An Improved Synthesis of Symmetrical N,N′-Alkylidene-bis-amides

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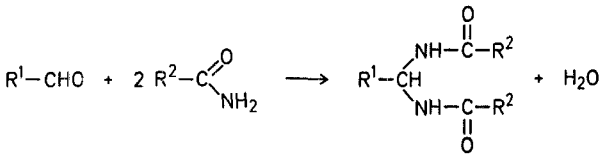
Symmetrical N,N′-alkylidene-bis-amides (**3**) are usually prepared by the direct reaction of an aldehyde (**1**) with the corresponding carboxamide (**2**).



1 **2** **3**

The procedures commonly used[1] have various limitations. One method[2,3], involving heating acetamide with paraformaldehyde, entails a 19-hour reaction time. Another procedure[4], comprising heating acetamide with various aldehydes in the presence of acetic acid, requires 4 hours, entails a purification problem, and gives poor yields in some cases. An approach limited to the preparation of N,N′-methylene-bis-amides[5] involves heating an amide with hexamethylenetetramine for 5 hours, and requires product decolorization.

The reaction time is greatly reduced by catalysis with strong acids, but this approach has been given less attention than those cited above. One such method, used for preparing N,N′-methylene-bis-acrylamide[6] and other water-insoluble

bis-amides[7], involves heating with dilute hydrochloric acid, a method not easily adaptable to preparing the water-soluble analogues. The same objection applies to an approach involving the condensation of an aldehyde with a nitrile in the presence of a substantial quantity of sulfuric acid[8].

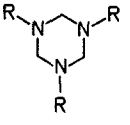
Turinsky[9] prepared N,N′-methylene-bis-stearamide and -bis-acetamide by heating the amides and paraformaldehyde at 155° with a catalytic quantity of 65% sulfuric acid for 15–30 minutes without a solvent. Feuer and Lynch[10] subsequently prepared N,N′-methylene-bis-acrylamide and -bis-methacrylamide rapidly and in good yields by refluxing equivalent quantities of the amide and paraformaldehyde with a catalytic amount of aqueous hydrochloric acid and a solvent (1,2-dichloroethane, b.p. 84°) in which the desired bis-amide is poorly soluble, thus permitting isolation by merely cooling and filtering. These promising procedures were apparently not studied further or used with other amides. We have modified this second approach by employing boiling toluene as the reaction solvent (which gives faster reaction at the higher temperature (b.p. 109°), and has desirably low solubility for the product bis-amide), and by employing distillation for the removal of the water formed (which gives a higher yield). Sulfonic acids have been found to be more active than hydrochloric acid on an equivalent basis. This procedure has been found to give good to excellent yields of crude bis-amides of good quality with a reaction time of 10–15 minutes. The results are summarized in Table 1. Our procedure is quite similar to that used by Bredereck et al.[11] for reacting amides with orthoformic esters, except that we do not employ a heating period prior to distillation. Wegler and Ballauf[12] applied a method similar to ours to the reaction of paraformaldehyde with propanamide at 1:1 molar ratio, but obtained no bis-amide.

Several reaction parameters were examined briefly in the case of N,N-methylene-bis-acetamide. The catalyst is added as conc. sulfuric acid, which is presumably converted rapidly to the corresponding sulfonic acid by reaction with the aromatic solvent. (Methane- or *p*-toluenesulfonic acids can be added as such, but no advantage results.) The use of 9 mmol acid per mole amide is sufficient to catalyze the reaction with azeotropic removal of water, and this constitutes the preferred quantity. No product was formed using 2 mmol, and a somewhat reduced yield was noted with 5 mmol. Quantities larger than 9 mmol show no advantage. Using total reflux, no reaction occurs at the 5 mmol level, but an 86% yield of good quality product was obtained with 9 mmol. Concentrated hydrochloric acid is less active than the sulfonic acid, since no product was formed by the distillation procedure at 5 mmol; excellent results were noted at 15 mmol. Trifluoroacetic acid catalyzes the reaction at 5 mmol, and is therefore as active as the sulfonic acid. It is noteworthy that it is retained in the reaction mixture, even though its boiling point (72°) is considerably below the distillation temperature. The following acids were inactive at the level indicated: acetic (40), chloroacetic (27), trichloroacetic (15), orthophosphoric (11); higher concentrations of these acids were not tested.

Toluene is the preferred reaction medium. Chlorobenzene and xylene gave equivalent results, but have no advantage. Unlike toluene, benzene gave no reaction at 5 mmol catalyst, possibly because the boiling point of benzene is too low to induce reaction.

As shown in Table 1, paraformaldehyde gives good results with various amides. Aqueous formaldehyde gave an 85% yield of a less pure product and required more distillation. Unlike paraformaldehyde, trioxane and diethoxymethane gave no bis-amide with 5 mmol catalyst; higher concentrations were not tried. Lower aliphatic aldehydes (propanal, butanal) distilled too easily from the reaction mixture to form bis-amides; the higher-boiling heptanal gave good results. Although an attempt to convert cyclohexanone to a bis-amide was unsuccessful, the procedure was extended to the preparation of tetrakis-amides from dialdehydes[13]. It is noteworthy that we were successful in preparing N,N′-methylene-bis-furamide, even though the furan ring is susceptible to decomposition in the presence of acids.

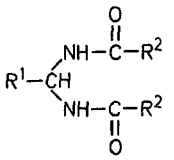
Attempts to use our procedure with formamide, N-methylacetamide, and trichloroacetamide were unsuccessful. Acrylamide gave the bis-amide with hydrochloric acid, as was also noted by Feuer and Lynch[10], but polymer was always formed with the sulfonic acid, which was also reported by others[12]. Methanesulfonamide gave a product identified as **4a** on the basis of analysis, and of mass and I.R. spectra.



4a R = $-SO_2-CH_3$
b R = $-COOC_2H_5$

Wegler and Ballauf[12] suggested the formation of this type of compound from paraformaldehyde and other aliphatic

Table 1. Symmetrical N,N′-Alkylidene-bis-amides



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R^1	R^2	Yield of crude product %	m.p.[a]
H	CH_3	90–95	195–198°[b]
(paraformaldehyde)	C_2H_5	75–95	200–202°[c]
	n-C_3H_7	84	186–188°[d]
		95	217–220°[e]
	n-$C_{17}H_{35}$	93	143–145°[f]
		63	177–179°[g]
	$-COOC_2H_5$	81	128–131°[g]
	CH_3	70	242°[h]
n-C_6H_{13}	CH_3	76	173–175°[i]

[a] After one recrystallization from butanol.
[b] Ref.[4], m.p. 197.5–198°; Ref.[5], m.p. 198–200°.
[c] A. EINHORN, Liebigs Ann. Chem. **361**, 123 (1908), gives m.p. 201°.
[d] Ref.[8], m.p. 183–186°.
[e] Ref.[8], m.p. 216–218°; M.A. GRADSTEN, M.W. POLLOCK, J. Amer. Chem. Soc. **70**, 3080 (1948), give m.p. 220–222°.
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[g] New compound.
[h] Ref.[4], m.p. 238°; M.C. PAULSON, J.M. MERSEREAU, Trans. Illinois State Acad. Sci. **47**, 94 (1955), give m.p. 239.5°; H. HELLMANN, G. AICHINGER, H.P. WIEDEMANN, Liebigs Ann. Chem. **626**, 35 (1959), give m.p. 256.5–257°.
[i] Ref.[4] and N. YANAIHARA, M. SAITO, Chem. Pharm. Bull. **15**, 128 (1967), give m.p. 171–172°.

sulfonamides, but they gave no supporting data. Ethyl carbamate similarly gave a 20% yield of the known **4b**[14]. N,N′-Methylene-bis-[ethyl carbamate] was not formed, even at 1:1 stoichiometry, even though good yields are obtainable in hydrochloric acid[2]. Ethyl oxamate formed the new derivative; there was no evidence in the case of triazine formation even at 1:1 molar ratio.

Melting points were taken in capillary tubes in a Mel-Temp apparatus and are uncorrected. I.R. spectra were determined in KBr pellets with a Perkin-Elmer Model 21 spectrophotometer. N.M.R. spectra were determined in DMSO-d_6 on a Varian T-60 spectrometer using tetramethylsilane as internal reference. Microanalyses were run by Schwarzkopf Microanalytical Laboratory.

The following procedure is typical.

N,N′-Methylene-bis-acetamide:
Acetamide (12 g, 0.2 mol), paraformaldehyde (3.3 g, 0.1 mol at 90% purity), and toluene (200 ml) are placed in a 500-ml Erlenmeyer flask equipped with an efficient magnetic stirrer and a stillhead for distillation. Stirring is begun, conc. sulfuric acid (6 drops ≈ 9 mmol per mole amide) is added, and the mixture is heated rapidly to distillation temperature on a hot plate. Fifty to 60 ml is distilled over 10–15 min.; separation of the product begins after 1–2 min. The reaction mixture is cooled in ice and filtered. The colorless product is washed with fresh toluene, sucked dry, and dried at 50° for 1–2 hr; yield: 12 g (93%); m.p. 176–181°. As indicated in Table 1, the crude product can be purified by recrystallization from butanol. The I.R. spectrum is identical with that obtained from a sample prepared by a published procedure[2].

The other bis-amides were prepared similarly. When using heptanal, the product was soluble in hot toluene and did not separate until the solution was chilled. It was noted in general that small amounts of impurities produced an unusually large depression in the melting points of bis-amides and tetrakis-amides[13].

1,3,5-Tris-[methanesulfonyl]-hexahydro-1,3,5-triazine (4a)[15]:
Methanesulfonamide (9.5 g, 0.1 mol) 37% formaldehyde (8.0 g, 0.1 mol), toluene (200 ml), and concentrated sulfuric acid (3 drops, 9 mmol per mole amide) were reacted as described above. The product, which separated as a solid on the walls of the flask, was filtered and dried; yield: 10.5 g (98%); m.p. 301° (dec.), from dimethylformamide. The same product was formed at 2:1 molar ratio.

$C_6H_{15}N_3O_6S_3$	calc.	C 22.4	H 4.7	N 13.1	S 29.9
	found	22.7	4.8	13.3	29.9

I.R. (KBr): 695, 767, 783, 795, 850, 928, 945, 980, 1030, 1140, 1150, 1190, 1265, 1330, 2950, 3030 cm^{-1}.

Mass spectrum: 79, 108 (base peak), 122, 135, 162, 186, 214, 242 321.

N,N′-Methylene-bis-furamide:

$C_{11}H_{10}N_2O_4$	calc.	C 56.5	H 4.3	N 12.0
	found	56.5	4.4	11.8

I.R. (KBr): 758, 835, 883, 920, 1005, 1105, 1135, 1190, 1240, 1300, 1325, 1390, 1475, 1525 (Amide II), 1575, 1595, 1640 (Amide I), 3330 cm^{-1}.

N.M.R. (DMSO-d_6): 8.78 (t, 2H, J=6 Hz, NH), 7.83 (m, 2H, O—C<u>H</u>=CH), 7.25 (m, 2H, CH—C<u>H</u>=C), 6.62 (m, 2H, CH=C<u>H</u>—CH), 4.80 (t, 2H, J=6 Hz, CH_2).

N,N′-Methylene-bis-[ethyl oxamate]:

$C_9H_{14}N_2O_6$	calc.	C 44.0	H 5.7	N 11.4
	found	44.0	5.9	11.4

I.R. (KBr): 783, 813, 827, 870, 1025, 1060, 1118, 1225, 1310, 1395, 1530 (Amide II), 1695 (Amide I), 1755, 3300 cm^{-1}.

N.M.R. (DMSO-d_6): 9.23 (broad t, 2H, J=6 Hz, NH), 4.62 (t, 2H, J = 6 Hz, NH—$C\underline{H}_2$—NH), 4.27 (q, 4H, J = 6 Hz, $C\underline{H}_2$—CH_3), 1.30 (t, 6H, J = 6 Hz, —CH_2—$C\underline{H}_3$).

The structure of the product was further confirmed by conversion to the N″, N‴-dibutyl derivative.

N″,N‴-Dibutyl-N,N′-methylene-bis-oxamide:
N,N′-Methylene-bis-[ethyl oxamate] (2.5 g, 0.01 mol), butylamine (3.0 g, 0.04 mol), and isopropanol (75 ml) were refluxed for 45 min. The reaction mixture, which gelled on cooling, was filtered and the product dried; yield: 2.0 g (67%) of crude product; m.p. 270–271°, from dimethylformamide (Ref.[16], m.p. 266–269°). The I.R. curve was identical with that of a sample prepared by an alternative procedure[16].

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