H, $OCH_3$), 6.48 (bs, 1H, NH), 6.97 (m, 3H, ArH), 7.2 (d, 2H, $J = 9$ Hz, ArH), 7.34 (t, 1H, $J = 8.5$ Hz, ArH), 8.4 (d, 2H, $J = 9$ Hz, ArH). Anal. calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.91. Found: C, 64.11; H, 5.23.

**2d.** Yield: 80%, m.p. 42–43 (Lit.[13] m.p. 43–44°C). IR (nujol): 3391, 3079, 3051, 1601, 1553, 1497, 885, 856, 744, 691 $cm^{-1}$. $^1H$ NMR: $\delta = 5.89$ (bs, 1H, NH), 6.88 (d, 2H, $J = 8$ Hz, ArH), 7.0 (t, 1H, $J = 8$ Hz, ArH), 7.3

(t, 2H, $J = 8$ Hz, ArH), 7.46 (s, 2H, ArH). Anal. calcd. for $C_{12}H_8Cl_3N$: C, 52.84; H, 2.93. Found: C, 52.60; H, 3.05.

Similar reactions of **1e** gave two products identified as **3e** (82%) m.p. 138–139°C (Lit.[11] m.p. 140°C) and aniline (46%) identified by direct comparison (IR, m.p. b.p.) with authentic sample.

II. Hexane washed NaH (45 mmol) was added to a stirred solution of amide (15 mmol) in dry DMF (20 mL). The reaction was stirred at room temperature (in case of **2d**, **2e**, **2h**, **2i**) or at 115°C (for **2i**, **2j**, **2k**) for 24 h. After addition of water the product was extracted with ethyl acetate ($3 \times 20$ mL). The organic layer was washed first with brine, then water and dried ($Na_2SO_4$). Removal of ethyl acetate gave a product which was further purified by passage through silica gel column using hexane–ethyl acetate (97:3) as eluent.

**2d.** Yield: 76%, m.p. 42–43°C (Lit.[13] m.p. 43–44°C). Identified as **2d** by direct comparison (IR. mmp) with sample prepared earlier.

**2e.** Yield: 52%, m.p. 58–59 (Lit.[14] m.p. 64°C). IR (nujol): 3413, 1591, 1507, 872, 804, 734, 691, $cm^{-1}$. $^1H$ NMR: $\delta = 6.1$ (bs, 1H, NH), 6.88–7.57 (m, 8H, ArH). Anal. calcd. for $C_{12}H_9Cl_2N$: C, 60.50; H, 3.78. Found: C, 60.63; H, 3.95.

**2h.** Yield: 50%, b.p. 260–262 (Lit.[15] b.p. 148–153°mm). IR (neat): 3537, 3382, 3055, 1569, 856, $cm^{-1}$. $^1H$ NMR: $\delta = 1.2$ (t, 3H, $J = 6.5$ Hz, $-CH_3$), 4.25 (q, 2H, $J = 6.5$ Hz, $NCH_2$-), 6.07 (bs, 1H, NH), 7.4 (s, 2H, ArH). Anal. calcd. for $C_8H_8Cl_3N$: C, 42.76; H, 3.56. Found: C, 42.94; H, 3.76.

**2i.** Yield: 47% thick liquid. IR (neat): 3418, 3070, 1600, 1507, 797, 750 $cm^{-1}$. $^1H$ NMR: $\delta = 1.28$ (t, 3H, $J = 6$ Hz, $-CH_3$), 3.17 (q, 2H, $J = 6$ Hz, $NCH_2$), 4.2 (bs, 1H, NH), 6.6 (d, 1H, $J = 9$ Hz, ArH), 7.2 (d, 1H, $J = 9$ Hz, ArH), 7.34 (s, 1H, ArH). Anal. calcd. for $C_8H_9Cl_2N$: C, 50.52; H, 4.73. Found: C, 50.77; H, 5.02.

**2j.** Yield: 14% (65% based on **1j** consumed), m.p. 53–54°C (Lit.[16] m.p. 54°C). IR (nujol): 3376, 1593, 744, 690 $cm^{-1}$. $^1H$ NMR: $\delta = 5.68$ (bs, 1H, NH), 7.26 (m, 10H, ArH). Anal. calcd. for $C_{12}H_{11}N$: C, 85.20; H, 6.50. Found: C, 85.42; H, 6.42.

**2k.** Yield: 35%, m.p. 107–108°C (Lit.[16] m.p. 108°C). IR (nujol): 3384, 1596, 1510, 845, 750, 695 $cm^{-1}$.$^1H$ NMR: $\delta = 3.8$ (s, 3H, $OCH_3$), 5.48 (bs, 1H, NH), 7.0 (m, 9H, ArH). Anal. calcd. for $C_{13}H_{13}NO$: C, 78.39; H, 6.53. Found: C, 78.15; H, 6.39.

**2l.** Starting compound **1l** recovered.

Reaction of the amide (**2e**) was then carried out with stirring at 125°C for 20 h. Usual workup gave two products.

**2e.** Yield: 40%, m.p. 58–59°C.

**4a** or **4b.** Yield: 14%, m.p. 154–155°C. IR (nujol): 1690, 1593, 1492, 935, 852, 731 $cm^{-1}$. $^1H$ NMR: $\delta = 4.77$ (s, 2H, $-OCH_2CO$), 6.37 (d, 1H, $J = 8$ Hz, ArH), 6.86 (dd, 1H, $J = 2$ and 8 Hz, ArH), 7.1 (d, 1H, $J = 2$ Hz, ArH), 7.31 (m, 2H, ArH), 7.6 (m, 3H, ArH). Anal. calcd. for $C_{14}H_{10}ClNO_2$: C, 64.74; H, 3.85. Found: C, 64.62; H, 4.02.



## Preparation of 5a

A mixture of **2e** (1 g, 4 mmol) and chloroacetyl chloride (1.2 mL, d-1.418, 12 mmol) was refluxed for 6 h, cooled and evaporated. The residue was dissolved in ethyl acetate (40 mL). The organic phase was washed with aq. $KHCO_3$ (20 mL, 2N) and water (40 mL) and evaporated to afford a thick liquid.

**5a.** Yield: (1.23 g) 93%, thick liquid. $^1H$ NMR: $\delta = 4.02$ (s, 2H, $-NCOCH_2Cl$), 7.13–7.71 (m, 8H, ArH). Anal. calcd. for $C_{14}H_{10}Cl_3NO$: C, 53.42; H, 3.18. Found: C, 53.12; H, 3.36.

## Conversion of Chloroamide 5a to Hydroxyamide 5b

To the trichloride (1.1 g, 3.5 mmol), was added aq. $Na_2CO_3$ (10%, 20 mL). The reaction mixture was refluxed for 24 h, cooled and extracted with ethyl acetate ($3 \times 25$ mL). Usual workup gave a thick gel, which was purified by column chromatography using silica gel in hexane–ethyl acetate system to provide products.

**2e.** Yield: (10%) and **5a**: (40%) identified by usual means.

**5b.** Yield: (0.184 g) 37%, thick liquid. IR (neat): 3442, 1676, 1593, 1476, 981, 797, 737, 695 $cm^{-1}$. $^1H$ NMR: $\delta = 3.4$ (bs, 1H, exchanges, OH), 4.1 (bs, 2H, $CH_2$), 7.0–7.7 (m, 8H, ArH).

Attempted cyclization of **5b** in NaH/DMF.

Hexane washed NaH (0.66 mmol) was added to a stirred solution of **5b** (100 mg, 0.33 mmol) in dry DMF (10 mL). Reaction was stirred at room temperature for 20 h. Usual workup and purification gave two products.

**1e.** Yield: (0.047 g) 47%, m.p. 103–104°C, identical (TLC, IR, mmp) with the compound prepared earlier.

**2e.** Yield: (0.028 g) 28%, m.p. 58–59°C, identical (TLC, IR, mmp) with the compound prepared earlier.

### General Procedure for the Preparation of 7a–f

A mixture of amine **2a–f** (4 mmol), chloroacetyl chloride (1.2 mL, d-1.418, 12 mmol) and pyridine (1 drop) was refluxed (for 12 h), cooled and excess chloroacetyl chloride was removed. Usual workup using ethyl acetate gave the product.

**7a.** Yield: 91%, thick liquid. $^1$H NMR: $\delta = 4.34$ (s, 2H, $CH_2Cl$), 7.31 (m, 7H, ArH), 8.83 (d, 2H, $J = 9$ Hz, ArH). Anal. calcd. for $C_{14}H_{11}ClN_2O_3$: C, 57.83; H, 3.78. Found: C, 57.71; H, 3.70.

**7b.** Yield: 95%, thick liquid. IR (neat): 1692, 1592, 1350, 948, 916, 904, 859, 792, 754 cm$^{-1}$. $^1$H NMR: $\delta = 2.57$ (s, 3H, $ArCH_3$), 4.34 (s, 2H, $CH_2Cl$), 7.88 (m, 6H, ArH), 8.88 (d, 2H, $J = 8$ Hz, ArH). Anal. calcd. for $C_{15}H_{13}ClN_2O_3$: C, 59.11; H, 4.27. Found: C, 58.97; H, 4.39.

**7c.** Yield: 68%, m.p. 105–106°C. IR (nujol): 1682, 1592, 1552, 1519, 1494, 1336, 921, 851, 783, 754 cm$^{-1}$. $^1$H NMR: $\delta = 4.23$ (s, 2H, $CH_2Cl$), 4.25 (s, 3H, $OCH_3$), 7.26 (m, 2H, ArH), 7.66 (bs, 1H, ArH), 7.86 (d, 3H, $J = 9$ Hz, ArH), 8.6 (d, 2H, $J = 9$ Hz, ArH) Anal. calcd. for $C_{15}H_{13}ClN_2O_4$: C, 56.16; H, 4.05. Found: C, 56.23; H, 4.24.

**7d.** Yield: 93%, thick liquid. IR (neat): 1711, 1654, 1595, 1496, 860, 764, 736, 688, cm$^{-1}$. $^1$H NMR: $\delta = 4.0$ (s, 2H, $CH_2Cl$ of one conformer), 4.23 (s, 2H, $CH_2Cl$ of other conformer), 7.48 (m, 7H, ArH, of both conformers). Anal. calcd. for $C_{14}H_9Cl_4NO$: C, 48.14; H, 2.58. Found: C, 48.20; H, 2.85.

**7f.** Yield: 94%, m.p. 117–118°C. IR (nujol): 1680, 1591, 1489, 783, 732, 700 cm$^{-1}$. $^1$H NMR: $\delta = 4.08$ (s, 2H, $CH_2Cl$), 7.37 (bs, 10H, ArH). Anal. calcd. for $C_{14}H_{12}ClNO$: C, 68.43; H, 4.89. Found: C, 68.56; H, 4.89.

### General Procedure for the Cyclization of 7a–f

A mixture of chloroamide (0.3 mmol) anhydrous $AlCl_3$ (46 mg, 0.35 mmol) and NaCl (20 mg) was heated at 160°C for 30 min. Usual work-up using ethyl acetate gave the product. **7a** and **7b** gave a tarry product, while **7c** gave the uncyclized hydroxy compound **7g**.

**7g.** Yield: (0.080 g) 91%, thick liquid. IR (neat): 3316, 1679, 1594, 1518, 1487, 1348, 882, 857, 784 cm$^{-1}$. $^1$H NMR: $\delta = 4.26$ (s, 2H, $CH_2Cl$), 5.94 (bs, 1H, OH), 7.29 (m, 3H, ArH), 7.66 (bs, 1H, ArH), 7.88 (d, 2H, $J = 9$ Hz, ArH), 8.63 (d, 2H, $J = 9$ Hz, ArH). Anal. calcd. for $C_{14}H_{11}ClN_2O_4$: C, 54.81; H, 3.59. Found: C, 55.21; H, 3.96.

**9d.** Yield: 83%, m.p. 157–159°C. IR (nujol): 1725, 1613, 1488, 872, 820, 753 cm$^{-1}$. $^1$H NMR: $\delta = 3.8$ (s, 2H, CO-$CH_2$), 6.46 (d, 1H, $J = 8$ Hz,

ArH), 7.31 (m, 3H, ArH), 7.63 (s, 2H, ArH). Anal. calcd. for: $C_{14}H_8Cl_3NO$: C, 53.76; H, 2.56. Found: C, 53.49; H, 2.77.

**9f.** Yield: 60%, m.p. 120°C (Lit.[17] m.p. 121°C). IR (nujol): 1713, 1612, 1593, 1503, 1480, 857, 834, 750 $cm^{-1}$. $^1H$ NMR: $\delta = 4.0$ (s, 2H, $-COCH_2$), 7.37 (d, 1H, $J = 8$ Hz, ArH), 8.0 (m, 8H, ArH). Anal. calcd. for: $C_{14}H_{11}NO$: C, 80.38; H, 5.26. Found: C, 80.17; H, 5.54.

## General Procedure for the Preparation of Analogues of Diclofenac

A solution of **9d** or **9f** (1.6 mmol), aq. NaOH (2N, 1.5 mL) and ethanol (15 mL) was refluxed for 4 h. The clear solution was cooled in an ice bath and acidified with conc. HCl. The precipitated crystals were collected and recrystallized from ethanol.

**8d.** Yield: 86%, m.p. 170°C. IR (nujol): 3355, 2650, 1684, 1585, 1499, 946, 856, 772 $cm^{-1}$. $^1H$ NMR: $\delta = 3.77$ (s, 2H, $CH_2CO$), 6.0 (broad, 1H exchanges NH/OH), 6.54 (d, 1H, $J = 8$ Hz, ArH), 7.2 (m, 3H, ArH), 7.37 (bs, 1H, exchanges OH/NH), 7.54 (s, 2H, ArH). Anal. calcd. for $C_{14}H_{10}NCl_3O_2$: C, 50.83; H, 3.02. Found: C, 50.98; H, 3.23.

**8f.** Yield: 88%, m.p. 114°C (Lit.[18] m.p. 114–116°C). IR (nujol): 3396, 1711, 1611, 1592, 1502, 750, 696 $cm^{-1}$. $^1H$ NMR: $\delta = 3.64$ (s, 2H, $-CH_2CO$), 6.66 (bd, 1H, $J = 8$ Hz, ArH), 6.77 to 7.68 (m, 10H, ArH, NH, –COOH). Anal. calcd. for $C_{14}H_{13}NO_2$: C, 74.00; H, 5.72. Found: C, 74.25; H, 5.54.

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