

Original Article

Synthesis and reaction mechanism of 3-(4-methoxyphenylazo) acrylic acid

Bing Liu^{1,2}, Runling Wang², Weiren Xu^{1,*}, Guilong Zhao¹, Lida Tang³, Xianchao Cheng², Hui Zhou²¹ Tianjin Key Lab of Molecular Design and Drug Discovery, Tianjin Institute of Pharmaceutical Research, Tianjin, China;² School of Pharmacy, Tianjin Medical University, Tianjin, China;³ Tianjin State Key Lab of Pharmacokinetics and Pharmacodynamics, Tianjin Institute of Pharmaceutical Research, Tianjin, China.

ABSTRACT: Using 4-methoxyphenylhydrazine hydrochloride (**1a**) as starting material, 2-[2-(4-methoxyphenyl) hydrazono] acetic acid (**2a**) was prepared after treatment with 1 equivalent of 2-oxoacetic acid, and 3-(4-methoxyphenyldiazo) acrylic acid (**3a**) was obtained with 2 equivalents of 2-oxoacetic acid through a novel reaction. The mechanism of reaction was analyzed with the help of charge distribution computation. This suggests that the novel reaction depends on the electronegativity of C9, which can be mainly affected by the substituents of the benzene ring.

Keywords: 3-(4-Methoxyphenylazo)acrylic acid, arylhydrazonoacetic acid, reaction mechanism, synthesis

1. Introduction

Arylhydrazines are a class of highly reactive compounds, which are used to synthesize dye and medicine intermediates; such as, indoles, indazoles and pyrazoles (1-5). In our efforts to synthesize 1-aryl-1,2,4-triazolin-5-one derivatives as anticancer agents, a novel reaction was found. Arylhydrazonoacetic acid was prepared from arylhydrazine by treatment with 2-oxoacetic acid as shown in Scheme 1. However, when **1a** was treated with 2 equivalents of 2-oxoacetic acid, product **3a** was isolated. Although the synthesis of **3a** from **1a** through a three step procedure has been published by Cevasco and co-workers (6), our one-pot reaction has not been reported, previously. We report the novel synthesis pathway of **3a** and a possible mechanism.

*Address correspondence to:

Dr. Weiren Xu, Tianjin Key Lab of Molecular Design and Drug Discovery, Tianjin Institute of Pharmaceutical Research, Tianjin 300193, China.
e-mail: xwrtj@yahoo.com.cn

2. Materials and Methods

2.1. Chemical reagents

p-Methoxyphenylhydrazine hydrochloride (**1a**), *p*-tolylhydrazine hydrochloride (**1b**), phenylhydrazine hydrochloride (**1c**) and (4-nitrophenyl)hydrazine hydrochloride (**1d**) were purchased from Linhai Duqiao Fine Chemical Factory, Zhejiang, China. 40% 2-oxoacetic acid was purchased from Shanghai Haiqu Chemical Co. Ltd., Shanghai, China. Acetic acid and sodium acetate were purchased from Tianjin First Chemical Factory, Tianjin, China.

2.2. Chemical experiment

The chemical structures of the compounds were confirmed by ¹H NMR, ¹³C NMR and ESI-MS as described below. **1b**, **1c**, and **1d** were also used to react with two portions of 2-oxoacetic acid under similar reaction conditions for the preparation of **3a**. However, their products were complicated, and no pure corresponding products could be isolated.

2.2.1. [(4-Methoxyphenyl) hydrazono]acetic acid (**2a**)

40% aqueous 2-oxoacetic acid (5.8 g, 31 mmol) was added dropwise to a solution of *p*-methoxyphenylhydrazine hydrochloride (6.0 g, 34 mmol) in water (120 mL) and a yellow precipitate formed. The solution was stirred for 1 h. The precipitate was then collected by filtration and dried *in vacuo* to obtain 2.68 g of 2-[(4-methoxyphenyl)hydrazono]acetic acid (**2a**) in 40% yield. Mp 75°C (dec). ¹H NMR (DMSO-*d*₆, 400 MHz), δ 12.07 (s, 1H), 11.00 (s, 1H), 7.06 (d, 2H, *J* = 7.2 Hz), 7.05 (s, 1H), 6.87 (d, 2H, *J* = 7.2 Hz), 3.69 (s, 3H); ¹³C NMR (DMSO-*d*₆, 400 MHz), δ 165.37, 154.16, 137.23, 124.31, 114.64, 114.29, 55.22. ESI-MS: *m/z* = 195.10 (M+1).

2.2.2. 3-(4-Methoxyphenyldiazo)acrylic acid (**3a**)

40% aqueous 2-oxoacetic acid (6.3 g, 34 mmol) was

added dropwise to a stirred solution of *p*-methoxyphenylhydrazine hydrochloride (**1a**) (3.0 g, 17 mmol), sodium acetate (1.5 g, 17 mmol), acetic acid (100 mL) and water (100 mL) in a three-neck flask at 10°C under a stream of nitrogen. The mixture was stirred for 1.5 h, and the precipitate was collected by filtration. 1.2 g of 3-(4-methoxyphenyldiazo)acrylic acid (**3a**) (in 34% yield) was obtained through recrystallization and dried *in vacuo*. Mp 50°C (dec). ¹H NMR (DMSO-*d*₆, 400 MHz), δ 12.95 (s, 1H), 7.83 (d, 1H, *J* = 14 Hz), 7.81 (d, 2H, *J* = 9 Hz), 7.10 (d, 2H, *J* = 9 Hz), 6.77 (d, 1H, *J* = 14 Hz), 3.86 (s, 3H); ¹³C NMR (DMSO-*d*₆, 400 MHz), δ 166.80, 163.26, 155.96, 146.46, 128.56, 125.33, 114.85, 55.78. ESI-MS: *m/z* = 207.11 (M+1).

2.2.3. (*p*-Tolylhydrazone) acetic acid (**2b**)

Compound **2b** was synthesized from *p*-tolylhydrazine hydrochloride **1b** with a 87% yield under similar reaction conditions for the synthesis of **2a**. Mp 110-111°C. ¹H NMR (DMSO-*d*₆, 400 MHz), δ 12.22 (d, 1H), 1.03 (s, 1H), 7.11 (s, 1H), 7.06 (d, 2H, *J* = 8.4 Hz), 7.02 (d, 2H, *J* = 8.4 Hz), 2.21 (s, 3H); ¹³C NMR (DMSO-*d*₆, 400 MHz), δ 165.31, 141.22, 129.71, 125.08, 119.06, 113.15, 20.23. ESI-MS: *m/z* = 178.10 (M+1).

2.2.4. (Phenylhydrazone)-acetic acid (**2c**)

Compound **2c** was synthesized from phenylhydrazine hydrochloride (**1c**) with a 95% yield under similar reaction conditions for the synthesis of **2a**. Mp

107-108°C. ¹H NMR (DMSO-*d*₆, 400 MHz), δ 12.30 (s, 1H); 11.11 (s, 1H); 7.26 (m, 2H); 7.12 (d, 2H, *J* = 8.8 Hz); 7.10 (s, 1H); 6.88 (t, 1H, *J* = 7.2 Hz); ¹³C NMR (DMSO-*d*₆, 400 MHz), δ 165.26, 143.54, 129.25, 125.94, 121.04, 113.15. ESI-MS: *m/z* = 165.11 (M+1).

2.2.5. [(4-Nitro-phenyl)-hydrazone]-acetic acid (**2d**)

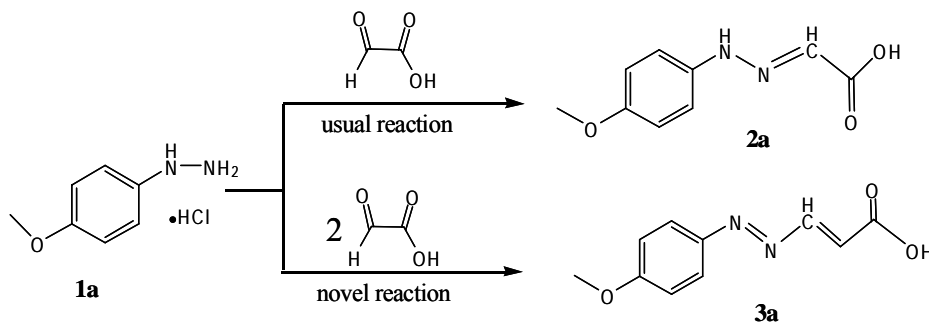
Compound **2d** was synthesized from (4-nitrophenyl) hydrazine hydrochloride (**1d**) with a 77% yield under similar reaction conditions for the synthesis of **2a**. Mp 170-171°C. ¹H NMR (DMSO-*d*₆, 400 MHz), δ 12.70 (s, 1H); 11.73 (s, 1H); 8.16 (d, 2H, *J* = 9.2 Hz); 7.27 (s, 1H); 7.21 (d, 2H, *J* = 9.2 Hz); ¹³C NMR (DMSO-*d*₆, 400 MHz), δ 164.60; 149.29; 140.39; 131.25; 125.68; 112.77. ESI-MS: *m/z* = 210.08 (M+1).

2.3. Computational experiment

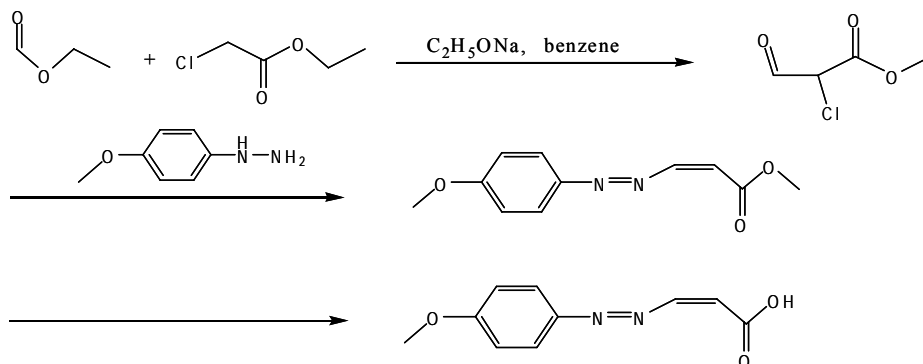
For comparison, the structures of **2a-d** were constructed by ChemOffice software, and then optimized with the density function theory at the B3LPY/6-31G(d) level by the Gaussian 98 software package (7-9). The charge distribution and bond lengths of all structures were calculated using optimized structures by the nature bond orbit method.

3. Results and Discussion

The reaction reported by Cevasco (Scheme 2) (6) used three steps to obtain the final product without any



Scheme 1. The two reactions of *p*-methoxyphenylhydrazine and 2-oxoacetic acid.



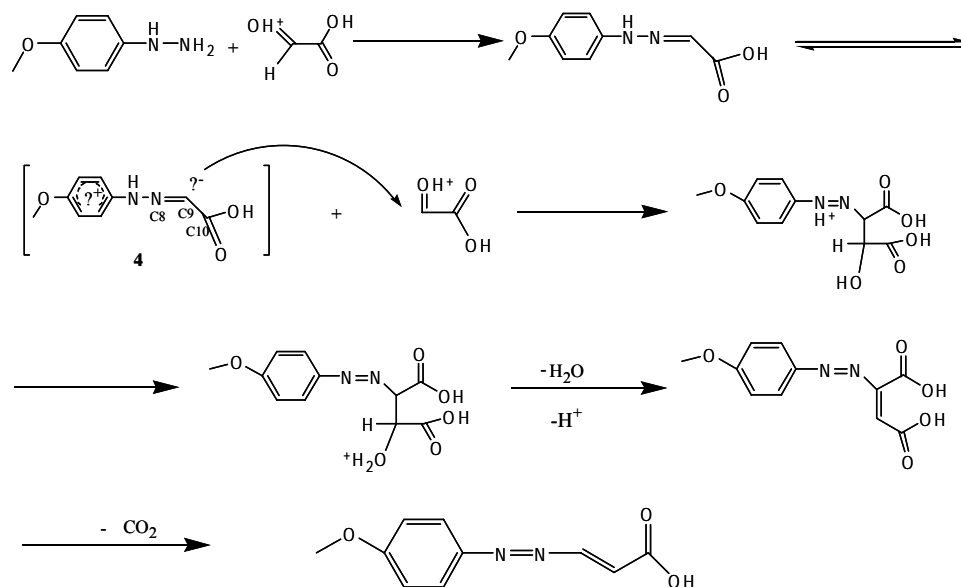
Scheme 2. The reaction reported by Cevasco and his co-workers (6).

disclosed isolated yields. However, some steps required complicated operations and harsh reaction conditions.

As outlined in Scheme 1, 2-[(4-methoxyphenyl)hydrazono]acetic acid (**2a**) was prepared from the usual reaction, while 3-(4-methoxyphenyldiazo)acrylic acid (**3a**) was synthesized through a novel reaction. The different substituents were also screened. The analogues **2b**, **2c**, and **2d** of **2a** can be prepared from *p*-tolylhydrazine hydrochloride (**1b**), phenylhydrazine hydrochloride (**1c**), and (4-nitrophenyl)hydrazine hydrochloride (**1d**) through the usual reaction. Nevertheless, when using **1b**, **1c**, and **1d** as starting materials, the possible analogues **3b**, **3c**, and **3d** were not obtained under similar reaction conditions for the preparation of **3a** from **1a**. The results suggest that the substituents with different electronegativities attached to the benzene ring play a critical role in this pathway.

A possible mechanism was proposed for the novel

reaction, which is shown in Scheme 3. First, 1 equivalent of 2-oxoacetic acid coupled with 1 equivalent of **1a** to form a Schiff's base **2a** through nucleophilic addition and the ensuing dehydration. Second, the electrons were redistributed because of the conjugation within **2a** (**6**), making C9 (following the labeling in Figure 1) and the benzene ring shows electronegativity and electropositivity, respectively. Then the carbonyl group of 2-oxoacetic acid was attacked by C9 through nucleophilic addition, forming a transient state with two carboxyl groups. Finally, **3a** was produced from the transient state through proton translocation, dehydration and decarboxylation in turn. In the whole process, the key point was the conjugated state **4** in which C9 was negative enough. In conjugated state **4**, the electronegativity of atom C9 was strongly enhanced by the substitution of the *p*-methoxy group in **2a**. This explains why the novel reaction could only happen to **2a**.



Scheme 3. The possible mechanism for the novel reaction.

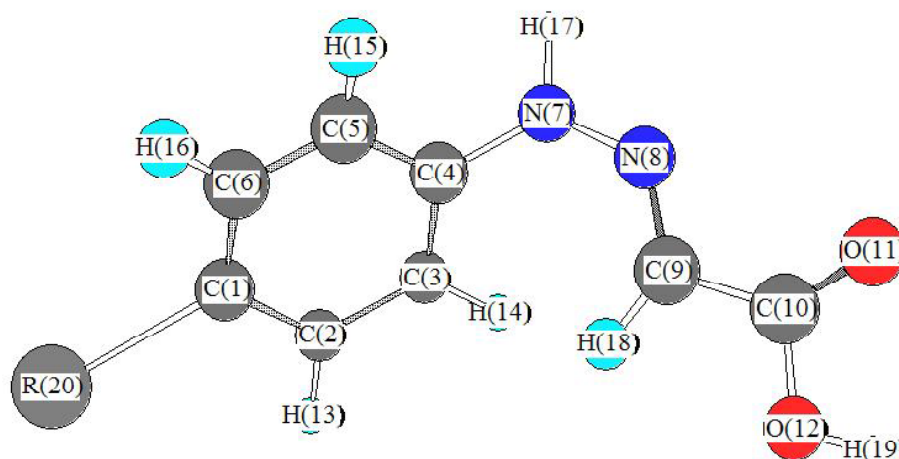


Figure 1. Atom labels of the computational structure.

Table 1. Charge distribution and bond length of compounds 2a-d calculated by B3LYP/6-31G(d) method

Compounds (Substituents)	2a (-OCH ₃)	2b (-CH ₃)	2c (-H)	2d (-NO ₂)
Charge distribution				
R	-0.205	0.034	-----	-0.27
Benzene ring	0.359	0.112	0.139	0.340
N7	-0.358	-0.36	-0.362	-0.365
N8	-0.200	-0.198	-0.198	-0.202
C9	-0.165	-0.159	-0.156	-0.130
C10	0.741	0.742	0.743	0.745
Bond length (pm)				
C4-N7	140.6	140.4	140.4	139.3
N7-N8	131.7	131.8	131.9	132.7
N8-C9	130.2	130.1	130.0	129.6
C9-C10	146.7	146.9	147.0	147.6

In order to support the above hypothesis, the charge distribution of the structures with different substitutions were computed with the DFT method at B3LYP/6-31G(d) level. Atom labels are displayed in Figure 1 for all structures, and the substituents are represented as R(20). As shown in Table 1, the charges of the benzene rings, atoms N7, N8 and C9 were influenced by the different substitutions in the benzenes rings, and it suggests that these fragments are in a large conjugation. The results, in which benzene rings and C9 showed electropositivity and electronegativity respectively, agree with the hypothesis of a conjugated state **4** in Scheme 3.

The postulate that C9 in **2a** had more electronegativity was also supported by the results of calculations. The charge distributions of C9 of **2a**, **2b**, **2c**, and **2d** were -0.165, -0.159, -0.156, and -0.130, respectively. Obviously, the quantity of electric charge of C9 increased with the capability of supplying electrons to substituent groups. The capability to supply electrons from methyl, hydrogen and nitro was weaker than that of methoxy, so the electronegativity of C9 of **2b**, **2c**, and **2d** was weaker than that of **2a**. The weaker electronegativity of C9 led to lower nucleophilicity of C9 of **2b**, **2c**, and **2d**, which could not give dominating products to form a novel reaction under similar conditions.

The strong conjugation in species **4** of Scheme 3 could also be supported by the analysis of bond lengths of structure **2a-2d** from Table 1. It is well known that the length of a standard C-N, C-C, N-N, and C=N are 147.0, 154.0, 140.0, and 128.0 pm, respectively. The bond lengths of C4-N7, N7-N8, and C9-C10 in **2a-2d** were shorter than their standard single bond length, respectively, and that of N8-C9 were longer than a standard double bond. Obviously, these four bonds equilibrated. This phenomenon suggests the fact that there are conjugations in molecule **2a-d**. As the electronegativity of C9 was critical in the reaction, the bond lengths of N8-C9 and C9-C10 were further analyzed for structures **2a-2d**. The structure **4** in Scheme 3 showed that N8-C9 and C9-C10 are double and single bonds. The average degree of these two bonds is related to the conjugation of the molecule. The results in Table 1 show the bond length of N8-C9 of **2a**

was the longest and that of C9-C10 was the shortest in comparison with other compounds. It also suggests that **2a** has more powerful conjugation.

In conclusion, arylhydrazonoacetic acids **2a-d** could be prepared by treatment with one equivalent of 2-oxoacetic acid through the usual pathway, and only 3-(4-methoxyphenyldiazo)acrylic acid **3a** could be synthesized by treatment with 2 equivalents of 2-oxoacetic acid under our reported conditions. We developed a more effective synthetic method for **3a** through this one-pot mild reaction. The mechanism suggests that the novel reaction depends on the degree of electronegativity of C9, which can be largely affected by the substituents of the benzene ring.

Acknowledgements

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