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N-Sulfonyl Amino Acid Amides, a Novel Class of Compounds with Fungicidal Activity [1]

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Abstract: Novel types of oomycete fungicides have been designed and prepared. The synthetic approach to these N-sulfonyl amino acid amides is outlined. Bioassays demonstrate their high efficacy against important plant diseases like *Phytophthora infestans* (tomato and potato late blight) and *Plasmopara viticola* (grape downy mildew). Structure–activity relationship studies are discussed.

Keywords: Amino acid derivative · Fungicide · *Phytophthora infestans* · *Plasmopara viticola* · Ugi reaction · Valinamide

Introduction

Oomycetes have always been a threat to mankind; for instance *Phytophthora infestans*, one representative of this group of phytopathogenic fungi, was responsible for the dramatic Irish potato famines of the nineteenth century [2]. The continuous search for new oomycete fungicides, driven by resistance problems and the need for environmentally safe pesticides, has focused recently on amino acid derivatives. With Bayer's iprovalicarb (**1**) [3] the first member of the class of N-carbamoyl valinamides recently reached the market, benthiavalicarb (**2**) is currently under development at Kumiai (Fig.) [4]. In these compounds, the amino acid valine is linked to a 1-phenylethylamine or 1-benzothiazolyl-ethylamine. Also amides like **3**, in which a N-carbamoyl valine is linked to a 2-phenylethylamine, have been described as agrochemical fungicides [5]. Very similar alkoxy-substituted 2-phenethylamines have also been reported to be part of fungicidally active arylalkoximino acetic acid amides *e.g.* **4** [6] and mandelamides like **5** [7]. A few years ago we decided to start a research program with the goal to improve the biological profile by replacing the carbamate moiety in **1**–**3** by different functional groups. Soon sulfonamides of type **6** were identified as compounds with distinct fungicidal activity especially against oomycetes. Interestingly, the sulfonyl function linked to valine is not only an even better substitute for the carbamate of valinamide **3**, but in connection with phenylglycine also mimics perfectly the oxime and hydroxy functions in compounds **4** and **5**.

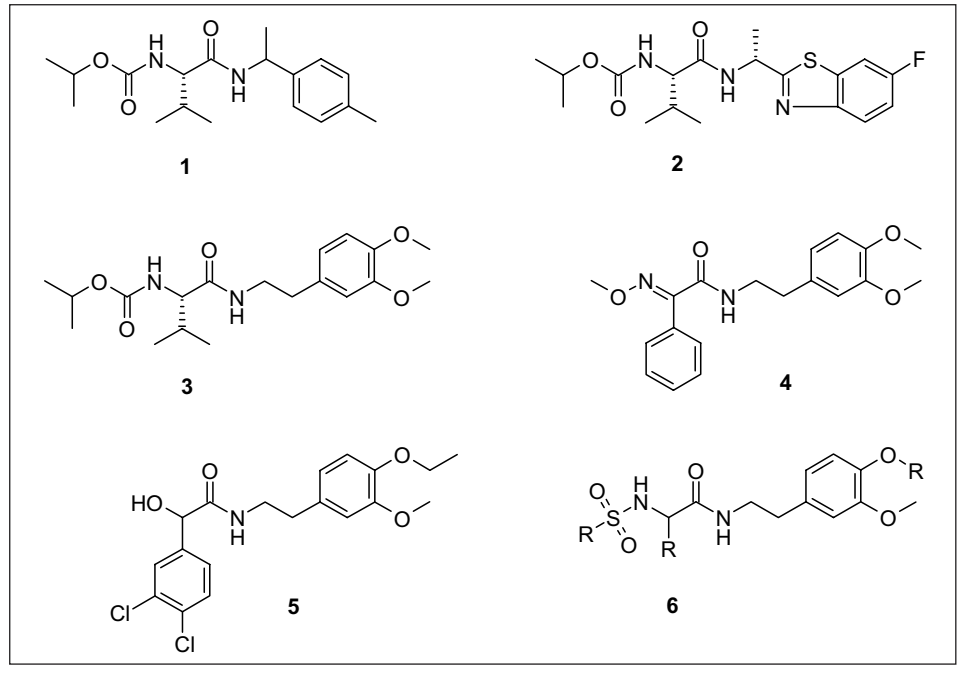

Fig. Fungicidally active amino acid amides, alkoximino acetic acid amides and mandelamides

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In this paper, we present the synthesis of novel N-sulfonyl amino acid amides and an analysis of their structure-activity relationships.

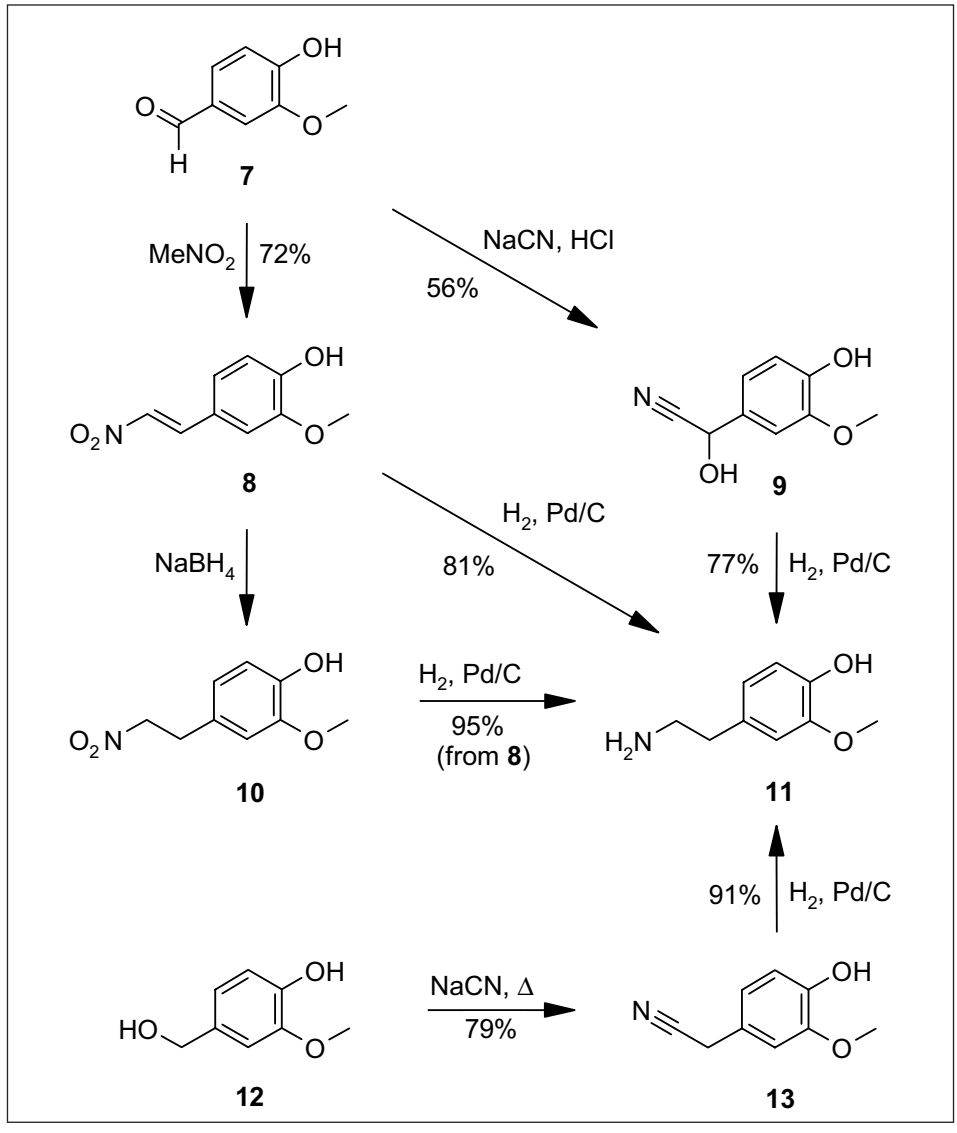
Chemistry

Synthesis of 2-(4-hydroxy-3-methoxyphenethyl)amine (11)

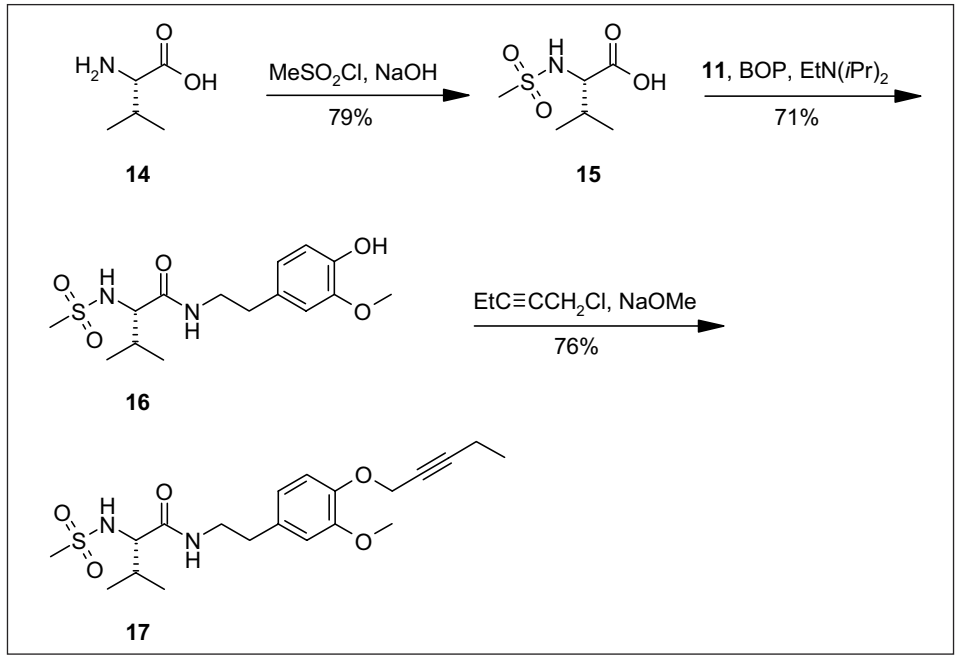
An important building block for the amine moiety is 2-(4-hydroxy-3-methoxyphenethyl)amine (**11**), also known as 3-O-methyldopamine or 3-methoxytyramine (Scheme 1). It is applied as a versatile precursor in the synthesis of tetrahydroisoquinoline [8] and morphine alkaloids [9], serotonin receptor antagonists [10], capsaicin-like agonists [11] and 5-lipoxygenase inhibitors [12]. In principle, **11** can be prepared by many different methods; three of which are highlighted in Scheme 1. A first possibility is the reduction, using either catalytic hydrogenation [13] or lithium aluminium hydride [14], of the nitrostyrene **8** which may be obtained by the Henry reaction of vanillin (**7**) and nitromethane. Another strategy is the catalytic hydrogenation of vanillin cyanohydrin (**9**) [15]. The third approach is the catalytic hydrogenation of the benzylcyanide (**13**), which can be obtained directly from vanillinol (**12**) through a quinoid transition state [16].

During the course of our work on N-sulfonyl amino acid amides, we required a reliable approach to relatively large quantities of **11**. The nitrostyrene route to **11** is probably the most widely applied, but in scale-up studies we found that both currently known reduction methods suffer from major disadvantages. Lithium aluminium hydride is impractical for bulk preparative work because of the hazards inherent in the use of this relatively expensive metal hydride and the difficult work-up procedures. Up-scaling the one-step catalytic hydrogenation of both the alkene and the nitro functions of **8** resulted in very variable and unsatisfactory results, accompanied by completely undesirable high exothermic reaction profiles. By splitting the hydrogenation of the alkene and nitro functions into two different steps, we could avoid the capricious results of the direct transformation of **8** to **11**. Thus, the sodium borohydride reduction of the nitrostyrene **8** to the phenylnitroethane **10** and its subsequent catalytic hydrogenation provided a high-yielding access to the phenethylamine **11**, which is well suited for its further transformation into N-sulfonyl amino acid amides.

The field of amino acid chemistry is already well documented [17]. In the syn-



Scheme 1. Different synthetic approaches to 2-(4-hydroxy-3-methoxyphenethyl)amine (**11**)



Scheme 2. Synthesis of N-sulfonylvalinamides

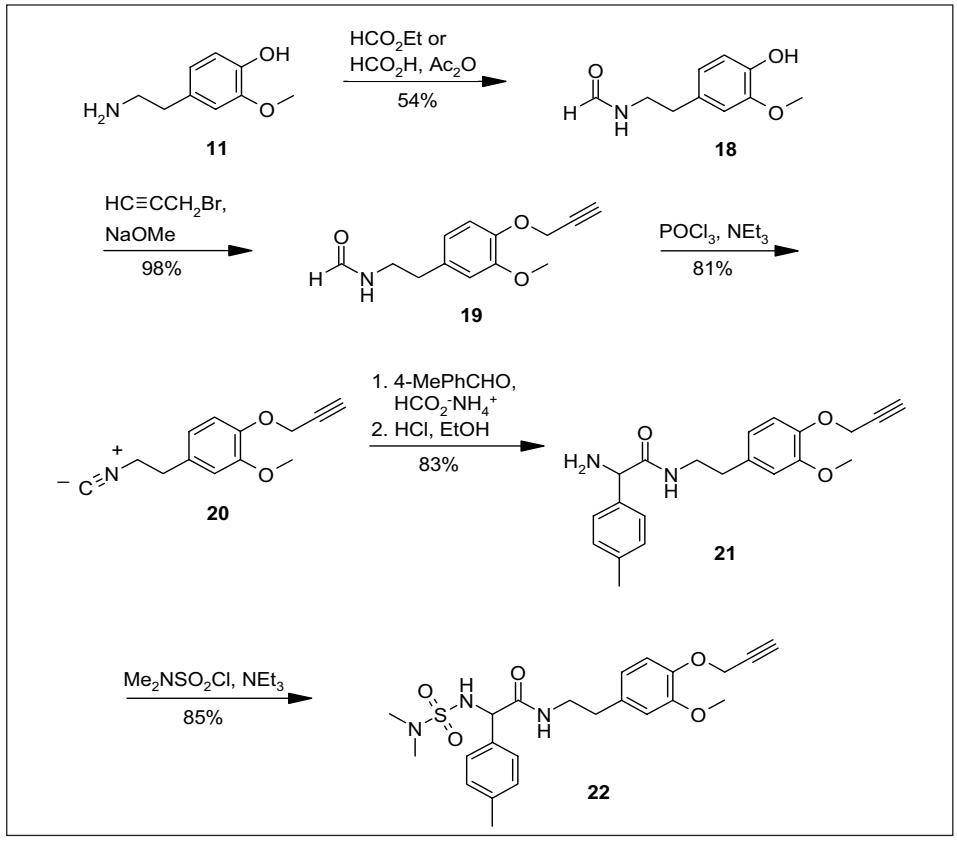
thesis of amino acid amides, the connection between the acid part and the amine moiety (the so-called peptide-coupling) generally seems to be the key step [18]. It turned out that two completely different peptide-coupling procedures were the optimum approaches to our envisioned N-sulfonyl-valinamides and -phenylglycinamides.

Synthesis of N-Sulfonylvalinamides

The N-sulfonylation of L-valine (**14**) under Schotten-Baumann conditions [19] led to the acid **15**, which could be reacted with **11** using Castro's reagent (BOP) [20] (Scheme 2). Alternatively, it was also possible to transform **15** into the corresponding acid chloride and to link it with **11**. In both cases the valinamide **16** was obtained in good yields and could be alkylated to the desired target compound **17**. Although rather strong bases were applied in this reaction sequence, no racemization was observed at the chiral centre of the amino acid. The epimerisation is probably prevented by the fact that because of the acidity of the sulfonamide hydrogen deprotonation took place rather at this position than at the α-carbon atom of valine.

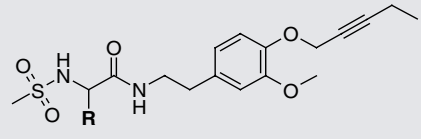
Synthesis of N-Sulfonylphenylglycinamides

In contrast to the above described route to N-sulfonylvalinamides, we decided to approach our envisioned N-sulfonylphenylglycinamides *via* an Ugi four-component condensation to obtain more flexibility in the introduction of substituents in the phenyl ring of the acid moiety. The Ugi reaction is a classical multi-component condensation, in which an amine, a carbonyl compound, a carboxylic acid, and an isocyanide are assembled in one step to an α-acylaminocarboxamide, and a new chiral centre is formed at the C-atom derived from the carbonyl group [21]. Recently multi-component reactions received much attention as a powerful tool for the generation of molecular diversity in combinatorial libraries and for the easy assembly of complex chemical structures [22]. The phenethylamine **11** was converted into the isocyanide **20** by standard N-formylation, O-propargylation and dehydration (Scheme 3). Hereby, the formyl group serves as protecting group of the amine function during the O-alkylation and as precursor for the formation of the isocyanide function. The Ugi reaction of the isocyanide **20** with *p*-tolualdehyde and ammonium formate, which is the amine as well as the acid com-



Scheme 3. Synthesis of N-sulfonylphenylglycinamides

Table 1. Structure–activity relationship study of the amino acid chain

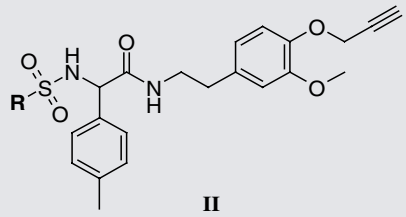


I

Entry	R	Conf.	EC_{80} values [ppm][a]	
			Phytophthora infestans (tomato late blight)	*Plasmopara viticola* (grape downy mildew)
Iprovalicarb (for comparison)			42	2
1	H	-	148	> 200
2	Me	L	> 200	> 200
3	$CH_2CH{=}CH_2$	D,L	9	49
4	*n*-Pr	L	60	20
5	*i*-Pr (**17**)	L	8	2
6	*c*-Pr	L	20	19
7	*s*-Bu	L	3	2
8	*i*-Bu	L	12	18
9	$CHEt_2$	D,L	16	16
10	$CH(OH)CH_3$	L	148	109
11	$CH_2CH_2CO_2H$	L	> 200	> 200
12	$CH_2CH_2SCH_3$	L	> 200	> 200
13	*c*-Hex	D,L	55	> 200
14	4-Cl-Ph	D,L	20	15

[a] EC_{80} value: calculated concentration in ppm obtained from greenhouse trials where the tested compound shows 80% activity.

Table 2. Structure–activity relationship study of the sulfonyl group



II

Entry	R	EC_{80} values [ppm][a]	
		Phytophthora infestans (tomato late blight)	*Plasmopara viticola* (grape downy mildew)
Iprovalicarb (for comparison)		42	2
1	Me	32	42
2	F_3C	-	104
3	Et	50	> 200
4	H_2C=CH	49	76
5	*n*-Pr	6	5
6	*i*-Pr	> 200	60
7	*n*-Bu	45	17
8	MeNH	10	10
9	Me_2N (**22**)	2	3
10	4-MePh	109	16

[a] EC_{80} value: calculated concentration in ppm obtained from greenhouse trials where the tested compound shows 80% activity.

ponent, led to a N-formylphenylglycinamide, which could be transformed into the free phenylglycinamide **21** by acidic hydrolysis. Finally, N-sulfonylation of **21** yielded the desired N-sulfonylphenylglycinamide **22**.

Biology

Influence of the Amino Acid Chain

The amino acid of general formula **I** (Table 1) needs a lipophilic backbone for fungicidal activity. The application of polar proteogenic amino acids like threonine (entry 10) and glutamic acid (entry 11) did not lead to good fungicidal activity. But several naturally occurring amino acids without polar groups like glycine (entry 1), alanine (entry 2) and methionine (entry 12) did not achieve fungicidal efficacy either. Examples for suitable amino acids are valine (entry 5) and isoleucine (entry 7), but also structurally related non-proteogenic amino acids like cyclopropylglycine (entry 6) and allylglycine (entry 3) were tolerated. The configuration of the chiral α-carbon atom is also important. The naturally occurring L-form shows in most of the cases higher activities than their D-enantiomers. However, the positive biological result of a racemic 4-chlorophenylglycine derivative (entry 14) encouraged us to venture also into this direction.

Influence of the Sulfonyl Group

The fungicidal activity of phenylglycinamides of the general formula **II** (Table 2) could be further increased by application of a n-propylsulfonyl function at the amino group (entry 5). The efficacy dropped with increasing or decreasing chain length of other linear sulfonyl substituents. However, best results were obtained with a dimethylsulfamoyl cap at the amino function (entry 9), delivering a compound acting effectively against the two major oomycete phytopathogens *Phytophthora infestans* and *Plasmopara viticola*. The incorporation of the amino group into a sulfinylamino-, alkylamino-, amide- or carbamate function – instead of protecting it with a sulfonyl group – led to totally inactive compounds.

Influence of the p-Phenol Substituent

One of the earlier findings during our expedition through the chemistry and biology of N-sulfonyl amino acid amides was the favourable activity of N-2-phenethylvalinamides of the general formula **III** (Table 3) with a 2-pentynyloxy substituent in the *para* position of the phenyl ring in the amine moiety (entry 6). Decreasing (entries 4 and 5) or increasing the chain length (entry 7) as well as introducing alkyl side branches on both sides of the C–C triple bond (entries 8 and 9) reduced the fungicidal efficacy. Surprisingly, the replacement of the 2-pentynyl group in entry 6 by a 4-halophenyl-propenyl moiety resulted in a further enhancement of biological activity (entry 10). Reducing the degree of unsaturation in the 4-chlorophenyl-propargyl sidechain of entry 10 led to decreased biological potency (entries 11–13).

Conclusion

The connection of N-sulfonyl amino acids with selected 4-alkynyloxy substituted 2-phenethylamines leads to novel amides with high fungicidal activity. Especially derivatives with valine and phenylglycine as amino acid moieties are distinguished by broad efficacy against the two major oomycete phytopathogens *Phytophthora infestans* (tomato and potato late blight) and *Plasmopara viticola* (grape downy mildew).

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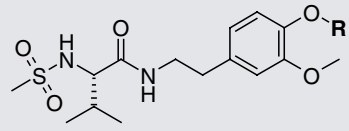
Table 3. Structure–activity relationship study of the *p*-phenol substituent



III

Entry	R	EC_{80} values [ppm][a]	
		Phytophthora infestans (tomato late blight)	*Plasmopara viticola* (grape downy mildew)
Iprovalicarb (for comparison)		42	2
1	H	> 200	> 200
2	Me	> 200	89
3	Et	109	53
4	$CH_2C\equiv CH$	55	18
5	$CH_2C\equiv CCH_3$	35	8
6	$CH_2C\equiv CCH_2CH_3$ (**17**)	8	2
7	$CH_2C\equiv CCH_2CH_2CH_3$	60	32
8	$CH(CH_3)C\equiv CCH_2CH_3$	45	109
9	$CH_2C\equiv CCH(CH_3)_2$	26	17
10	$CH_2C\equiv C$(4-Cl-Ph)	0.02	2
11	$CH_2CH=CH$(4-Cl-Ph)	6	2
12	$CH_2CH_2CH_2$(4-Cl-Ph)	10	60
13	CH_2CH_2O(4-Cl-Ph)	43	26

[a] EC_{80} value: calculated concentration in ppm obtained from greenhouse trials where the tested compound shows 80% activity.

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