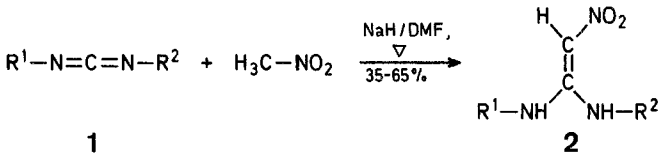
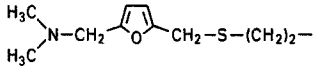
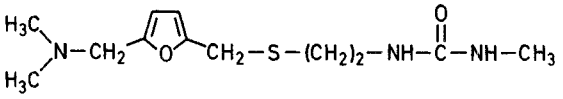


1 2

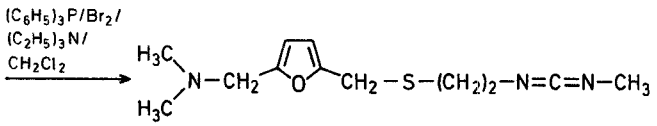
1,2	R^1	R^2
a	c-C_6H_{11}	c-C_6H_{11}
b		
c		H_3CO- 
d		n-C_4H_9
e		CH_3
f		Cl- 

Scheme A

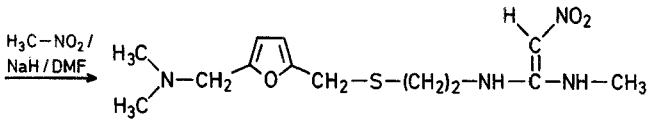
Nitromethylenation of carbodiimides **1** should be carried out under anhydrous conditions as the nitromethane carbanion is hydrolysed in moist air. The use of other solvents and bases affords less satisfactory results. This method competes favourably with traditional approaches[4-8], affording the title compounds after standard work-up in moderate to good yields (Table). The utility of this synthesis has been substantiated by the preparation of large amounts of the well-known ulcerostatic agent ranitidine[13] (**2e**), from the easily available **1e**[14] (Scheme **B**), avoiding the troubles encountered in the stepwise substitution of 1-nitro-2,2-bis[methylthio]-ethylene[15].



3



1e



2e

Scheme B

A great number of the older[16,17] and more recent methods[18,19] developed for large-scale preparation of the starting carbodiimides renders the synthesis reported here of general interest.

N-Methyl-N'-{2-[(5-dimethylaminomethyl)-furan-2-ylmethylthio]-ethyl}-carbodiimide (1e):

To a solution of triphenylphosphine (2.55 g, 9.72 mmol) in dichloromethane (20 ml), cooled to 0°–5 °C, bromine (0.50 ml, 9.73 mmol) is added dropwise. The resulting solution is stirred for 5 min at room temperature. Thereafter it is cooled to 0°–5 °C, and a solution of triethylamine (2.7 ml, 20.28 mmol) in dichloromethane (20 ml) is added dropwise. To the resulting suspension small portions of *N*-methyl-*N'*-{(2-[(5-dimethylaminomethyl)-furan-2-ylmethylthio]-

A New Approach to 1-Nitro-2,2-bis[alkyl- or arylamino]ethylenes: A New Synthesis of Ranitidine

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The versatile reactivity of the nitromethane carbanion allows the preparation of 1-nitro-2-alkyl (or aryl)-ethylenes. This methodology comprises nitromethylation of the carbon-oxygen[1,2] or carbon-nitrogen[3] double bond, followed by elimination of a molecule of water or amine. Various multi-step approaches have been reported[4,5] for the preparation of 1-nitro-2,2-bis[alkyl- or arylamino]ethylenes (**2**). A widely used method consists of nitromethylation of carbon disulfide, followed by alkylation of the intermediary salt of 1-nitro-2,2-dithioethylene, and final substitution by alkyl- or arylamines[6,7,8]. Nucleophilic attack of the nitromethane carbanion on the central carbon of the dithiocumulene moiety in carbon disulfide occurs in the initial step. Having in mind that carbodiimides **1** possess the diazacumulene subunit[9-12], isoelectronic to carbon disulfide, we elaborated a one-step approach to the title compounds according to Scheme **A**.

Table. 1-Nitro-2,2-bis[alkyl- or arylamino]ethylenes **2a–f**

Product	Reaction Conditions Temperature/Time	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a] or Lit. m.p. [°C]
2a	100 °C/90 min	60	204–206° (C_2H_5OH/C_2H_5OAc)	$C_{14}H_{25}N_3O_2$ (267.4)
2b	90 °C/60 min	37	165–167° (i-C_3H_7OH)	161–162°[4]
2c	60 °C/80 min	41	168–170° (C_2H_5OH/ether)	165–168°[21]
2d	60 °C/80 min	35	174–177° (i-C_3H_7OH)	$C_{12}H_{17}N_3O_2$ (235.3)
2e	300 °C/90 min	65	141–143° (C_2H_5OH/C_2H_5OAc)[b]	142–143°[20]
2f	90 °C/80 min	42	165–168° (C_2H_5OH/ether)	$C_{14}H_{12}ClN_3O_2$ (289.7)

[a] Satisfactory microanalyses obtained: C ± 0.3, H ± 0.3, N ± 0.3. [b] As the hydrochloride.

ethyl}-urea (**3**; prepared according to Ref.[20]; 2.0 g, 7.77 mmol) are added during 1 h. After 2 h stirring, water (20 ml) is added, the organic phase is separated, and dried with sodium sulphate. On evaporation of the solvent, a viscous solid material remains. This is extracted with light petroleum (6 × 20 ml) and the combined extracts are evaporated affording a pale yellow, chromatographically pure oil; yield: 1.1 g (52%).

$C_{12}H_{19}N_3OS$ (253.4) calc. C 56.88 H 7.56 N 16.59
found 56.58 7.43 16.70

I.R. (film): ν = 2940, 2860, 2820, 2775, 2123, 1550, 1452, 1438, 1342, 1260, 1198, 1105, 790, 698, 611 cm^{-1}.

Nitromethylenation of Carbodiimides 1; General Procedure:
A solution of nitromethane (1.35 g, 22.0 mmol) in dry dimethylformamide (10 ml) is added dropwise under dry nitrogen to a suspension of sodium hydride (0.48 g, 11.0 mmol) in dry dimethylformamide (20 ml). After 30 min stirring at ambient temperature, a solution of carbodimide **1** (10 mmol) in dry dimethylformamide (20 ml) is added. The reaction is continued under the conditions indicated in the Table, cooled, and then water (0.5 ml) is added. The precipitated material is removed by filtration and the filtrate evaporated in vacuo. The crude product is purified either by direct crystallisation or by previous chromatography on silica gel (Merck, 0.05–0.2 mm).

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