Migration to Electron-Deficient Nitrogen. A One Pot Synthesis of Aromatic and Heteroaromatic Amines from Carboxylic Acids

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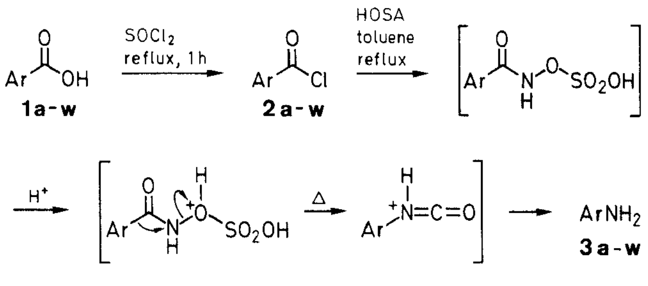
Treatment of a range of aroyl and heteroaryol chlorides with hydroxylamine-*O*-sulphonic acid in dry toluene, under reflux, gives good yields of the corresponding arylamine.

The Lossen, Hofmann, Curtius and Schmidt reactions are the classical methods for the conversion of carboxylic acids or their derivatives into the corresponding amine containing one carbon atom fewer. Among numerous other reactions involving migration from carbon to electron-deficient nitrogen,[1] of particular relevance to the present work is the Neber rearrangement.[2] Here, in the formation of α-amino ketones from oxime tosylates the leaving group from nitrogen is *p*-toluenesulphonate ion. The latter may be replaced by hydrogen sulphate ion or by sulphuric acid if hydroxylamine-*O*-sulphonic acid (HOSA) is employed to react with the rearrangement substrate. Thus, for example, aryl alkyl oximes rearrange to give *ca* 90% yields of *N*-aryl aliphatic amides when reacted with HOSA at steam-bath temperature.[3] To date HOSA has been employed with considerably less success for the conversion of carboxylic acids into the corresponding amines in the manner of the classical transformations mentioned at the beginning of this paper. Reaction of hexanoic acid with HOSA in mineral oil at 170–180 °C gave only a 23% yield of 1-aminopentane,[4] and, in the conversion of a range of mono-, di-, and trimethoxybenzoic acids into the corresponding amines, by reaction with HOSA in polyphosphoric acid at 115–120 °C, yields ranged from 0 to 35%.[5]



1-3	Ar	1-3	Ar	1-3	Ar
a	Ph	**i**	3-BrC$_6$H$_4$	**q**	2-O$_2$NC$_6$H$_4$
b	2-MeOC$_6$H$_4$	**j**	4-BrC$_6$H$_4$	**r**	3-O$_2$NC$_6$H$_4$
c	3-MeOC$_6$H$_4$	**k**	2-IC$_6$H$_4$	**s**	4-O$_2$NC$_6$H$_4$
d	4-MeOC$_6$H$_4$	**l**	3-IC$_6$H$_4$	**t**	4-NCC$_6$H$_4$
e	2-ClC$_6$H$_4$	**m**	4-IC$_6$H$_4$	**u**	2-pyridyl
f	3-ClC$_6$H$_4$	**n**	2-MeC$_6$H$_4$	**v**	3-pyridyl
g	4-ClC$_6$H$_4$	**o**	3-MeC$_6$H$_4$	**w**	2-quinolinyl
h	2-BrC$_6$H$_4$	**p**	4-MeC$_6$H$_4$		

We now report a convenient procedure for accomplishing such conversions, in yields of purified products ranging from 51 to 86%. The arylcarboxylic acid is first converted into the acid chloride by treatment with thionyl chloride, which is then heated under reflux with one equivalent of HOSA in dry toluene until the all acid chloride has been consumed. The results for the conversion of a range of acids (ArCO$_2$H, **1a–w**) into the amines (ArNH$_2$, **3a–w**) are shown in the Table.

Table. Aryl- and Heteroarylamines **3a–w** Prepared

Product	Reaction Time (h)	Yield (%)	bp (°C)/Torr or mp (°C) (solvent)[a]	mp (°C) ArNHAc (EtOH/H_2O)	Lit. mp (°C) ArNHAc
3a	1	67	184/760	113–114	114[6]
3b	1	65	224–225/760	83–85	85[7]
3c	4	57	250–252/760	79–80	81[6]
3d	1	70	57 (EtOH/H_2O)	129–130	130[6]
3e	1	86	95–97/11	86–87	88[6]
3f	2	77	110–112/12	71–72	73[6]
3g	12	59	67–69 (EtOH/H_2O)	176–177	178[6]
3h	2	61	31-32 (EtOH/H_2O)	98–99	100[7]
3i	4	62	251/760	88–89	88[6]
3j	9	61	66 (EtOH/H_2O)	165–166	167[6]
3k	3	60	60–61 (PE)	108–109	109[6]
3l	6	61	30–32 (PE)	117–118	119[6]
3m	9	69	60–62 (PE)	182–183	184[6]
3n	4	59	82–84/9	107–108	109[7]
3o	6	58	170–172/10	64–65	66[7]
3p	7	59	43–44 (EtOH/H_2O)	151–152	153[7]
3q	2	51	70–72 (H_2O)	92	92[6]
3r	4	59	111–113 (H_2O)	154	154[6]
3s	10	59	147–148 (EtOH/H_2O)	214–215	216[6]
3t	12	51	86 (PE)	205–206	205[7]
3u	3	54	95–96/10	69–70	71[6]
3v	8	57	62–63 (EtOH/H_2O)	130–132	133[6]
3w	3	51	129 (EtOH/H_2O)	254–256[b]	256[b]

[a] PE = petroleum ether, bp 60–80 °C.

[b] mp of picrate (Et_2O/EtOH).

In three cases the reaction failed to give the desired amine. After 24 hours 3,5-dinitrobenzoyl chloride had not reacted at all; 2-thiophenecarbonyl chloride was all consumed, but none of the amine could be isolated; and 2,6-bis(trifluoromethyl)benzoyl chloride gave only an intractable tar. The rearrangement step in the reaction, which takes place under acidic conditions, must resemble those in the Curtius and Schmidt processes, in that a positively charged species is lost from the nitrogen atom (as opposed to the anions involved in the Hofmann and Lossen reactions).

The analogy with the Schmidt reaction is particularly close. *ortho*-Substituted benzoic acids undergo the Schmidt reaction faster and at lower temperatures than others,[1] and the same is true for the groups of isomeric monosubstituted benzoic acids studied in the present work. Further, 4-methoxybenzoic acid reacts much more rapidly than other 4-substituted acids in both the Schmidt and HOSA reactions. With that exception, the reaction times in our studies were in the order *ortho* > *meta* > *para* for any set of isomers. The method here has advantages over the Hofmann, Lossen, and Curtius procedures in that it can be carried out in a one pot manner and (unlike the other one pot process, the Schmidt) avoids the use of hazardous azides.

Melting points are uncorrected; the starting materials **1a–w** are all commercially available.

Aryl- and Heteroarylamines 3a–w; General Procedure:

The carboxylic acid **1** (0.25 mol) is heated under reflux for one hour with $SOCl_2$ (15 mL), then the excess of reagent is removed by vacuum distillation at the water pump. The acid chloride **2** is dissolved in sodium-dried toluene (25 mL), HOSA (2.85 g, 0.25 mol) is added, and the whole is stirred and boiled under reflux until TLC reveals that all the acid chloride has been consumed (see Table for reaction times). The solution is cooled, poured into cold water (50 mL), and made basic by the addition of 2 M NaOH. The toluene layer is separated and combined with further Et_2O extracts (3 × 25 mL) of the aqueous phase. The organic solution is washed with water (2 × 25 mL), then with brine, then dried (Na_2SO_4), and the solvent is removed from the filtered solution on the rotary evaporator. The residue (the amine) is distilled or crystallised, as appropriate. Boiling points quoted in the Table are for distillations in a Kugelrohr apparatus; the melting points of the derivatives cited were undepressed on admixture with authentic samples.

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