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AMIDINOETHYLATION—A NEW REACTION—III

THE AMIDINOETHYLATION OF AMINO-COMPOUNDS: A FACILE SYNTHESIS OF 3-AMINOSUBSTITUTED-N,N'-SUBSTITUTED-PROPANAMIDINES[1]

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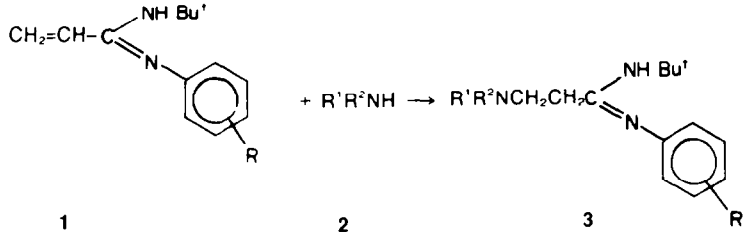
Abstract—The amidinoethylation of amino compounds takes place by the addition of amines to the C=C double bond of a variety of N,N'-substituted-propenamidines **1**. The most nucleophilic amines such as piperidine, morpholine and pyrrolidine add under very smooth conditions: 1 hr reflux in acetonitrile as solvent and without catalyst. Aliphatic amines such as cyclohexylamine and diisopropylamine require more drastic conditions, higher heating temperature and longer reaction time. Aromatic amines add in the presence of acetic acid; however under these conditions transamidination side reactions are observed. These results illustrate the activation of the C=C double bond of propenamidines by the conjugated amidine function thus providing a new class of Michaël acceptors for amino compounds. Furthermore the amidinoethylation makes available 3-aminosubstituted-N,N'-substituted-propanamidines **3** not easily accessible by other classical synthetic methods.

We have previously published the amidinoethylation reaction of thiols[2] and of compounds with active methylene[1] by their Michaël addition to propenamidines. To further illustrate this new reaction, we now report on the nucleophilic addition of amino compounds to propenamidines.

It is well known that non-aromatic heterocyclic or simple aliphatic amines add easily to the C=C double bond of propenenitrile,[3-5] propenoate,[6,7] propenamide,[8,9] vinylketones[10] or vinylsulfones[11] with or without catalyst. We have found that such amines add also to N,N'-substituted-propenamidines **1**[12,13] forming the 3-amino-substituted-N,N'-substituted-propanamidines **3** without catalyst. As models of vinylamidines **1** we have chosen the easily accessible N-t-butylpropenamidine derivatives recently described.[12] However, this reaction should work just as well whatever be the N-substituents (e.g. isopropyl[13]).

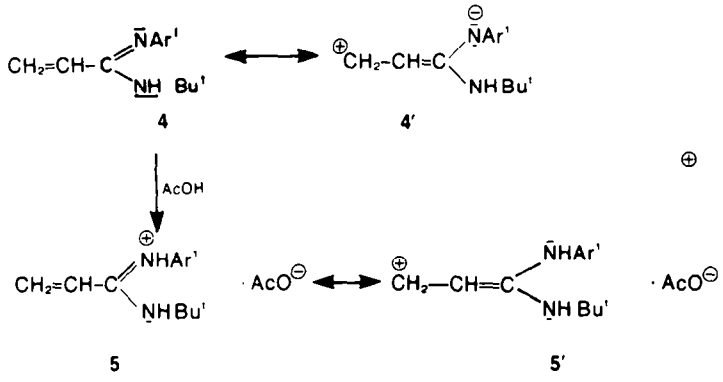


1 2 3

With piperidine, morpholine or pyrrolidine as the amine **2**, high yields have been obtained on heating equimolar amounts of **1** and **2** in acetonitrile at reflux during 1 hr (Table 1 products **3a–h**). The reaction with less nucleophilic amines such as cyclohexylamine or diisopropylamine requires longer heating time at higher temperature, neat or in 50% aqueous dimethylformamide; yields are lower (Table 1, products **3i–p**).

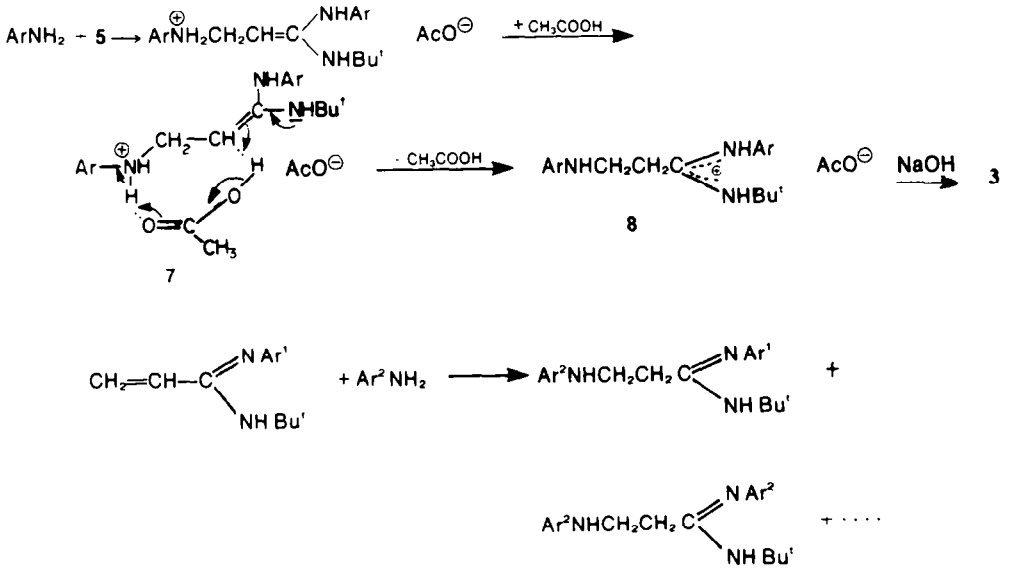
Usually the addition of aromatic amines to activated olefins is acid catalysed[14-18] (acetic acid or lewis acid) although it has been once shown[19] that the aromatic amine itself can play the role as the basic catalyst. We have observed that the non-catalysed addition of aromatic amines to propenamidines **1** requires much more drastic conditions than with aliphatic amines; e.g. heating at reflux (208°) the propenamidine **1r** (Table 1) with 2-chloroaniline as solvent during 18 hr leads to **3r** in 23% yield. The use of $SnCl_4$ as catalyst facilitates considerably the reaction by refluxing 2 hr in *o*-dichlorobenzene as solvent **1r** and **2r**. The addition product **3r** was isolated in 39% yield. The highest yields have been gained by heating a mixture containing 1 equiv of **1**; 1,5 equiv of the aromatic amine **2** and 1,5 equivs of acetic acid. The amidine **4** being a stronger base than the aromatic amine **2**, **1** would be completely protonated with one equivalent of acetic acid, the remaining half would protonate part of the amine **2**. The protonated propenamidine **5** was more activated towards nucleophiles than the free base **4** (no charge separation in the resonance form **5'**; *cf.* to the charge separation in the resonance form **4'**), thus the β-carbon in propenamidinium acetate **5** would be more electrophilic than in **4**. Thus the first (probably the rate-determining) step is the addition of anilines to **5** and acetic acid catalyses the proton-transfer from the acid to the α-carbon perhaps via a complex[3a,19,20] such as **7** leading to the acetate **8** of the final product **3**.

Good yields in propanamidines were obtained only when Ar^1 and Ar^2 were identical (Table 1 compounds **3q–v**). Indeed, when Ar^1 and Ar^2 were, a transamidination



different reaction took place leading to a mixture of amidines and thus lowering the yield (Table 1 compounds **3w–y**). These transamidination reactions are favored under acidic conditions.[21,22]

bond of propenamidines **1** illustrates the activation by the conjugated amidine function. This provides, with propenamidines, a new class of Michaël acceptors for amino compounds. Furthermore, this reaction makes



The major interest of the amidinoethylation reaction of amines depend on the preparation of 3 - amino substituted - N,N' - substituted - propanamidines **3** by other methods e.g. starting from the 3-amino substituted-propanenitrile then building-up the amidine function. We have failed in such attempts.

Heating pure compound **3d** during several hours at about 150° resulted in the recovery of some starting propenamidine **1d** thus showing that the amidinoethylation is reversible as other Michaël reactions.

All compounds **3** described are new, their analytical and spectral data confirm the assigned structure **3**. The molecular formulae have been confirmed by elementary analysis and mass spectra (Table 1). The ^{1}H-NMR spectra have been recorded and all signals attributed (Table 2). Their IR spectra display a characteristic strong absorption of the amidine function in the 1625–1640 cm^{-1} region, some other characteristic bands for each compounds are also tabulated (Table 3).

In conclusion, the amidinoethylation of amino compounds by the addition of amines to the C=C double easily available 3-amino substituted-N,N'-substituted propanamidines not easily accessible by other classical methods. These have shown an interesting pharmacological activity.[23]

EXPERIMENTAL

M.ps were determined on a kofler hot-stage apparatus. B.ps are uncorrected, IR spectra were measured on a Perkin–Elmer 177 spectrophotometer as KBr pellets or when liquid on film over NaCl plates. ^{1}H-NMR were recorded on a Varian T-60 or Jeol JNM-MH 100 instrument using TMS as internal standard. Mass spectra were recorded on a Hitachi Perkin–Elmer RMU-6D instrument. The synthesis of N,N'-substituted propenamidines **1** has been reported earlier.[12,13]

General procedures

Method A: *Compounds* **3a–h**. The amine **2** (0.01 mol) was added to **1** (0.01 mol) in acetonitrile (20 ml) and the mixture heated at reflux during 1 hr. The soln was cooled and the end-product **3** usually crystallised spontaneously; it was then recrystallised from the appropriate solvent (Table 1).

Method B: *Compounds* **3i–l**. A mixture of 1 equiv of **1** and 1 eqüiv of cyclohexylamine was heated 3 hr at 120°. It was then

Table 1. 3-Aminosubstituted N,N'-t-butylpropanamidines 3

Product No	R	R_1 R_2	Yield (%)	Method	m.p. (solvent)	Molecular formula [a]	Mass Spectra m/e M^+
3a	4-OCH_3	$-(CH_2)_5-$	78	A	77°C (MeCN)	$C_{19}H_{31}N_3O$	317
3b	4-NO_2	$-(CH_2)_5-$	86	A	106°C (MeCN or EtOH)	$C_{18}H_{28}N_4O_2$	332
3c	2-Cl	$-(CH_2)_5-$	92	A	76°C (MeCN)	$C_{18}H_{28}N_3Cl$	322
3d	2-CH_3	$-CH_2)_2O(CH_2)_3-$	75	A	59°C (MeCN or Ether)	$C_{18}H_{29}N_3O$	303
3e	3-Cl	$-(CH_3)_2O(CH_2)_2-$	78	A	89°C (MeCN)	$C_{17}H_{26}N_3OCl$	324
3f	4-Cl	$-(CH_2)_2O(CH_2)_2-$	68	A	105°C (MeCN)	$C_{17}H_{26}N_3OCl$	324
3g	2-CN	$-CH_2)_4-$	97	A	99°C (MeCN)	$C_{18}H_{26}N_4$	298
3h	2-NO_2	$-(CH_2)4-$	65	A	122°C (MeCN)	$C_{17}H_{26}N_4O_2$	318

Table 1 (*Contd*).

Product N°	R	R_1	R_2	Yield (%)	Method	m.p. (solvant)	Molecular formula[a]	Mass Spectra m/e M^+
3i	2-Cl	c-hexyl	H	71	B	73°C pentane	$C_{19}H_{30}N_3Cl$	336
3j	2-H_3C	c-hexyl	H	50	B	82°C pentane	$C_{20}H_{33}N_3$	315
3k	2,6-diCl	c-hexyl	H	72	B	68°C pentane	$C_{19}H_{29}N_3Cl_2$	370
3l	4-$H_5C_2O_2C$	c-hexyl	H	82	B	77°C EtOH	$C_{22}H_{35}N_3O_2$	373
3m	3-F_3C	c-hexyl	H	77	C	56°C pentane	$C_{20}H_{30}N_3F_3$	369
3n		c-hexyl	H	50	C	72°C pentane	$C_{19}H_{31}N_3$	301
3p	4-NO_2	i-prop	i-prop	70	D	67°C MeCN	$C_{19}H_{32}N_4O_2$	348

Table 1 (*Contd*).

Product n.°	R	R_1	R_2	Yield (%)	Method	m.p. (solvant)	Molecular formula[a]	Mass Spectra m/e M⁺
3g	4-CO_2Et	4-CO_2Et-C_6H_4-	H	80	C	105°C CH_3OH	$C_{25}H_{33}N_3O_4$	439
3r	2-Cl	2-Cl-C_6H_4-	H	75	C	70°C pentane	$C_{19}H_{23}N_3Cl_2$	364
3s	4-Cl	4-Cl-C_6H_4-	H	88	C	103°C hexane	$C_{19}H_{23}N_3Cl_2$	364
3t	4-Me	4-Me-C_6H_4-	H	75	C	124°C pentane	$C_{21}H_{29}N_3$	324
3u	2-CN	2-CN-C_6H_4-	H	89	C	142°C C_2H_5-OH	$C_{21}H_{23}N_5$	345
3v	4-NO_2	4-NO_2-C_6H_4-	H	75	C	216°C CH_3CN	$C_{19}H_{23}N_5O_4$	385
3w	2-Me	4-CO_2Et-C_6H_4-	H	42	C	84°C C_2H_5OH	$C_{23}H_{31}N_3O_2$	381
3y	3-Cl	4-CO_2Et-C_6H_4	H	30	C	102°C hexane	$C_{22}H_{28}N_3O_2Cl$	401

a) The microanalyses were satisfactory agreement with the calculated values (C ± 0,3 % ; H ± 0,3 % ; N ± 0,4 %)

Table 2. ^{1}H-NMR data for compounds 3a–y

Product N°	δ (ppm) in $CDCl_3$ or DMSO – d_6 (a)(b)
3 a	7,2(1 NH); 6,4 – 6,9 (4 m, Ar H); 3,70 (3s, $ArOCH_3$); 1,9 – 2,6 (8 m, ); 1,2 – 1,8 [9δ (1,4) C_4H_9-t and 6 m, ).
3 b	6,6 – 8,3 (4m, ArH + 1NH (7,95)); 2,1 – 2,7 (8 m, ); 1,3 – 1,9 [9s (1,4) C_4H_9-t and 6 m ].
3 c	7,56 (1NH); 6,62 – 7,36 (4 m, ArH); 2,2 – 2,48 (6 m, CH_2 – N ); 1,92 – 2,16 (2 m, $-CH_2$ – ); 1,96 – 1,8 [9s (1,96) C_4H_9-t and 6 m ].
3 d	6,2 – 7,3 (4 m, ArH + 1 NH); 3,4 – 3,8 (4 m, ); 1,8 – 2,5 (3δ, $ArCH_3$ (2,0), 8 m,  ; 1,4 (9s, C_4H_9-t).
3 e	6,4 – 7,3 (4 m, ArH + 1NH); 3,5 – 3,8 (4 m, ); 2,0 – 2,7 (8 m ); 1,4 (9s, C_4H_9-t).
3 f	6,28 – 7,28 (4 m, ArH, + 1NH (6,86)); 3,6 – 3,8 (4 m, ); 2,32 – 2,6 (6 m, CH_2 – ); 2,08 – 2,18 (2 m, CH_2 – ), 1,44 (9s, C_4H_9-t)
3 g	6,9 (1NH); 6,7 – 7,6 (4 m, ArH); 2,0 – 2,9 (8 m, ); 1,6 – 2,0 (4 m, ); 1,4 (9s, C_4H_9-t).
3 h	6,6 – 7,9 (4 m, ArH + 1NH); 2,3 – 2,8 (6 m; CH_2 – ); 2,0 – 2,25 (2t, CH_2 1,5 – 1,9 (4 m, ); 1,3 (9s, C_4H_9-t).
3 i	7,4 – 6,4 (5m, ArH + 1 NH); 2,65 (2t $-CH_2$ – ), 2,5 – 0,6[23 m, $C_6H_{11}NHCH_2$; 1,4 (s, C_4H_9 – t)],
3 j	7,3 – 6,4 (5 m, Ar H + 1 NH); 2,7 (2t, $-CH_2$ – ); 2,5 – 0,8[26 m, $C_6H_{11}NHCH_2$–; 2,1 (s, $ArCH_3$); 1,45 (s, C_4H_9 – t).].
3 k	7,4 (1 , ); 7,2 – 6,5 (3 m, ArH); 2,65 (2t, $-CH_2$ –); 2,4 – 0,8[23 m, $C_6H_{11}NH$ – CH_2 ; 1,45 (S, C_4H_9 – t)].

Table 2 (*Contd*).

Product N°	δ (ppm) in $CDCl_3$ or DMSO - d_6 (a)(b)
3 l	7,9 - 6,6 (4 m, ArH); 6,9 (1NH); 4,3 (2q, $-O-CH_2-$); 2,65 (2t, $-CH_2$; 2,5 - 0,7 [26 m, $C_6H_{11}NHCH_2-$, $-O-CH_2-CH_3$; 1,4 (s, C_4H_9- t)].
3 m	7,35 - 6,65 (5 m, ArH + 1NH); 2,75 (2t, $-CH_2-C\lesssim^{N}_{N}$); 2,45 - 0,65 [23 m, $C_6H_{11}NHCH_2$; 1,4 (s, C_4H_9 - t)]
3 n	7,4 - 6,4 (6 m, ArH + 1 NH); 2,65 (2t, $CH_2-C\lesssim^{N}_{N}$); 2,5 - 0,8 [23 m, $C_6H_{11}NHCH_2$ 1,4 (s, C_4H_9 - t)].
3 p	8,2 - 6,7 (4 m, ArH); 7,4 (1 NH); 3,2 (2 h, CH $(CH_3)_2$); 2,7 (2t, N - CH_2-); 2,3 (2t, $-CH_2-C\lesssim^{N}_{N}$); 1,5 (9s, C_4H_9-t); 1,1 (12 d, $C\lesssim^{CH_3}_{CH_3}$).
3 q	6,3-8,1(ArH); 4,35 (2x2q,O-CH_2-); 3,5 (N-H); 3,3 (2t, N-CH_2-); 2,4(2t, $-CH_2-C\lesssim^{N}_{N}$); 1,95 (NH); 1,3 - 1,4 [(9s tBu); (2 x 3t, $O-CH_2-CH_3$)].
3 r	6,2 - 7,5 (8 m, ArH); 4,45 (2 x NH); 3,25 (2q, N- CH_2-); 2,3 (2t, $CH_2-C\lesssim^{N}_{N}$); 1,45 (9s, t-Bu)
3 s	6,2 - 7,4 (8 m, ArH); 1,35 (1 , $C\lesssim^{N}_{NH}$); 2,6 (1 , ArNH); 3,2 (2t, N-CH_2); 2,35 (2t, $CH_2C\lesssim^{N}_{N}$); 1,4 (9s, t-Bu).
3 t	6,0 - 7,2 (8 m, ArH); 4,2 ($C\lesssim^{N}_{NH}$); 3,25 (2t, N-CH_2 + 1NH); 2,3 (3s, Ar^1CH_3); 2,2 (3S, Ar^2CH_3 et $CH_2-C\lesssim^{N}_{N}$); 1,4 (9s, t-Bu).
3 u	6,1 - 7,7 (8 m, ArH); 4,8 (2 x NH), 3,35 (2q, N-CH_2); 2,4 (2t, $-CH_2$); 1,45 (9s, tBu).
3 v	6,4 - 8,5 (8 m, ArH); 3,7 ($C\lesssim^{N}_{NH}$); 3,35 (2t, N-CH_2-); 2,45 (2t, CH_2); 1,8 (Ar^2NH), 1,4 (9s, t-Bu).
3 w	6,2 - 8,12 (8 m, ArH); 4,8 ($C\lesssim^{N}_{NH}$); 4,28 (2q, $O-CH_2$ CH_3); 3,52 (ArNH); 3,18 (2t, N-CH_2-); 2,36 (2t, $CH_2C\lesssim^{N}_{N}$); 2,04 (3s, $ArCH_3$); 1,24 - 1,36 [(9s, t-Bu); (3t, $-OCH_2CH_3$)].
3 y	6,1 - 8,1 (8 m, ArH); 4,35 (2q, O-CH_2- + 2 NH); 3,2 (2m, NH - CH_2-) 2,35 (2t, $-CH_2-C\lesssim^{N}_{N}$); 1,1 - 1,4 [(9s, t-Bu); (3t, $-OCH_2CH_3$)].

a) s = singlet; d = doublet; t = triplet; q = quadruplet; h = heptuplet; m = multiplet.

b) solvent for compound 3y.

Table 3. Infra-red spectra for compounds 3a–y

Product N°	ν (cm^{-1}); KBr (a)
3a	3240(m,NH) 3050(m,CH) 2940(S,CH_2) 1640(VS,C=N) 1560(S,C=C)
3b	3220(m,NH) 3040(m,CH) 2940(S,CH_2) 1630(VS,C=N) 1590(VS,C=C) 1550 (VS,NO_2) 1330 (VS,NO)
3c	3240(m,NH) 3060(m,CH) 2940(S,CH_2) 1630(VS,(C=N) 1560(VS, C=C)
3d	3230(m,NH) 3030(m,CH) 2960(S,CH_2) 1630(VS,C=N) 1590(S, C=C)
3e	3240(m,NH) 3060(m,CH) 2960(S,CH_2) 1630(VS,C=N) 1580(S, C=C)
3f	3240(m, NH) 3050(m,CH) 2960(S,CH_2) 1630(VS,C=N) 1550(S, C=C)
3g	3230(m,NH) 3060(m,CH) 2970(S,CH_2) 1625(VS,C=N) 1590(S,C=C) 2220 (S,C=N
3h	3240(m,NH) 3060(m,CH)2960(S,CH2) 1630(VS,C=N 1600(S,C=C) 1560 (VS,NO_2)1350 (S,NO)
3i	3260 (w, NH); 3220 (w, NH); 1625 (S, C = N); 1570 (S, C = C)
3j	3260 (w, NH); 1625 (S, C = N); 1560 (S, C = C
3k	3240 (w, NH); 3180 (w, NH); 1635 (vs, C = N); 1550 (s, C = C) ; 760 (m, C–Cl);
3l	3240 (m, NH); 3160 (w, NH); 1710 (s, C = O); 1640 (s, C = N); 1600 (s, C = C)
3m	3240 (w, NH); 1630 (s, C = N); 1550 (C = C ; 1120 (vs, –CF);
3n	3270 (m, NH); 3240 (w, NH); 1625 (vs, C = N); 1565(C = C)
3p	3220 (w, NH); 1630 (s, C = N); 1580 (s, C = C) 1550 (s, NO_2 ass); 1320 (vs, NO_2 sym).
3q	3400 (S,NH); 3390 (S,NH); 1695 (VS, C=O); 1640 (VS, C=N); 1590 (S,C=C)
3r	3430 (m,NH); 3400 (m, NH); 1620 (VS, C=N); 1585 (m, C=C)
3s	3420 (m,NH); 3400 (m,NH); 1630 (S,C=N); 1600 (m,C=C)
3t	3440 (m,NH); 1635 (vS,C=N); 1570 (C=C,W)
3u	3395 (S,NH); 3460 (S,N–H); 2230 (S,C≡N); 1630 (vS,C=N); 1590 (S,C=C)
3v	3410 (m,NH); 3395 (m,NH); 1640 (m,C=N); 1600 (m, C=C); 1530 (S,as–NO_2); 1320 (vS, S–NO_2).
3w	3395 (S,NH); 1690 (S,C=O); 1640 (S,C=N); 1595 (S,C=C);
3y	3410 (m,NH); 3380 (S,NH); 1690 (S,C=O); 1635 (S,C=N); 1590 (S,C=C).

a) vs = very strong; s = strong; m = medium; w = weak.

kept overnight and the residue recrystallised from the appropriate solvent (Table 1).

Method C: *Compounds* **3m–n**. To a 50% aqueous soln of DMF (20 ml) 0.01 mol of **1** and 0.01 mol (1,2 ml) of cyclohexylamine were added. The mixture was heated 4 hr under reflux. The cooled soln was then extracted with $CHCl_3$, the organic phase washed twice with water, dried and concentrated. The residue was recrystallised from the appropriate solvent (Table 1).

Method D: *Compounds* **3p**. A mixture containing 2,47 g (0,01 mol) of **1p** in 20 ml diisopropylamine was heated under reflux during 7 days. The excess amine was then evaporated to dryness and the residue (**3p**) recrystallised from EtOH.

Method E: *Compounds* **3q–y**. To a soln containing 0.0135 mol of **1** (1 eq) in 30 ml ethyleneglycoldimethylether or EtOH, 0.0202 mol (1.5 eq) of **2** and 1,15 ml (1.5 eq) AcOH was added. The mixture was heated 15 hr under reflux. It was then cooled, diluted with $CHCl_3$ and thoroughly extracted with 1 M NaOH. The organic phase was dried over $MgSO_4$ and the filtered soln concentrated to dryness. The solid residue was then recrystallised from the appropriate solvent (Table 1).

Other procedures with aromatic amines

(a) *Non catalysed addition*. To 30 ml *o*-chloraniline, 2,35 g (0.01 mol) of **1r** was added and the soln heated under reflux during 18 hr. The excess amine was then vacuum-distilled off and the solid residue **3r** crystallised from EtOH–water or pentane, yield: 0.84 g (23%); m.p. 70°.

(b) *Catalysed by* $SnCl_4$. To 25 ml *o*-dichlorobenzene, 2.4 ml $SnCl_4$ (0.02 mol) was added. Then 4.73 g (0.02 mol) of **1r** followed by 2.1 ml (0.02 mol) *o*-chloraniline were added and the mixture heated under reflux during 2 hr. After cooling, the mixture was extracted with HCl (about 1 M). The aqueous acidic phase was made strongly alkaline with 30% NaOH aq and then extracted with $CHCl_3$. The organic phase was dried then evaporated to dryness. The unreacted *o*-chloraniline was vacuum distilled off and the solid **3r** recrystallised, yield: 2,84 g (39%).

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