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A NOVEL ROUTE TO N-STYRYLAMIDES

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ABSTRACT: A general synthesis of N-styrylamides starting from amides and phenylacetaldehyde is described. Condensation of the amide, aldehyde and benzotriazole affords N-(1-benzotriazol-1-yl-2-phenylethyl)amides **2** from which the benzotriazole molecule is smoothly eliminated.

N-Styrylamides have long attracted attention due to their biological activity[1-3] and synthetic utility.[4] An early preparative procedure involved thermal decomposition of alkylidenebisamides prepared from β-aryl- acetaldehydes and primary amides.[5] This process required high temperatures and was later supplemented by other methods (for a review see ref. [4]). Several preparations of N-styrylbenzamides have recently been developed in connection with alkaloid syntheses, but limitations are evident: i) the condensation of N-methylbenzamides with phenylacetaldehyde dimethylacetals is limited to secondary amides;[6] ii) the oxidation of an N-(β-phenylethyl)benzamide to the corresponding β-acetoxy derivative, followed by thermal generation of the double bond succeeds only when

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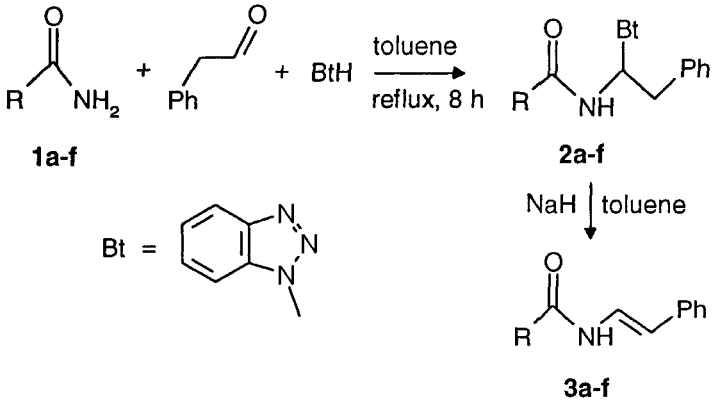
electron-donating substituents are present on the aromatic ring;[7] iii) the benzoylation of N-(2-phenylthio-2-phenylethyl)benzamide, followed by oxidation to the sulfoxide and subsequent phenyl sulfoxide elimination is more general and affords N-styryl benzamides in good yields,[6] but requires the use of starting materials which are difficult to prepare.

N-[(1-Benzotriazol-1-yl)alkyl]amides, easily prepared by the condensation of benzotriazole, an aldehyde and an amide, have been utilized by our group as versatile reagents for many synthetic purposes.[8,9] We now wish to report a convenient preparation of N-styrylamides **3** from N-[1-(benzotriazol-1-yl)-2-phenylethyl]amides **2**. This route from readily available starting materials is more simple than the most general of those previously reported.[7]



Compounds **2a-f** (Table 1) were easily prepared by refluxing a mixture of amide, phenylacetaldehyde and benzotriazole in equimolecular amounts with azeotropic removal of the water. Both aliphatic and aromatic amides gave stable products **2** in moderate to good yields. Derivatives **2** were fully characterized by their ^{1}H and ^{13}C spectra and by elemental analysis in the case of new compounds (Table 1). For an alternative preparation of amides **2** recently developed in our group, see ref. [10]

Table 1. Preparation of N-[1-(benzotriazol-1-yl)-2-phenylethyl]amides **2** and N-styrylamides **3.**

Cpd	R	Yield	mp	calcd			found		
		(%)	(°C)	C	H	N	C	H	N
2a	Ph	70	180-182[a,b]						
2b	4-MeC_6H_4	48	186-187[b]	74.12	5.66	15.73	74.35	5.87	15.81
2c	4-$MeOC_6H_4CH_2$	42	128-130[c]	71.47	5.74	14.50	71.73	5.86	14.14
2d	$PhCH_2$	86	120-122[b]	74.12	5.66	15.73	74.55	5.67	15.85
2e	Et	44	175-176[c]	69.35	6.17	19.04	69.65	6.21	18.87
2f	pyrid-3-yl	33	164-165[c]	69.94	4.99	20.40	70.01	4.98	20.40
3a	Ph	93[d]	181-182[c,e,f]	80.68	5.87	6.28	81.00	6.02	6.15
3b	4-MeC_6H_4	91[d]	194-195[c,e]	80.97	6.38	5.91	80.82	6.44	5.84
3c	4-$MeOC_6H_4CH_2$	94[d]	152-153[c,e]	76.37	6.41	5.24	76.08	6.55	5.38
3d	$PhCH_2$	84[d]	130-132[c,e]	80.97	6.38	5.91	80.62	6.37	5.86
3e	Et	89[d]	135-137[c,e]	75.39	7.48	8.00	75.68	7.50	7.72
3f	pyrid-3-yl	95[d]	158-159[c,e]	74.97	5.40	12.50	74.69	5.41	12.48

[a] Lit.[9] mp 180-182 °C. [b] From methanol. [c] From hexane/ethyl acetate. [d] Mixture of Z- and E-isomers. [e] E-isomer. [f] Lit.[5] mp 180 °C.

Benzotriazole was smoothly eliminated from **2a-f** by heating with 1.1 equivalents of sodium hydride in toluene or THF to give N-styrylamides **3a-f** (Table 1) in good yields. A mixture of Z- and E- isomers was usually obtained in which the E-isomer always predominated. Sodium carbonate can also be used as the base for benzotriazole molecule elimination, although it takes more time and the yields are somewhat lower. The structures of all N-styrylamides **3** have been confirmed by ^1H and ^{13}C NMR spectra and elemental analyses.

In summary, the use of benzotriazole promotes condensation of the amide and phenylacetaldehyde and is then eliminated to yield N-styrylamides. Due to the

simplicity, high yields and availability of starting materials this methodology is the route of choice for the preparation of N-styrylamides.

EXPERIMENTAL SECTION

Preparation of N-(1-benzotriazol-1-yl-2-phenylethyl)amides 2. Typical procedure. A mixture of benzotriazole (11.9 g, 0.1 mol), phenylacetaldehyde (1.20 g, 0.1 mol), the appropriate amide (0.1 mol) and p-toluenesulfonic acid (catalytic amount) was refluxed in dry benzene or toluene (50 ml) for 8 h. Water formed during the reaction was removed azeotropically by a Dean-Stark apparatus. The solvent was removed under reduced pressure, and the residue was dissolved in chloroform (100 ml). The resulting solution was washed with 10% Na_2CO_3 (3 x 50 ml) and water (50 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue was crystallized from an appropriate solvent (Table 1).

N-(1-Benzotriazol-1-yl-2-phenylethyl)benzamide (2a).

^{1}H NMR (DMSO-d_6, ppm): δ 3.78 (dd, 1H, J=13.6 Hz and J=7.5 Hz), 3.89 (dd, 1H, J=13.7 Hz and J=8.0 Hz), 7.09-7.18 (m, 2H), 7.23 (symm. m., 2H), 7.34 (d, 2H, J=7.8 Hz), 7.40 (dd, 1H, J=8.2 Hz and J=1.0 Hz), 7.47 (symm. m, 2H), 7.56 (symm. m, 2H), 7.88 (dd, 2H, J=6.9 Hz and J=1.5 Hz), 8.05 (dd, 1H, J=8.3 Hz and J=0.9 Hz), 8.09 (dd, 1H, J=8.4 Hz and J=0.8 Hz), 9.95 (d, 1H, J=8.0 Hz). ^{13}C NMR (DMSO-d_6, ppm): δ 38.7, 64.8, 111.1, 119.0, 124.0, 126.8, 127.2, 127.6, 128.2, 128.3, 129.2, 131.9, 132.2, 132.9, 136.1, 145.0, 166.6.

N-(1-Benzotriazol-1-yl-2-phenylethyl)-4-methyl-benzamide (2b).

^{1}H NMR (DMSO-d_6, ppm): δ 2.33 (s, 3H), 3.74-3.88 (m, 2H), 7.09-7.34 (m, 8H),

7.38 (ddd, 1H, J=8 Hz, J=7 Hz and J=1 Hz), 7.55 (ddd, 1H, J=8 Hz, J=7 Hz and J=1 Hz), 7.80 (d, 2H, J=8 Hz), 8.04 (dd, 1H, J=8.3 Hz and J=0.9 Hz), 8.10 (dd, 1H, J=8.4 Hz and J=0.9 Hz), 9.85 (d, 1H, J=8.1 Hz). ^{13}C NMR (DMSO-d_6, ppm): δ 21.0, 38.7, 64.8, 111.2, 119.0, 124.0, 126.8, 127.2, 127.6, 128.3, 128.9, 129.3, 130.1, 132.2, 136.2, 142.1, 145.0, 166.4.

N-(1-Benzotriazol-1-yl-2-phenylethyl)-2-(4-methoxyphenyl)-acetamide (2c).

^{1}H NMR ($CDCl_3$, ppm): δ 3.41 (s, 3H), 3.61 (symm. m, 2H), 3.76 (s, 3H), 6.78 (dd, 2H, J=6.6 Hz and J=2.1 Hz), 6.87-6.93 (m, 1H), 6.96 (dd, 2H, J=6.6 Hz and J=2.1 Hz), 7.02-7.05 (m, 2H), 7.12-7.17 (m, 3H), 7.25-7.40 (m, 3H), 7.62 (dd, 1H, J=8.3 Hz and J=0.9 Hz), 7.97 (dd, 1H, J=8.1 Hz and J=1.1 Hz). ^{13}C NMR ($CDCl_3$, ppm): δ 40.2, 42.1, 55.1, 63.0, 110.1, 114.2, 119.3, 124.2, 125.7, 127.1, 127.6, 128.6, 129.0, 130.3, 132.8, 134.7, 145.3, 158.7, 171.4.

N-(1-Benzotriazol-1-yl-2-phenylethyl)-2-phenyl-acetamide (2d).

^{1}H NMR ($CDCl_3$, ppm): δ 3.47 (s, 2H), 3.63 (dd, 2H, J=7.4 Hz and J=2.7 Hz), 6.9-7.0 (m, 1H), 7.0-7.1 (m, 4H), 7.1-7.2 (m, 3H), 7.2-7.4 (m, 5H), 7.62 (d, 2H, J=8.3 Hz), 7.96 (d, 1H, J=8.2 Hz). ^{13}C NMR ($CDCl_3$, ppm): δ 40.2, 42.9, 63.1, 110.2, 119.2, 124.2, 127.1, 127.3, 127.6, 128.7, 128.9, 129.1, 129.2, 132.9, 133.9, 134.8, 145.3, 171.0.

N-(1-Benzotriazol-1-yl-2-phenylethyl)-propanamide (2e).

^{1}H NMR ($CDCl_3$, ppm): δ 1.04 (t, 3H, J=7.6 Hz), 2.21 (symm. m, 2H), 3.72 (symm. m, 2H), 6.95 (symm. m, 1H), 7.15 (symm. m, 5H), 7.31 (symm. m, 1H), 7.39 (symm. m, 1H), 7.64 (symm. m, 2H), 7.97 (dd, 1H, J=8.3 Hz and J=1.0 Hz). ^{13}C NMR ($CDCl_3$, ppm): δ 9.6, 29.5, 40.9, 63.5, 110.6, 119.6, 124.6, 127.6, 128.1, 129.0, 129.4, 133.4, 135.4, 145.6, 174.3.

Table 2. ^{1}H NMR data of N-styrylamides **3** (δ, ppm).

Cpd	=CH-, d, (J, Hz)	Ph and R	=CH-N, dd, (J, Hz)	NH-C=O, d, (J, Hz)
3a[a]	6.28 (14.6)	7.16-7.38 (m, 5H), 7.43-7.58 (m, 3H), 7.86 (symm. m, 2H)	7.74 (14.6, 10.8)	8.12 (10.8)
3b[b]	6.49 (14.8)	2.38 (s, 3H), 7.18-7.20 (m, 1H), 7.29-7.36 (m, 4H), 7.39-7.42 (m, 2H), 7.92 (symm. m, 2H)	7.70 (14.8, 10.0)	10.60 (10.0)
3c[a]	5.99 (14.5)	3.58 (s, 2H), 3.78 (s, 3H), 6.88 (dd, 2H, J=6.5 Hz and J=1.9 Hz), 7.19 (dd, 2H, J=6.5 Hz and J=1.9 Hz), 7.21-7.24 (m, 5H)	7.48 (14.5, 10.7)	7.66 (10.7)
3d[a]	6.01 (14.6)	3.62 (s, 2H), 7.1-7.4 (m, 10H)	7.50 (14.6, 10.7)	7.88 (m)
3e[a]	6.18 (14.6)	1.21 (t, 3H, J=7.6 Hz), 2.35 (q, 2H, J=7.6 Hz), 7.10-7.29 (m, 5H)	7.55 (14.6, 10.6)	8.51 (10.6)
3f[b]	6.53 (15.0)	7.20 (t, 1H, J=7.8 Hz), 7.34 (t, 2H, J=7.8 Hz), 7.44 (d, 2H, J=7.8 Hz), 7.58 (dd, 1H, J=8.0 Hz and J=4.8 Hz), 8.35 (dt, 1H, J=8.0 Hz and J=1.5 Hz), 8.79 (dd, 1H, J=4.8 Hz and J=1.5 Hz), 9.18 (d, 1H, J=1.5 Hz)	7.71 (15.0, 9.5)	10.86 (9.5)

[a]$CDCl_3$. [b]DMSO-d_6.

Table 3. ^{13}C NMR data of N-styrylamides **3** (δ, ppm).

Cpd	solvent	=CH-	Ph, =CH-N and R	HNC=O
3a	$CDCl_3$	113.2	122.6, 125.2, 126.3, 126.7, 128.2, 128.3, 131.7, 133.0, 135.5	164.1
3b	DMSO-d_6	112.7	21.0, 124.3, 125.2, 126.2, 127.7, 128.7, 129.0, 130.5, 136.7, 142.0	163.9
3c	$CDCl_3$	113.1	42.6, 55.2, 114.5, 122.5, 125.5, 125.9, 126.6, 128.6, 130.3, 135.9, 159.0	168.9
3d	$CDCl_3$	113.7	43.8, 122.9, 125.9, 127.0, 127.9, 129.0, 129.4, 129.7, 134.5, 136.2	169.0
3e	$CDCl_3$	112.7	9.5, 29.5, 112.7, 122.8, 125.4, 126.4, 128.5, 136.1	171.9
3f	DMSO-d_6	113.7	123.6, 123.8, 125.4, 126.5, 128.7, 129.1, 135.4, 136.4, 148.8, 152.4	162.7

N-(1-Benzotriazol-1-yl-2-phenylethyl)-3-pyridinecarboxamide (2f).

^{1}H NMR ($CDCl_3$, ppm): δ 3.88 (d, 2H, J=7.5 Hz), 7.11-7.29 (m, 7H), 7.33 (dt, 1H, J=8.3 Hz and J=1.0 Hz), 7.44 (dt, 1H, J=8.1 Hz and J=1.0 Hz), 7.76 (d, 1H, J=8.4 Hz), 8.00 (dd, 1H, J=8.3 Hz and J=0.9 Hz), 8.12 (symm. m, 1H), 8.67 (dd, 1H, J=4.9 Hz and J=1.7 Hz), 8.93 (d, 1H, J=9.0 Hz), 9.10 (symm. m, 1H). ^{13}C NMR ($CDCl_3$, ppm): δ 40.3, 63.7, 110.2, 119.3, 123.4, 124.5, 127.3, 127.9, 128.7, 128.9, 129.1, 133.1, 135.0, 135.6, 145.3, 148.6, 152.6, 165.7.

Preparation of N-styrylamides 3. Typical procedure. Sodium hydride (0.08 g, 3.3 mmol) was added to a stirred solution of **2** (3 mmol) in dry toluene (10 ml). The reaction mixture was refluxed for 4 h, cooled and diluted with diethyl ether (50 ml). The organic solution was washed with 10% Na_2CO_3 (3 x 25ml) and water (25 ml), and dried over $MgSO_4$. The solvent was removed in vacuo to yield a pure mixture of Z/E isomers, from which the E-isomer was crystallized as the major product (Table 1). The NMR spectra data for N-styrylamides of general formula **3** are summarized in Tables 2 and 3.

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