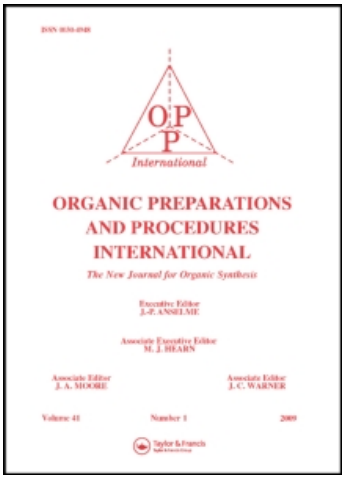

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SYNTHESIS OF N-ARYL ENAMINOSULFONES AND IMPROVED PREPARATION OF N-SUBSTITUTED ENAMINONITRILES

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SYNTHESIS OF N-ARYL ENAMINOSULFONES AND IMPROVED PREPARATION OF N-SUBSTITUTED ENAMINONITRILES

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(10/26/83)

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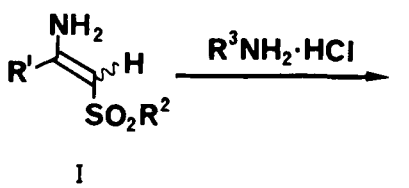
Previously, we have reported a general synthesis of β-iminosulfones or tautomeric enaminosulfones, by the reaction of sulfonyl carbanions with nitriles.[1] It was not possible, however, to extend this method to the



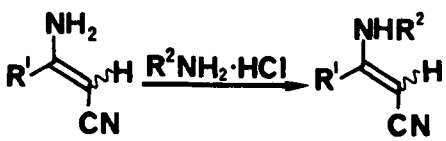
I II

	R^1	R^2	R^3
a)	Ph	Me	Ph
b)	Ph	Me	*p*-tolyl
c)	Ph	Ph	Ph
d)	*m*-tolyl	Ph	Ph
e)	*m*-tolyl	Ph	*p*-tolyl
f)	*p*-tolyl	NMe_2	Ph
g)	*p*-tolyl	NMe_2	*p*-tolyl

synthesis of N-substituted enaminosulfones. There has been no general synthetic method of N-substituted type enaminosulfones so far reported except for the one example by Knorr et al.[2] who prepared 2-anilinopropenyl

phenyl sulfone from corresponding β-ketosulfone *via* 2-methyl-2-anilino(phenylsulfonyl)propanenitrile. An attemt to prepare N-substituted enaminosulfones by the direct reaction of N-unsubstituted enaminosulfones or enaminonitriles with primary amines failed under mild conditions; high temperature and pressure are necessary for this reaction to occur. Attention was focused upon the synthesis of title compounds at low temperature under atmospheric pressure. We attempted to obtain N-substituted enaminosulfones by the reaction of amine hydrochlorides and enaminosulfones and found that a series of N-aryl enaminosulfones (II) can be obtained by this method under mild conditions and in high yield. Our method is, however, limited to the preparation of N-aryl enaminosulfones; in spite of repeated attempts, N-alkyl enaminosulfones were never obtained.

In addition to the synthesis of N-aryl enaminosulfones, our method is also applicable for preparation of N-substituted enaminonitriles (IV). A



III IV

	R^1	R^2		R^1	R^2
a)	Me	Me	g)	*p*-tolyl	Me
b)	Ph	Me	h)	Me	Ph
c)	*p*-tolyl	Me	i)	Me	*p*-tolyl
d)	*m*-tolyl	Me	j)	Ph	Ph
e)	Me	Et	k)	Ph	*p*-tolyl
f)	Ph	Et			

general synthetic method[3] for N-aryl enaminonitriles involves the reaction of 3-aminocrotononitrile or cinnamonitrile with various aromatic primary amines at high temperature. In addition, only N-aryl type enaminonitriles have been reported by Meyer's method.[3] Gill *et al.*[4] and Dedina *et al.*[5] also synthesized N-substituted enaminonitriles by a method similar to Meyer's under drastic conditions. In contrast, our improved method expanded the scope to the synthesis of all types of N-substituted

TABLE 1. Enaminosulfones and Nitriles

Cmpd	[a]mp.(°C)[b]or bp.(°C/mm)	Yield (%)	E:Z	Formula	Found(%)[l] C	H	N	(Calcd.,%) C	H	N
IIa	94-95 (EtOH)	66[h]	1:5	$C_{15}H_{15}NO_2S$	65.62	5.53	4.85	(65.91)	(5.53)	(5.13)
IIb	69 (EtOH)	51[h]	1:3	$C_{16}H_{17}NO_2S$	66.66	6.11	4.83	(66.87)	(5.96)	(4.88)
IIc	79-80 (EtOH)	73[h]	1:2	$C_{20}H_{17}NO_2S$	71.44	5.33	4.12	(71.62)	(5.11)	(4.18)
IId	106-107 (EtOH)	66[h]	1:4	$C_{21}H_{19}NO_2S$	71.78	5.66	3.72	(72.18)	(5.48)	(3.72)
IIe	79-80 (EtOH)	43[h]	1:4	$C_{22}H_{21}NO_2S$	72.57	6.05	3.82	(72.71)	(5.82)	(3.85)
IIf	115 (EtOH)	97[i]	1:3	$C_{17}H_{20}N_2O_2S$	64.40	6.49	8.80	(64.53)	(6.37)	(8.86)
IIg	117 (EtOH)	90[i]	1:3	$C_{18}H_{22}N_2O_2S$	65.23	6.78	8.39	(65.43)	(6.37)	(8.86)
IVa	49-49.5[c] 138.5/7	83[j]	20:1	$C_5H_8N_2$	-	-	-			
IVb	66 (Benzene)	82[k]	7:1	$C_{10}H_{10}N_2$	75.66	6.25	17.71	(75.92)	(6.37)	(17.71)
IVc	121 (Benzene)	76[k]	9:1	$C_{11}H_{12}N_2$	76.73	7.09	16.94	(76.71)	(7.02)	(16.27)
IVd	103 (Benzene)	92[k]	7:1	$C_{11}H_{12}N_2$	76.87	6.89	16.59	(76.71)	(7.02)	(16.27)
IVe	47.5[d] (Ether-Hexane)	83[k]	20:1	$C_6H_{10}N_2$	-	-	-			
IVf	53 (Ether-Hexane)	77[k]	5:1	$C_{11}H_{12}N_2$	76.70	7.01	16.26	(76.71)	(7.02)	(16.27)
IVg	74 (Benzene-Hexane)	70[k]	5:1	$C_{12}H_{14}N_2$	77.66	7.46	15.31	(77.38)	(7.58)	(15.04)
IVh	117.5[e] (Benzene-Hexane)	88[k]	6:1	$C_{10}H_{10}N_2$	-	-	-			
IVi	102-103[f] (Benzene-Hexane)	88[k]	6:1	$C_{11}H_{12}N_2$	-	-	-			
IVj	128-137[g] (Benzene-Hexane)	86[k]	4:3	$C_{15}H_{12}N_2$	-	-	-			
IVk	159-162 (Benzene-Hexane)	87[k]	5:1	$C_{16}H_{14}N_2$	82.21	6.19	11.68	(82.02)	(6.02)	(11.68)

[a] All compounds gave satisfactory IR data. [b] Solvent in parentheses. [c] Lit.[4] mp. 52-56°, lit.[5] mp. 54-55°, bp. 146-148 °C/15mmHg. [d] Lit.[4] mp. 45-46°. [e] Lit.[7] 116-117°. [f] Lit.[3] 102°. [g] Lit.[8] 128-137°. [h] Method A. [i] Method B. [j] Method C. [k] Method D. [l] S analyses as follows [Found, % (Calcd., %)]: IIa; 11.40(11.73), IIb; 11.47(11.15), IIc; 9.96 (9.56), IId; 9.22(9.17), IIe; 9.22(8.82), IIf; 10.50(10.13), IIg; 10.10(9.70).

TABLE 2. PMR data of N-Arylenaminosulfones(II)

Cmpd	$\delta(CDCl_3)$
IIa(E)	1.72(s,b, NH) 2.67(s, CH_3) 4.55(s, =CH-) 6.6-8.0(m, Ar)
(Z)	3.10(s, CH_3) 5.21(s, =CH-) 6.5-8.0(m, Ar) 8.93(s,b, NH)
IIb(E)	1.72(s,b, NH) 2.34(s, $NC_6H_4C\underline{H}_3$) 2.64(s, SO_2CH_3) 4.50(s, =CH-) 6.5-8.0(m, Ar)
(Z)	2.19(s, $NC_6H_4C\underline{H}_3$) 3.06(s, SO_2CH_3) 5.10(s, =CH-) 6.5-8.0 (m, Ar) 8.85(s,b, NH)
IIc(E)	1.61(s,b, NH) 4.60(s, =CH-) 6.5-8.0(m, Ar)
(Z)	5.23(s, =CH-) 6.5-8.0(m, Ar) 9.20(s,b, NH)
IId(E)	1.62(s,b, NH) 2.36(s, CH_3) 4.63(s, =CH-) 6.5-8.0(m, Ar)
(Z)	2.25(s, CH_3) 5.22(s, =CH-) 6.5-8.0(m, Ar) 9.19(s,b, NH)
IIe(E)	1.72(s,b, NH) 2.33(s, $NC_6H_4C\underline{H}_3$) 2.34(s, $C_6H_4C\underline{H}_3$) 4.61(s, =CH-) 6.5-8.0(m, Ar)
(Z)	2.21(s, $NC_6H_4C\underline{H}_3$) 2.25(s, $C_6H_4C\underline{H}_3$) 5.17(s, =CH-) 6.5-8.0 (m, Ar) 9.12(s,b, NH)
IIf(E)	2.41(s, $C_6H_4C\underline{H}_3$) 2.55(s, $N(CH_3)_2$) 2.97(s,b, NH) 4.38(s, =CH-) 7.35(d, J=8Hz, C_6H_4) 7.91(d, J=8Hz, C_6H_4) 6.8-7.2 (m, NC_6H_5)
(Z)	2.34(s, $C_6H_4C\underline{H}_3$) 2.81(s, $N(CH_3)_2$) 5.00(s, =CH-) 6.64(d, J=8Hz, C_6H_4) 7.08(d, J=8Hz, C_6H_4) 6.8-7.2(m, NC_6H_5) 8.77 (s,b, NH)
IIg(E)	2.41(s, $C_6H_4C\underline{H}_3$) 2.26(s, $NC_6H_4C\underline{H}_3$) 2.56(s, $N(CH_3)_2$) 2.96 (s,b, NH) 4.41(s, =CH-) 6.82(d, J=8Hz, C_6H_4) 7.12(d, J= 8Hz, C_6H_4) 7.27(d, J=8Hz, NC_6H_4) 7.88(d, J=8Hz, NC_6H_4)
(Z)	2.33(s, $C_6H_4C\underline{H}_3$) 2.20(s, $NC_6H_4C\underline{H}_3$) 2.80(s, $N(CH_3)_2$) 4.95

(s, =CH-) 6.54(d, J=8Hz, NC_6H_4) 6.89(d, J=8Hz, NC_6H_4) 7.09(d, J=8Hz, C_6H_4) 7.24(d, J=8Hz, C_6H_4) 8.71(s,b, NH)

TABLE 3. PMR data of N-substituted Enaminonitriles(IV)

Cmpd	δ ($CDCl_3$)
IVa(E)	2.06(s, CH_3) 2.69(d, J=5Hz, $NHC\underline{H}_3$) 4.74(s, =CH-) 4.80(s, b, NH)
(Z)	1.94(s, CH_3) 2.98(d, J=5Hz, $NHC\underline{H}_3$) 3.68(s, =CH-)
IVb(E)	2.84(d, J=5Hz, $NHC\underline{H}_3$) 3.99(s, =CH-) 4.57(s,b, NH) 7.4-7.6 (m, C_6H_5)
(Z)	3.15(d, J=5Hz, $NHC\underline{H}_3$) 3.98(s, =CH-) 4.83(s,b, NH) 7.4-7.6 (m, C_6H_5)
IVc(E)	2.37(s, $C_6H_4C\underline{H}_3$) 2.82(d, J=5Hz, $NHC\underline{H}_3$) 3.95(s, =CH-) 4.56 (s,b, NH) 7.24(d, J=8Hz, C_6H_4) 7.42(d, J=8Hz, C_6H_4)
(Z)	2.37(s, $C_6H_4C\underline{H}_3$) 3.14(d, J=5Hz, $NHC\underline{H}_3$) 3.95(s, =CH-) 4.82 (s,b, NH) 7.21(d, J=8Hz, C_6H_4) 7.27(d, J=8Hz, C_6H_4)
IVd(E)	2.38(s, $C_6H_4C\underline{H}_3$) 2.82(d, J=5Hz, $NHC\underline{H}_3$) 3.96(s, =CH-) 4.56 (s,b, NH) 7.2-7.3(m, C_6H_4)
(Z)	2.38(s, $C_6H_4C\underline{H}_3$) 3.14(d, J=5Hz, $NHC\underline{H}_3$) 3.96(s, =CH-) 4.82 (s,b, NH) 7.2-7.3(m, C_6H_4)
IVe(E)	1.219(t, J=7.3Hz, $NCH_2C\underline{H}_3$) 2.10(s, CH_3) 2.99(d,q, J=5.1, 7.3Hz, $NHC\underline{H}_2CH_3$) 3.78(s, =CH-) 4.26(s,b, NH)
(Z)	1.217(t, J=7.3Hz, $NCH_2C\underline{H}_3$) 1.89(s, CH_3) 3.31(d,q, J=5.1, 7.3Hz, $NHC\underline{H}_2CH_3$) 3.74(s, =CH-) 4.77(s,b, NH)
IVf(E)	1.28(t, J=7.3Hz, $NCH_2C\underline{H}_3$) 3.12(d,q, J=5.1, 7.3Hz, $NHC\underline{H}_2$-CH_3) 4.00(s, =CH-) 4.72(s,b, NH) 7.3-7.6(m, C_6H_5)
(Z)	1.23(t, J=7.3Hz, $NCH_2C\underline{H}_3$) 3.50(d,q, J=5.1, 7.3Hz, $NHCH_2$-CH_3) 3.95(s, =CH-) 4.39(s,b, NH) 7.3-7.6(m, C_6H_5)
IVg(E)	1.28(t, J=7.6Hz, $NCH_2C\underline{H}_3$) 2.38(s, $C_6H_4C\underline{H}_3$) 3.11(d,q, J= 5.2, 7.6Hz, $NHC\underline{H}_2CH_3$) 4.68(s,b, NH) 7.23(d, J=8Hz, C_6H_4) 7.43(d, J=8Hz, C_6H_4)
(Z)	1.26(t, J=7.6Hz, $NCH_2C\underline{H}_3$) 1.68(s, $C_6H_4C\underline{H}_3$) 3.50(d,q, J= 5.2, 7.6Hz, $NHC\underline{H}_2CH_3$) 4.34(s,b, NH) 7.19(d, J=8Hz, C_6H_4) 7.28(d, J=8Hz, C_6H_4)

IVh(E) 2.25(s, CH_3) 4.40(s, =CH-) 6.17(s,b, NH) 7.0-7.7(m, C_6H_5)
(Z) 1.95(s, CH_3) 3.99(s, =CH-) 6.79(s,b, NH) 7.0-7.7(m, C_6H_5)

IVi(E) 2.23(s, CH_3) 2.34(s, $C_6H_4\underline{CH_3}$) 4.29(s, =CH-) 6.06(s,b, NH) 7.02(d, J=8Hz, C_6H_4) 7.15(d, J=8Hz, C_6H_4)
(Z) 1.90(s, CH_3) 2.34(s, $C_6H_4\underline{CH_3}$) 3.94(s, =CH-) 6.70(s,b, NH) 6.95(d, J=8Hz, C_6H_4) 7.02(d, J=8Hz, C_6H_4)

IVj(E) 4.67(s, =CH-) 6.10(s,b, NH) 6.7-7.7(m, Ar)
(Z) 4.40(s, =CH-) 6.7-7.7(m, Ar and NH)

IVk(E) 2.22(s, $C_6H_4\underline{CH_3}$) 4.55(s, =CH-) 6.05(s,b, NH) 7.07(d, J=8Hz, C_6H_4) 7.17(d, J=8Hz, C_6H_4) 7.2-7.7(m, C_6H_5)
(Z) 2.34(s, $C_6H_4\underline{CH_3}$) 4.33(s, =CH-) 6.85(s,b, NH) 6.63(d, J=8Hz, C_6H_4) 6.93(d, J=8Hz, C_6H_4) 7.2-7.7(m, C_6H_5)

enaminonitriles.

Thus, both N-alkyl and N-aryl enaminonitriles were obtained conveniently in high yield under exceedingly mild reaction conditions. An attempt to extend this route to the synthesis of N,N-disubstituted enaminosulfones and enaminonitriles by use of secondary amine hydrochlorides failed.

EXPERIMENTAL SECTION

The starting enaminosulfones were prepared from nitriles and sulfones.[1] Enaminonitriles were obtained according to Thorpe's method.[6] The infrared spectra were measured as KBr pellet on Nippon Bunko IR-A-302 spectrophotometer. PMR spectra were measured at 270 MHz on Jeol JNM-GX-270 spectrometer with TMS as an internal reference.

General Procedure.- A mixture of 50 mmoles of enaminosulfone or enaminonitrile, 100 mmoles of amine hydrochloride and 25 ml of ethanol(or methanol for nitriles) was heated at reflux (70°) for 3 hrs (5 hrs in methanol). Water and ether may then be added to the reaction mixture and the ethereal layer separated, dried and evaporated. The residue may then be recrystallized or distilled under reduced pressure (see Table 1). Alternatively, the reaction may be cooled to 0° and the precipitated

product collected, washed with water, dried and crystallized. The reaction mixture may also be evaporated to dryness and treated with water and ether as described above.

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SYNTHESIS OF t-BUTOXYCARBONYL AND BENZYLOXYCARBONYL AMINO ACID AMIDES

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A series of amides of Boc-[1] and Z-amino acid (Table) was needed in amounts $\geqslant$100 mmoles for α,β-dehydropeptide synthesis.[2] We have found the amides to be easily obtained directly from Boc- and Z-amino acid by means of isobutyl chlorocarbonate and of a large excess on concentrated aqueous ammonia, thus alleviating the need to use active esters and organic