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Inorganic base-catalyzed formation of antivirally active *N*-substituted benzamides from α -amido sulfones and *N*-nucleophile

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Abstract

Background: Heteronucleophiles as well as carbanionic reagents can be used to react with α -amido sulfones, thus giving the opportunity to prepare a large array of amino derivatives. Since, novel 1,3,4-oxadiazole-2-thiol derivatives can serve as potent nucleophiles, we employed 5-substituted phenyl-1,3,4-oxadiazole-2-thiols as the nucleophilic source of nitrogen in the reaction with α -amido sulfones.

Results: A series of *N*-substituted benzamides bearing 1,3,4-oxadiazol unit were prepared for the first time by the reaction of *in situ* generated protected imine from α -amido sulfones with 5-substituted phenyl-1,3,4-oxadiazole-2-thiols as the source of nitrogen nucleophile. Some of the synthesized products displayed favourable antiviral activity against *cucumber mosaic virus* (CMV) in preliminary antiviral activity tests. The title compounds **5c**, **5o** and **5r** revealed curative activity of 42.2%, 48.7% and 40.5%, respectively against CMV (inhibitory rate) compared to the commercial standard Ningnanmycin (53.4%) at 500 μ g/mL.

Conclusion: A practical synthetic route to *N*-benzoyl- α -amido sulfones by the reaction of 5-substituted phenyl-1,3,4-oxadiazole-2-thiols as the source of nitrogen nucleophiles with *in situ* generated protected imine from *N*-benzoyl- α -amido sulfones is presented. The reaction catalyzed by an inorganic base has considerable significance to exploit the potential of α -amido sulfones in organic synthesis.

Background

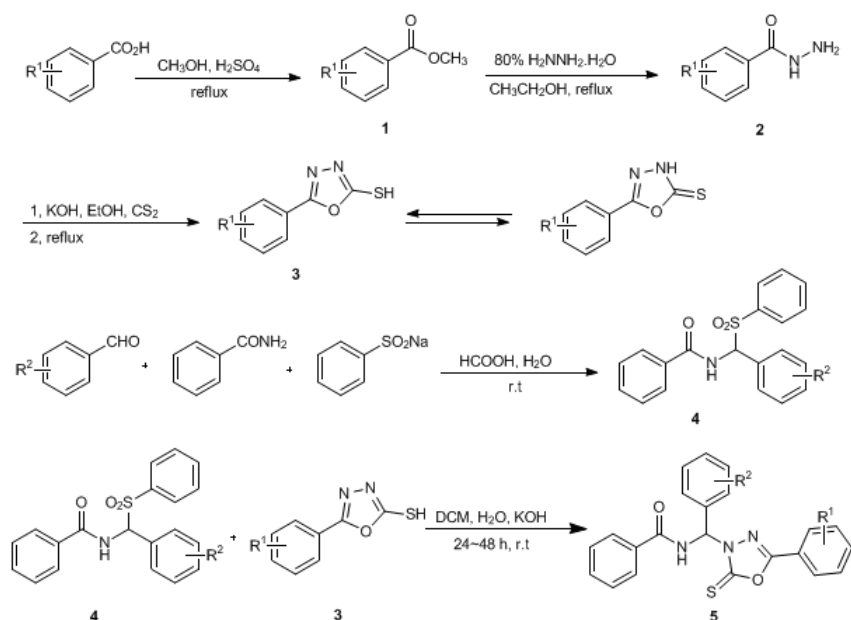
α -Amido sulfones are known for their wide range of application in asymmetric synthesis [1]. Different carbanionic nucleophiles can be reacted with α -amido sulfones, affording a wide variety of amino derivatives [2-7]. In addition, considerable research has been conducted on the reaction of nitrogen nucleophiles and α , β -unsaturated carbonyls [8-11]. Heteronucleophiles as well as carbanionic reagents can react with α -amido sulfones, thus giving the opportunity to prepare a large array of amino derivatives. Furthermore, a series of amino derivatives containing 1, 3, 4-oxadiazole ring were synthesized by the reaction of 1, 3, 4-oxadiazole-2-thiol with suitably substituted amines and formaldehyde in ethanol [12]. Based on these reports, we executed an

inorganic base-mediated reaction of 5-substituted phenyl-1, 3, 4-oxadiazole-2-thiols as the source of nitrogen nucleophiles with *N*-benzoyl- α -amido sulfones to produce *N*, *N*-aminals. Interestingly, the resulting compounds bearing a 1, 3, 4-oxadiazole ring are often associated with significant fungicidal and insecticidal activities [13-15]. Nevertheless, as of today, there has been no report on antiviral activities of *N*-substituted benzamides bearing 1,3,4-oxadiazol unit. We report synthetic and antiviral studies of the title compounds in the ensuing sections.

Results and Discussion

The synthetic route to the title *N*-substituted benzamides **5** is shown in Scheme 1. In order to prepare the key electrophilic component *N*-benzoyl- α -amido sulfones **4** for the final reaction, a three components reaction involving aromatic aldehyde, benzamide and sodium sulfonate was used by modifying the procedure reported by Chemla [16]. The reaction was fast, free of any significant side products

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Scheme 1 Synthetic sequence to *N*-substituted benzamide analogues **5** containing 1,3,4-oxadiazole ring.

formation and the pure product was isolated in moderate yield through recrystallization. The sulfones were characterized by ^1H NMR, ^{13}C NMR and IR spectral data. Finally, reaction of nitrogen nucleophiles **3** with *N*-benzoyl- α -amido sulfones in the presence of basic catalyst KOH in CH_2Cl_2 at room temperature afforded the desired *N*-substituted benzamides **5** bearing 1,3,4-oxadiazole group [Additional file 1]. The reaction conditions were optimized by taking compound **5a** as the model. The effect of different solvents and bases was studied at room temperature with a fixed reaction time of 24 h (Table 1). Under these conditions, dichloromethane (CH_2Cl_2) provided the product in higher yield compared to toluene, tetrahydrofuran (THF) or acetonitrile. Amongst the various bases screened for the experiment, KOH gave the best result and higher

conversion was achieved when 1.2 equiv of KOH was used instead of 1.0 equiv. Under optimized conditions, the isolated yield of the *N*-substituted benzamides **5a** reached as high as 70% when the reaction mixture was stirred for 24 h in CH_2Cl_2 using 1.2 equiv of KOH.

Antiviral activity and structure-activity relationship

The results of *in vivo* antiviral activity studies of the *N*-substituted benzamides **5a-5u** against CMV are given in Table 2. Ningnanmycin was used as the reference antiviral agent. Most of the compounds showed promising results in terms of curative bioactivities at 500 $\mu\text{g/mL}$. The comparison of the antiviral activity of the products with commercial reference leads to the following conclusions: (a) The antiviral activity is affected by the type of the substituents present in the compound. The compounds containing 2-fluorophenyl or 4-fluorophenyl group showed better anti-CMV activity compared with those derived from other groups. In particular, *N*-substituted benzamides **5o** ($\text{R}^1 = o\text{-F}$, $\text{R}^2 = p\text{-Cl}$) and **5c** ($\text{R}^1 = p\text{-F}$, $\text{R}^2 = m\text{-Cl}$) displayed moderate curative rates (48.7% and 42.2%, respectively) against CMV at the concentration of 500 $\mu\text{g/mL}$. These values were comparable to the curative rate (53.4%) shown by the commercial reference Ningnanmycin, and superior to other compounds bearing different substituents. (b) Substituents have a certain influence on the activity. Compared with the compounds **5o** and **5c** bearing suitably substituted aryl substituents, the compounds bearing an unsubstituted phenyl ring, such as **5a** and **5n**, showed lower inhibitory activities. (c) The structural modification caused by changing the substituents (R^1 and R^2) in

Table 1 Effect of different solvents and bases for the synthesis of **5a**^a

Entry	Solvent	Base	Equiv	Yield (%) ^c
1	Toluene	KOH	1.2	30
2	THF	KOH	1.2	58
3	CH_3CN	KOH	1.2	63
4	CH_2Cl_2	KOH	1.2	70
5 ^b	CH_2Cl_2	KOH	1.0	64
6	CH_2Cl_2	Na_2CO_3	1.2	52
7	CH_2Cl_2	NaOH	1.2	65

^a Unless otherwise noted, reactions were carried out with 0.5 mmol (1.0 equiv) of **4a**, 0.6 mmol (1.2 equiv) of **3a** in 5.0 mL solvent and 1 mL H_2O using 0.6 mmol (1.2 equiv) of basic catalyst at room temperature for 24 h. ^b Reaction was carried out with 0.5 mmol (1.0 equiv) of KOH at room temperature for 24 h. ^c Isolated yield after chromatographic purification.

Table 2 Curative effect of the title compounds 5 against CMV in vivo ^a

Agent	R ¹	R ²	Curative effect (%)
5a	<i>m</i> -Cl	H	24.2
5b	<i>m</i> -Cl	<i>o</i> -F	35.1
5c	<i>m</i> -Cl	<i>p</i> -F	42.2
5d	<i>m</i> -Cl	<i>o</i> -Cl	30.6
5e	<i>m</i> -Cl	<i>p</i> -Cl	28.2
5f	<i>m</i> -Cl	<i>o</i> -OCH ₃	22.9
5g	<i>m</i> -Cl	<i>p</i> -CH ₃	27.5
5h	<i>m</i> -Cl	<i>o</i> -NO ₂	32.1
5i	<i>m</i> -Cl	<i>p</i> -NO ₂	38.5
5j	<i>m</i> -Cl	<i>m</i> -NO ₂	36.0
5k	H	<i>p</i> -CH ₃	27.8
5l	H	<i>p</i> -NO ₂	35.0
5m	H	<i>p</i> -F	36.0
5n	<i>p</i> -Cl	H	26.2
5o	<i>p</i> -Cl	<i>o</i> -F	48.7
5p	<i>p</i> -Cl	<i>p</i> -F	35.8
5q	<i>p</i> -Cl	<i>p</i> -CH ₃	36.4
5r	<i>p</i> -Cl	<i>o</i> -OCH ₃	40.5
5s	<i>p</i> -Cl	<i>o</i> -Cl	37.9
5t	<i>p</i> -Cl	<i>p</i> -Cl	30.2
5u	<i>p</i> -Cl	<i>p</i> -NO ₂	27.2
Ningnanmycin			53.4

^a All antiviral tests were carried out at the concentration of 500 µg/mL.

the phenyl ring have a wide impact on anti-viral activity of the prepared compounds. Bioactivity of various compounds having the same substituents at different positions of the phenyl ring is various. Thus, amongst the compounds **5b**, **5c**, **5o** and **5p** containing the same substituents at different positions of the phenyl ring, the compound **5o** carrying 4-chloro and 2-fluoro groups in their respective phenyl rings exhibited better bioactivity than others. Although these compounds, in general, exhibited slightly lower activity in comparison with the commercial reference Ningnanmycin at the concentration of 500 µg/mL, some suitably substituted *N*-substituted benzamides bearing 1,3,4-oxadiazol moiety showed favourable antiviral activity in the preliminary studies. Subtle structural variation might lead to enhancement of activity and should be the direction of future research.

Experimental

Chemistry

The melting points of the products were determined on an XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. The IR spectra were recorded on a Bruker VECTOR 22 spectrometer in a KBr disk. ¹H NMR (500 MHz), ¹³C NMR (125 MHz) and ¹⁹F NMR (470 MHz) spectral analyses were performed on a JEOL-ECX 500 NMR spectrometer at room temperature using TMS as an internal standard and CDCl₃ as the

solvent. Elemental analysis was performed on an Elementar Vario-III CHN analyzer. Analytical TLC was performed on silica gel GF254. Column chromatographic purification was carried out using silica gel. All the solvents and materials were of analytical-grade. Intermediate **1**, intermediate **2** and 5-substituted phenyl-1,3,4-oxadiazole-2-thiol **3** were prepared according to the reported methods [17,18] and used without further purifications [Additional file 2].

Antiviral biological assay

The leaves of *Nicotiana tabacum* L. inoculated with CMV were selected and grinded in phosphate buffer and filtered through double-layer pledget. The filtrate was centrifuged at 8000 g and the supernatant liquid was the crude extract of virus. The whole experiment was carried out at 4°C. Absorbance values were estimated at 260 nm using an ultraviolet spectro-photometer.

$$\text{virus concn} = (A_{260} \times \text{dilution ratio}) / E_{1\text{ cm}}^{0.1\%, 260\text{ nm}}$$

Preparation of medicaments

Tested compounds and 2% Ningnanmycin aqua used as a reference antiviral agent were first dissolved in minimum volume of *N,N*-dimethylformamide (DMF) and then diluted with distilled water containing 1% Tween 20 at 500 µg/mL concentration.

Curative effect of compounds against CMV in vivo

Growing leaves of *Chenopodium amaranticolor* of the same age were selected. Crude extracts of CMV were dipped and inoculated with a brush on the whole leaves, which were previously scattered with silicon carbide. The leaves were washed by water after inoculation for 0.5 h and then dried. The compound solution was smeared on the left side of leaves, and the solvent was smeared on the right side for control. All plants were cultivated at 28 ± 1°C with an illumination of 10000 Lux. The local lesion numbers appearing 6-7 d after inoculation were counted. Three repetitions were conducted for each compounds. The inhibition rate of the compound was calculated according to the following formula (av denotes average):

$$\text{inhibition rate(\%)} = \frac{\text{av local lesion no. of right leave (not treated with compound)} - \text{av local lesion no. of left leave (smeared with compound)}}{\text{av local lesion no. of right leave (not treated with compound)}} \times 100\%$$

Conclusion

We have demonstrated a general and practical route for the synthesis of the *N*-substituted benzamides bearing 1,3,4-oxadiazol moiety in the presence of an inorganic base as the catalyst. The reaction of 5-substituted

phenyl-1,3,4-oxadiazole-2-thiol which serves as the source of *N*-nucleophile with *in situ* generated protected imine from *N*-benzoyl- α -amido sulfones provides a ready access to a series of structurally diverse *N*, *N*-aminals. The antiviral tests indicated that some of the synthesized compounds possessed of moderately high curative activity against CMV. The structure of the target products needs to be optimized to enhance their antiviral activity. Further studies on mechanistic aspects, enantioselectivities and asymmetric variants of catalysts for this reaction are currently being investigated in our group.

Additional material

Additional file 1: Yield and elemental analyses data for title compounds 5a-u. Which contains the table about structure, yield and elemental analyses data for title compounds **5a-u**.

Additional file 2: Experimental details and data of title compounds 5a-u. Which includes the experimental procedure, spectroscopic data of intermediate **3**, intermediate **4**, title compounds **5a-u**, copies of ^1H NMR and ^{13}C NMR.

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Authors' contributions

The current study is an outcome of constructive discussion with BAS, SY, LHJ and DYH who offered necessary guidance to YJ to carry out his synthesis and characterization experiments. YJ was also involved in the drafting of the manuscript. XW performed the antiviral tests; HXQ carried out the ^1H NMR, ^{13}C NMR and ^{19}F NMR spectral analyses. ZCW and WMX participated in the scientific discussion pertaining to the manuscript. BAS and associate PSB were involved in revising the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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