## **ORIGINAL PAPER**

## Efficient synthesis of glutaric acid from L-glutamic acid via diazoniation/hydrogenation sequence

### Wei Zhang, Meng-Yun Rao, Zhong-Jun Cheng, Xiao-Yan Zhu, Kai Gao, Jian Yang, Bo Yang, Xia-Li Liao\*

Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, China

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The practical synthetic preparation of glutaric acid has remained a major challenge to date. In the present study, glutaric acid was synthesised by way of one-pot diazoniation/hydrogenation of the readily available L-glutamic acid under aqueous conditions on a gram-scale with good yields. This is the first example of the deamination of the aliphatic primary amine via diazoniation and could afford a practical approach to the production of glutaric acid. © 2014 Institute of Chemistry, Slovak Academy of Sciences

Keywords: glutaric acid, L-glutamic acid, diazoniation/hydrogenation, sodium nitrite, hypophosphorous acid

#### Introduction

Glutaric acid (I, Fig. 1) is among the substantially important fine chemicals. It is widely used in fine chemistry, agriculture, medicine and architecture (Johnson et al., 1993). In the plastics industry, it is the essential raw material for the production of polymeric materials such as polyvinyl chloride (PVC), polyester, polyamide, resin, synthetic rubber, etc. (Besson et al., 2005). It has been reported that *I* exhibited some important physiological activities such as neurotoxicity (Kölker et al., 1999), inhibition of glutamate uptake (Porciúncula et al., 2000; Rosa et al., 2007), inhibition of energy production (Silva et al., 2003) and membrane translocation (Mühlhausen et al., 2008), etc.

Currently, the production of I is largely dependent on the recovery of byproducts from the process of manufacturing adipic acid (Castellan et al., 1991; Tullo et al., 2002). However, this incurs significant drawbacks such as complex process, purification difficulty and high cost. In addition, the outcome is always uncertain due to the yield being closely dependent on the production process of adipic acid. With continuous improvements to the processing technique of



Fig. 1. Synthesis of glutaric acid (I) from L-glutamic acid (II). Reaction conditions: i) NaNO<sub>2</sub>, mineral acid (H<sub>2</sub>SO<sub>4</sub> or HCl or H<sub>3</sub>PO<sub>4</sub>) and H<sub>3</sub>PO<sub>2</sub> (see Table 1) or another reductant (see Table 2), -5-0 °C, 10–12 h.

adipic acid, the *I* outputs obtained therefrom have decreased accordingly. Meanwhile, the chemical synthesis of *I* has emerged as a further option, having been synthesised by the catalytic oxidation of cyclopentene (Orita et al., 1986; Choudary et al., 1991; Antonelli et al., 1998; Griffith et al., 2000; Wang & Dai, 2002; Griffith & Kwong, 2003; Chen et al., 2006a, 2006b; Che et al., 2006; Shoair & Mahamed, 2006; Saedi et al., 2012a, 2012b), 1,5-pentanediol (Iwahama et al., 2000; Chen et al., 2007; Balaraman et al., 2013), 1,3cyclohexanedione (Yuan & Zhao, 2010; Tachikawa et al., 2013), dihydropyran (English & Dayan, 1957), tetrahydropyran (Smith & Scarborough, 1980), 2cyclohexenone (Travis et al., 2002), cyclopentane-1,2-

<sup>\*</sup>Corresponding author, e-mail: xlliao@yahoo.com

diol (Gao et al., 2009), or glutaraldehyde (Chu et al., 2012), by the acidic hydrolysis of glutaronitrile (Marvel & Tuley, 1925), by  $\gamma$ -butyrolactone (Paris et al., 1957) or by electrosynthesis (Lyalin & Petrosyan, 2009). However, all these methods entailed the use of expensive substrates or catalysts, harsh conditions or toxic reagents. Hence, the practical production of *I* by chemical synthesis represents a challenge.

L-Glutamic acid (II) (Fig. 1) is one of the natural essential amino acids. It is readily available and is used extensively in the pharmaceutical and food industries. Simple replacement of the amino group with hydrogen could readily transform II to glutaric acid (I) due to the similarity in their chemical structures. Diazonium compounds, mostly aromatic diazonium salts, are recognised as important intermediates in organic synthesis because they can be expediently converted to aryl halides, phenols, arenes, nitro arenes, cyano arenes, etc. (Mo et al., 2013; He et al., 2014). Replacement of the diazonium group with hydrogen usually requires an appropriate reductant to afford the transformation. To date, a number of reducing agents such as ethanol (Clarke & Taylor, 1923; Bogert & Mandelbaum 1923; Bigelow et al., 1926; Coleman & Talbot, 1933; Wallingford & Krueger, 1939; Roe & Graham, 1952; Baqi & Müller, 2012), alkaline formaldehyde (Brewster & Poje, 1939), borohydride (Hendrickson, 1961; Rieker et al., 1969), thiophenol (Shono et al., 1979), bisulphite (Shapiro et al., 1970; Geoffroy et al., 2001), ethyl acetate (Bacherikov et al., 2004; Meng & Cai, 2005), phosphorous acid (Kornblum et al., 1952) and hypophosphorous acid (or hypophosphite) (Kornblum, 1941; Adams & Kornblum, 1941; Robison & Robison, 1956; Mitsuhashi et al., 2000) have been developed. However, to the best of our knowledge, the transformation of aliphatic amines has been disclosed only rarely in comparison with the numerous reports on aromatic amines. Nickon and Hill (1964) and Doldouras and Kollonitsch (1978) conducted the deamination of aliphatic amines with hydroxylamine-O-sulphonic acid, whilst the preparation of  $\alpha$ -hydroxy acids by the diazoniation of natural amino acids was disclosed by Kolitz et al. (2009); however, there has been no report on the deamination via diazoniation of aromatic amines. Furthermore, it was reported that, in contrast with aromatic amines, aliphatic primary amines did not react with nitrous acid below a pH value of 3.0 (Kornblum & Iffland, 1949). Hypophosphorous acid  $(H_3PO_2)$  is a potent and readily available reducing reagent which is used ubiquitously in chemical, pharmaceutical and dyestuff fields. Herein, a new method for the preparation of I from II via a diazoniation/hydrogenation sequence with  $H_3PO_2$  is presented.

#### Experimental

L-Glutamic acid (Shanghai, China) of chemical pu-

rity was used as received. Melting points (uncorrected) were determined on an RY-1 instrument (Shanghai, China). IR spectra were recorded on a Bio-Rad FTS-40 FTIR spectrometer (Bio-Rad, USA). <sup>1</sup>H NMR spectra were measured on a Bruker Avance DRX 500 spectrometer (Bruker, Germany) at 298 K and the HRESI-MS data were recorded on a Bruker MicrOTOF Q-II mass spectrometer (Bruker, Germany).

# Typical procedure of deamination with hypophosphorous acid

A 500-mL three-necked round-bottom flask containing water (150 mL) was cooled in an ice-salt bath  $(-10^{\circ}C \text{ to } -5^{\circ}C)$  for 10 min. H<sub>2</sub>SO<sub>4</sub> (98 mass %, 32.5 mL, 598 mmol) was added carefully through a dropping funnel with stirring. Following the addition, an aqueous solution of  $NaNO_2$  (23.5 g of  $NaNO_2$ , 30 mL of water, 340 mmol) was added drop-wise through another dropping funnel and the solution was stirred for a further 10 min, followed by the drop-wise addition of precooled  $H_3PO_2$  (50 mass %, 53.9 g, 408 mmol) over 10–15 min. L-Glutamic acid (II) (5 g, 34 mmol) was added carefully by stages maintaining the reaction temperature at -5-0 °C. The reaction mixture was stirred for 10–12 h (monitored by TLC; developing solvent system: 1-butanol/acetic acid/water ( $\varphi_r = 4 : 1 : 1$ ); visualisation by ninhydrin and bromocresol green), the pH was adjusted to approximately 5.0 with an aqueous solution of NaOH (10 mass %) and the solvent was evaporated under diminished pressure at  $40 \,^{\circ}$ C to a volume of about 200 mL. The thick liquid was extracted with hot ethyl acetate (55 °C, 3  $\times$  200 mL). (Note: additional extractions with hot ethyl acetate could improve the yield by a few per cent; extraction with other organic solvents such as ethyl ether, dichloromethane, chloroform, 1,2-dichloroethane, etc. could also afford moderate to good yields, but hot ethyl acetate was chosen for its low toxicity and cost.) The combined organic extracts were washed with brine (50 mL), dried with  $MgSO_4$ , followed by concentration under diminished pressure to yield colourless flaky crystals of I~(3.57 g, yield of 80 %). M.p. 95–98 °C; IR (KBr),  $\nu_{\rm max}/{\rm cm}^{-1}$ : 3033, 2956, 1697, 1444, 982; HRESI-MS, m/z (found/calc.): 155.0316/155.0314 ([M + Na]<sup>+</sup>); <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O),  $\delta$ : 2.34–2.27 (4H, m, HOOCCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>COOH), 1.80–1.73 (2H, m,  $HOOCCH_2CH_2CH_2COOH).$ 

#### **Results and discussion**

Commercially available  $H_3PO_2$  (50 mass % aqueous solution) was first chosen to perform the dediazoniation due to its strong reducing ability. The diazonium salt was formed in the presence of sulphuric acid and NaNO<sub>2</sub>, followed by a hydrogenation or dediazoniation process with the assistance of  $H_3PO_2$  (Fig. 1).

Table 1. Optimisation of reaction conditions using  $H_3PO_2$  as reductant<sup>a</sup>

Entry	II/mg	${ m H_3PO_2/equiv}$	Acid	$\mathrm{Yield}/\%$
1	50	8	$H_2SO_4$	37
$^{2}$	50	10	$H_2SO_4$	64
3	50	12	$H_2SO_4$	88
4	50	14	$H_2SO_4$	87
5	50	12	HCl	$^{\rm cp}$
6	50	12	$H_3PO_4$	28
7	5000	12	$H_2SO_4$	80

a) General reaction conditions: II (50 mg, 0.34 mmol), mineral acid (H<sub>2</sub>SO<sub>4</sub>, 98 mass %, 6.5 mL; or HCl, 37 mass %, 10 mL; or H<sub>3</sub>PO<sub>4</sub>, 85 mass %, 8.2 mL), NaNO<sub>2</sub> (235 mg, 3.4 mmol), H<sub>3</sub>PO<sub>2</sub> (8–14 equivs); cp = complex products.

In order to preclude the formation of the byproducts resulting from the attacks from nucleophiles such as water and carboxylic groups of the substrate within the reaction system, the use of a great excess of reductants was necessary to guarantee the yield of the target product. The  $H_3PO_2/II$  ratio (in equivalents (equivs)) was optimised (entries 1–4, Table 1). The highest yield (88 %, entry 3) was obtained when 12 equivalents of  $H_3PO_2$  (14 equivalents, entry 4) did not enhance the yield. On the other hand, the replacement of  $H_2SO_4$  with HCl (entry 5) afforded complex products which could only be separated with difficulty, while with  $H_3PO_4$  it afforded a much lower yield (28 %, entry 6).

Under the optimised reaction conditions, the substrate mass increase up to 5 grammes (see Experimental for details) was possible with a satisfactory yield (80 %, entry 7).

Some other reducing reagents were tested in this reaction. Ammonium hypophosphite (entry 1, Ta-

ble 2), sodium hypophosphite (entry 3) and potassium hypophosphite (entry 5) all afforded complex products, while calcium hypophosphite (entry 7) and  $H_3PO_2$  (entry 9) both afforded moderate yields (64 % and 68 %, respectively). When a double volume of sulphuric acid was employed in the cases of hypophosphorous acid salts, moderate to low yields of 51 %, 41 %, 22 % and 17 %, respectively, were obtained (entries 2, 4, 6 and 8). One possible reason is that the addition of a large amount (12 equivalents) of hypophosphorous acid salt might have neutralised the  $H_2SO_4$ required for effective diazoniation and also for preventing the side-reactions of diazonium salt by potential nucleophiles. Beyond the phosphorus-containing reagents, no target product could be found in the presence of ethanol (entry 10), ethyl acetate (entry 11) or sodium bisulphite (entry 12). However, it afforded a 70 % yield in the combined action of formaldehyde (HCHO) and NaOH (entry 13). None of these reducing agents emerged as a reductant superior to  $H_3PO_2$ for this transformation in terms of the chemical yield of I.

From previous reports on the dediazoniation mechanism (Kornblum, 1944; Kornblum et al., 1950; DeTar & Kosuge, 1958; Skrunts et al., 1983; Wassmundt & Kiesman, 1997; Pazo-Llorente et al., 2006), a possible mechanism for the free radical chain for the deamination of *II* via the diazoniation/hydrogenation sequence using  $H_3PO_2$  as the reductant is shown in Fig. 2. The diazonium salt (III) was first formed in the presence of  $NaNO_2$  and mineral acid, followed by the formation of the 1,2,3-oxadiazolium salt (IV) by the neighbouring nucleophilic attack from the 1-carboxylic group. Next, the free radical chain initiation resulted from the interaction between IV and  $H_3PO_2$ , leading to the glutaric acid radical (V) and the free radical  $[H_2PO_2]$  (VI). The radical V could subsequently be converted to Iby extracting a hydrogen radical from H<sub>3</sub>PO<sub>2</sub> along

Entry	<i>II</i> /mg	$\operatorname{Reductant/equiv}$	Acid	Yield/%	Reference
1	50	$\rm NH_4H_2PO_2/12$	$H_2SO_4$	ср	_
2	50	$NH_4H_2PO_2/12$	$H_2SO_4^b$	51	_
3	50	$NaH_2PO_2/12$	$H_2SO_4$	$^{\rm cp}$	_
4	50	$NaH_2PO_2/12$	$H_2 SO_4^b$	41	_
5	50	$KH_2PO_2/12$	$H_2SO_4$	$^{\rm cp}$	Mitsuhashi et al. (2000)
6	50	$KH_2PO_2/12$	$H_2SO_4^b$	22	Mitsuhashi et al. (2000)
7	50	$Ca(H_2PO_2)_2/12$	$H_2SO_4$	64	Mitsuhashi et al. (2000)
8	50	$Ca(H_2PO_2)_2/12$	$H_2 SO_4^b$	17	Mitsuhashi et al. (2000)
9	50	$H_3PO_3/12$	$H_2SO_4$	68	Kornblum et al. (1952)
10	50	EtOH/50	$H_2SO_4$	$\mathbf{nr}$	Coleman and Talbot (1933)
11	50	EtOAc/25	$H_2SO_4$	$\mathbf{nr}$	Bacherikov et al. (2004)
12	50	$NaHSO_3/12$	HCl	$\mathbf{nr}$	Geoffroy et al. (2001)
13	50	HCHO/2 + NaOH/5	HCl	70	Brewster and Poje (1939)

Table 2. Screening of reductants<sup>a</sup>

a) General reaction conditions: II (50 mg, 0.34 mmol), mineral acid (entries 1, 3, 5, 7:  $H_2SO_4$ , 98 mass %, 6.5 mL; entries 9–13: as reported in the corresponding reference), NaNO<sub>2</sub> (235 mg, 3.4 mmol), reductant (entries 1–8: 12 equivs; entries 9–13: as reported in the corresponding reference); b) the amount of  $H_2SO_4$  was increased to 13 mL; cp = complex products; nr = no reaction.



Fig. 2. Possible mechanism for diazoniation/hydrogenation sequence.

with the formation of the free radical VI. On the other hand, this radical can react with IV to yield phosphorous acid (H<sub>3</sub>PO<sub>3</sub>) and V. As the reaction mechanism of the diazoniation/hydrogenation process using H<sub>3</sub>PO<sub>2</sub> was not thoroughly understood (Romanova & Demidenko, 1975; Golubev et al., 2006), more investigation was needed to elucidate this transformation mechanism.

#### Conclusions

In summary, a new method for the preparation of glutaric acid from L-glutamic acid via diazoniation is presented. This protocol could be conducted with simple procedures and on a grammesscale of the substrate. The unprecedented diazoniation/hydrogenation strategy on the aliphatic primary amines was successfully performed using hypophosphorous acid as an efficient reductant. This may provide a novel approach to the deamination of such substrates, and further studies on the substrates' scope and reaction mechanisms are currently underway.

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