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Note

Reactions with 1-Benzotriazolecarboxylic Acid Chloride. V[1]. Synthesis of Sulfonylureas and Related Compounds

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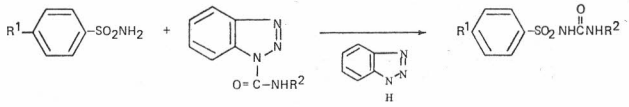
Sulfonylureas and related compounds, with hypoglycemic activity were synthetized, starting from corresponding sulfonylamide salts and 1-carbamoylbenzotriazoles.

Usually, sulfonylureas I with hypoglycemic activity were prepared in two commonly used ways. The first is based on the reaction of arylsulfonyl isocyanates[2] or arylsulfonyl carbamates[3–6] with amines, and the second on the reaction of sulfonylamide salts with isocyanates[6–8] or amidocarbonic acid derivatives[2,6].

As a part of our work on the application of 1-carbamoylbenzotriazole derivatives II in organic synthesis[9], we have recently described it as a very useful reagent for preparing ureas[1] in the reaction with primary and secondary amines. The reaction proceeded by means of direct nucleophilic attack of the amino group on the carbonyl, activated by a benzotriazole substituent.

In order to test the generality of the observed behaviour of II in the reaction with amines, the reaction with sulfonylamides III was investigated. The reaction was found to be a convenient route to sulfonylureas I, with regard to the useful properties of carbamoylbenzotriazoles, stable solids, which could be handled more easily with safety than isocyanate or phosgene, and because of the high yields obtained.

Temperatures (about 100 °C) for the reaction of sulfonylamides III, at which there was no evidence of dissociation of II into benzotriazole and isocyanate (as checked by IR spectroscopy of II in dioxane solution at 80 °C) indicated a direct nucleophilic attack of the sulfonylamide amino group on carbonyl, following the mechanism proposed for the formation of ureas[1].

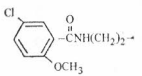
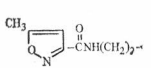
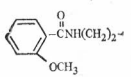


III II I

The reaction was carried out in dioxane or dimethylformamide solution at elevated temperature for 1 to 5 h. The reaction mixture was evaporated to dryness at reduced pressure. Sulfonylureas I were isolated by acidification of the water solution of the residue.

TABLE

Preparation of Sulfonylureas Ia—Ie

Compound	R^1	R^2	Reaction conditions solvent/time/h	temp./°C	Method of isolation	Yield %	m. p./°C	lit. m. p./°C
Ia	CH_3	CH_3	DMF / 1	95	A	67	168—170	170—172[10]
Ib	CH_3	i-C_3H_7	Dioxane / 1	100	A	79	148—150	141—143[10]
Ic	CH_3	n-C_4H_9	DMF / 2	95	A	62	122—126	127—129[10]
Id	CH_3	c-C_6H_{11}	Dioxane / 1	100	A	93	167—169	170—173[10]
Ie	Cl	CH_3	Dioxane / 1	100	A	62	186—190	188—189[10]
If	Cl	n-C_3H_7	Dioxane / 4	100	A	65	128—130	126—128[10]
Ig	Cl	n-C_4H_9	Dioxane / 1	100	A	89	115—117	115—116[10]
Ih	Cl	c-C_6H_{11}	Dioxane / 1	100	B	62	155—157	158—159[10]
Ii		c-C_6H_{11}	Dioxane / 5	100	B	76	168—172	168—172[8]
Ij			Dioxane / 4	100	B	80	190	189[6b]
Ik		c-C_6H_{11}	Dioxane / 1	100	A	75	186—188	184[5]
Il	CH_3		Dioxane / 5	100	B	65	168—171	171—173[2]

EXPERIMENTAL

Preparation of Sulfonylureas I: General Procedure

Sulfonylamide sodium salt III (5 mmol), 1-carbamoylbenzotriazole II (5 mmol) and an appropriate solvent (30 ml) were heated at 95—100 °C and the sulfonylurea thus formed was isolated by two methods:

Method A. — The solvent was evaporated in vacuo and 15% hydrochloric acid was added. After standing in a water bath at 60 °C for 0.5 h the product was filtered off.

Method B. — The insoluble part of the reaction mixture was filtered off, dissolved in 75 ml of water and the product was precipitated by the addition of 5% hydrochloric acid (to pH 3—4).

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SAŽETAK

Reakcije klorida 1-benzotriazolkarboksilne kiseline.V. Sinteza sulfonilurea i srodnih spojeva

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Opisana je priprava sulfonilurea i srodnih spojeva koji imaju hipoglikemijsko djelovanje. U sintezi se polazi od soli sulfonilamida i 1-karbamoilbenzotriazola.

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