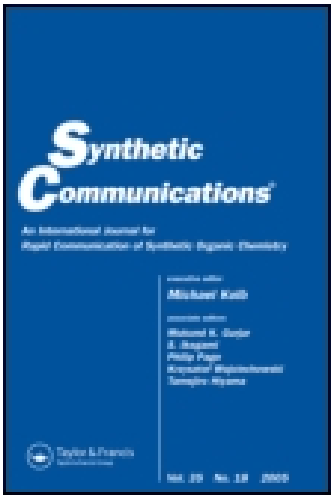


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Novel Method for Synthesizing Aldonophenylhydrazono-lactones

Jizhou Wang [a] , Lei Wang [b] , Xiaofei Meng [a] & Peiying Zhang [a]

[a] Department of Organic Chemistry , School of Pharmaceutical Sciences, Beijing Medical University , Beijing, 100083, P. R. China

[b] Medical & Healthy Analytical Center , Beijing Medical University , Beijing, 100083, P. R. China

Published online: 20 Aug 2006.

To cite this article: Jizhou Wang , Lei Wang , Xiaofei Meng & Peiying Zhang (1998) A Novel Method for Synthesizing Aldonophenylhydrazono-lactones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:13, 2317-2324, DOI: 10.1080/00397919808004284

To link to this article: http://dx.doi.org/10.1080/00397919808004284

SYNTHETIC COMMUNICATIONS, 28(13), 2317-2324 (1998)

A NOVEL METHOD FOR SYNTHESIZING ALDONOPHENYLHYDRAZONO-LACTONES

Jizhou Wang [a]* Lei Wang [b] Xiaofei Meng [a] and Peiying Zhang [a]
[a] Department of Organic Chemistry, School of Pharmaceutical Sciences, Beijing Medical University, Beijing 100083, P. R. China
[b] Medical & Healthy Analytical Center, Beijing Medical University, Beijing 100083, P. R. China

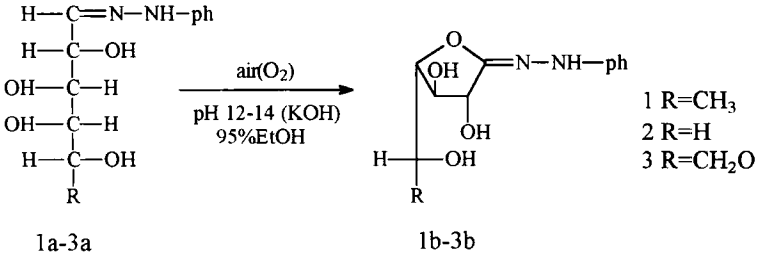
Abstract: A novel method for synthesizing aldonophenylhydrazono-lactones is described, utilizing cuprammonia ion ($Cu(NH_3)_4^{2+}$) as catalyst, ammonium hydroxide as base and 95% alcohol as solvent. Compared with previous method[6], it shortens the reaction time, increases the yield and widens the reaction range.

In recent years, much attention has been given to glycosidase inhibitors, due to their potential use in treating diabetes or as antivirus or anticancer agents[1,2].Such inhibitors could also be useful for preparing affinity ligands for the purification of specific glycosidases or glycosyltransferases [3].

Analogs resembling the transition state for glycosidase-catalyzed hydrolysis might act as glycosidase inhibitors because their steric and electrostatic resemblance to such in the transition state closely resemble those of the transition states.

* To whom correspondence should be addressed. Present address: Department of Pharmaceutical Chemistry, Rutgers University, Piscataway, NJ 0054-8020, USA

Compared with substrate analog-based inhibitors, they usually have stronger inhibiting activities due to their stronger affinity with the enzymes. Saccharide lactones are good examples of this kind of transition state analog. The pharmacological tests of some 1,5-lactones have been reported.[4,5] Nevertheless, their applications are limited due to their rather low stability. Saccharide phenylhydrazono lactones (aldonophenylhydrazono-lactones), a kind of novel compound synthesized recently, are not only closely similar to saccharide lactones in steric and electronic properties but are also more stable than the latter, so they promise to become efficient glycosidase inhibitors. Three D-aldonophenylhydrazono-1,4-lactones(1b, 2b, 3b) and their L-isomers were synthesized by El Khadem et al. [6]under the following conditions: solutions of the phenylhydrazones of 6-deoxy-D-galactose (D-fucose) (1a), D-arabinose (2a) and D-galactose (3a), and their L-enantiomers in aqueous ethanol containing enough KOH to bring the pH to 12-14 were stirred at room temperature in the presence of air. The reaction times are 4-5 days. See scheme 1

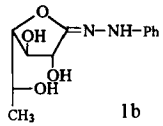
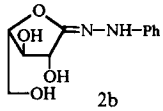
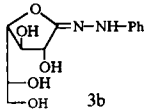
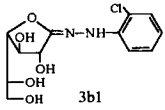
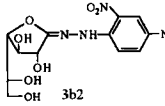
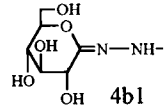
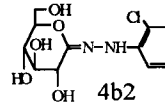
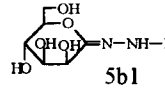


1a-3a 1b-3b

Scheme 1

We repeated their experiments and found that reactions were not observed after two weeks when using the phenylhydrazones of D-glucose and D-mannose. arylhydrazones of galactose which have electron withdrawing groups in the aryl

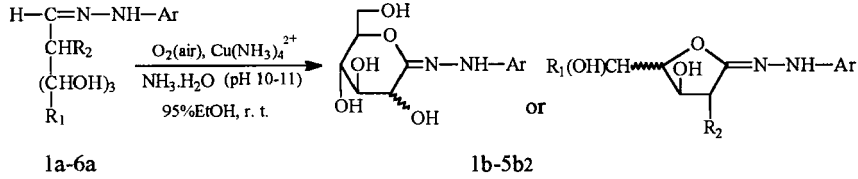
Table 1

Starting materials	Products	Reaction time			% Yield	
		Lit.[6]	Method A	Method B	Lit.[6]	Method A or B
D-fucose-phenyl-hydrzaone(1a)	 1b	5-6 days	~20 mins	~2 hrs.	21	75
D-arabinose-phe-nylhydrazone(2a)	 2b	5-6 days	~1 hr	~5 hrs.	6	71
D-galactose-phe-nylhydrazone(3a)	 3b	5-6 days	~5 mins	~30 mins.	49	91
D-galactose 2-chlo rophenylhydrazone (3a1)	 3b1	(–)	~1.5hr	~5.5hrs.		78
D-galactose 2, 4-Dinitrophenyl -hydrazone(3a2)	 3b2	(–)	~3.5hrs.	~12hrs.		85
D-glucose phenyl hydrazone(4a1)	 4b1	(–)	~1hr	5.5hrs.		83
D-glucose-2chloro phenylhydrazone (4a2)	 4b2	(–)	~3hrs.	13hrs.		72
D-mannose phenyl hydrazone (5a1)	 5b1	(–)	~3.5hrs.	15hrs.		84

Notes: no reaction is observed after two weeks.

groups don't work either. So we decided to introduce a catalyst and investigate the influence of base and solvent on this reaction. Eventually, a simple, rapid high-yielding and widely applicable method was found.

We found that $Cu(NH_3)_4^{2+}$ was able to increase the reaction rate sharply and had the advantages of easy access, safety and low cost. Solvent and base also had obvious effects on reaction rate and yield under the presence of $Cu(NH_3)_4^{2+}$. For example, the reaction rates could change with the solvents, and the order is CH_3OH, C_2H_5OH> CH_3NO_2, CH_3CN, $CHCl_3$ > DMF > THF, the yield varied with the solvent in the order CH_3OH, C_2H_5OH>THF, DMF > CH_3NO_2,CH_3CN, $CHCl_3$; the reaction rates also varied with the bases (pH 11-12), and the order was KOH>NH_3(H_2O>Et_2NH, Et_3N> ion exchange resin (OH^-), but the order of the yield is NH_3(H_2O >>Et_2NH, Et_3N> ion exchange resin (OH^-) > KOH. So the optimal condition was utilizing $Cu(NH_3)_4^{2+}$ as catalyst, 95% alcohol as solvent, NH_3(H_2O (pH 10-11)as base and either bubbling air 10 mins. 2 hrs. or keeping the mixture still in air for 30 mins.10 hrs. at room temperature. (see table I).



1a-6a 1b-5b2

Scheme 2

All the structures of above compounds were identified by IR, MS, NMR and Elemental Analysis. Compared with literature[6], we simplified the method determining the ring-size. The size of ring is identified through NMR spectrum in Me2SO-D6 (including ^1H,^{13}C, ^1H-^1H COSY, ^{13}C-^1H COSY and D_2O exchange),

especially through ^1H-^1H COSY spectrum. When Me_2SO-D_6 is used as solvent in ^1H-^1H COSY experiments, we may find that all-OH protons not only give strong signals, but also strongly correlate -CH protons at the same carbons. During the reaction, one OH proton is involved in ring formation, so compared with starting hydrazones, if C_4-OH proton disappears in the product(in this case, the correlation signal of C_4-OH proton and C_4-H proton will not be found in ^1H-^1H COSY spectrum.), indicating saccharide phenylhydrazono-1,4-lactone is formed; if C_5-OH proton disappears(in this case, the correlation signal of C_5-OH proton and C_5-H proton will not be found in ^1H-^1H COSY spectrum.), the product will be saccharide phenylhydrazono-1,5-lactone. We found that N-phenyl-D-gluconohydrazono-lactone and N-phenyl-D-mannonohydrazono-lactone have 1,5-lactone structures, while N-phenyl-D-galactonohydrazono-lactone has 1,4-lactone structure.

In summary, an efficient method was reported here. We think that it promises to be a general method for synthesizing aldonophenylhydrazono-lactones, especially for those less reactive saccharide phenylhydrazones.

General Procedure:

To the solutions of saccharide phenylhydrazones (0.5 mmol) in 100 ml 95% EtOH adjusted to the pH to 10-11 by enough NH3(H2O, CuSO4 (0.5 mmol) is added. The mixture is either stirred by bubbling air for 10 mins.-3 hrs. (Method A) or kept still in air for 30 mins.-15 hrs. (Method B) at room temperature. When the reaction is over, the mixture is filtered and neutralized with 50% HAc/alc to the pH of 7-7.4. The filtrate is concentrated under reduced pressure to a syrup. The pure product may be obtained through recrystallization or chromatography on silica gel. (Warning: If pH is higher than 13, there will be serious side-reactions.)

Physical and spectroscopic data for selected compounds:

3b1 *N-(2-chlorophenyl)-D-galactonohydrazono-1,4-lactone*, colorless needles; mp. 162-163°C. $[\alpha]_D$=-70.1°(c, 0.1, EtOH); ν (KBr), 1680(O-C=N) and 1598(C=C); EI/MS, m/z 302(M^+); ^{1}H NMR (500MHz, DMSO-d_6), phenyl ring protons, meta δ 7.34(d, 1H, H-3'), δ 7.20(t, 1H, H-5'), ortho δ 7.28(d, 1H, H-6'), para 6.71(t, 1H, H-4'); active protons, δ 7.64(s, 1H, NH), δ 5.82(d,1H, OH-2), δ 5.67(d,1H, OH-3), δ 5.11(d, 1H, OH-5), δ 4.80(t, 1H, OH-6); CH protons δ 4.41(t, 1H, $J_{2\text{-}3}$ = 5.0Hz, H-2), δ 4.17(dd, 1H, $J_{4\text{-}5}$= 7.5Hz, H-4), δ 4.11(dd, 1H, $J_{3\text{-}4}$ = 6.5Hz, H-3), δ 3.62(m,1H, $J_{5\text{-}6}$ = 5.9Hz, H-5), δ 3.49(m, 2H, H-6, H-6'); ^{13}C NMR data, δ125 MHz, DMSO-d_6), δ 152.4(C=N); phenyl ring carbons, δ 141.6(C-1'), δ 128.8(C-3'), δ 127.9(C-5'), δ 118.7 (C-2'), δ 116.0(C-4'), δ 113.2(C-6'); other ring carbons δ 83.8(C-4), δ 74.4(C-2), δ 74.0(C-3); side chain carbons, δ 69.2(C-5), δ 61.9(C-6); Anal. Calcd. for $C_{12}H_{15}N_2O_5Cl$: C, 47.68, H,4.97, N, 9.27, Found: C, 47.62, H,4.90, N, 9.23.

4b1 *N-phenyl-D-gluconohydrazono-1, 5-lactone*, yellow needles, mp. 131-132. $[\alpha]_D$=-67.3° (c, 0.08, EtOH). ν (KBr) 1688(O-C=N) and 1601(C=C); EI/MS, m/z 268 (M^+); ^{1}H NMR (500MHz, DMSO-d_6), phenyl ring protons, meta δ 7.71(m, 2H), ortho and para δ 7.54(m, 3H); active protons, δ 5.11(s, 1H, NH), δ 5.07(d, 1H, OH-4), δ 5.03(d, 1H, OH-3), δ 4.61(t, 1H, OH-6), δ 4.33(t,1H, OH-2); CH protons δ 4.40(d, 1H, $J_{2\text{-}3}$=8.7Hz, H-2), δ 3.72(dd, 1H, $J_{6\text{-}6'}$=25.5Hz, $J_{5\text{-}6'}$=10.5Hz, H-6'), δ 3.63($J_{3\text{-}4}$= 17.6Hz, H-3), δ 3.52(dd, 1H, H-6), δ 3.37(dd,1H, J4-5=9.3Hz, H-4), δ 3.27(m, 1H, H-5); ^{13}C NMR data, δ 125 MHz, DMSO-d_6), δ 150.9(C=N); phenyl ring carbons, δ 131.4(C-1'), δ 129.2(C-2'), δ 122.3(C-3'), δ 118.4(C-4'); other ring

carbons δ 79.0 (C-5), δ 77.1(C-4), δ 71.6 (C-3), δ 69.9(C-2); side chain carbons, δ 61.0(C-6); Anal. Calcd. for $C_{12}H_{16}N_2O_5$: C 53.73, H 5.97, N 10.45; Found: C 53.62, H 5.91, N 10.51.

5b1 *N-phenyl-D-mannonohydrazono-1,5-lactone*, pale yellow syrup. $[\alpha]_D$=-70.5° (c, 0.11, EtOH); ν (KBr) 1678(O-C=N) and 1602(C=C); EI/MS, m/z 268 (M^+); ^{1}H NMR (500MHz, DMSO-d_6), phenyl ring protons, meta 7.74(s, 2H), ortho and para 7.57(s, 3H); active protons, δ 7.98(s, 1H, NH), δ 5.30(d, 1H, OH-4), δ 4.88(d,1H, OH-3), δ 4.63(d,1H, OH-2), δ 4.46(m, 1H, OH-6); CH protons δ 4.54(d, 1H, J_{5-6}=4.65Hz, H-5), δ 4.23(d, 1H, $J_{6-6'}$=6.70Hz, $J_{5-6'}$= 4.65Hz, H-6'), δ 4.07(dd, 1H, J_{2-3}= 5.35Hz, J_{3-4}= 8.50Hz, H-2), δ 3.88(t, 1H, H-6), δ 3.84(m, 1H, H-3), δ 3.74(d, 1H, J_{4-5}= 4.35Hz, H-4),; ^{13}C NMR data, δ 125 MHz, DMSO-d_6), δ 151.0(C=N); phenyl ring carbons, δ 135.2(C-1'), δ 129.3(C-3'), δ 123.1(C-4'), δ 117.3(C-2'); other ring carbons δ 78.3(C-5), δ 72.5(C-4), δ 72.0(C-3), δ 67.0(C-2); side chain carbons, δ 65.1(C-6); Anal. Calcd. for $C_{12}H_{16}N_2O_5$: C 53.73, H 5.97, N 10.45; Found: C 53.78, H 6.03, N 10.52.

Acknowledgement:

This program is supported by National Science Foundation of China. We are also much indebted to Professor Xiao-Tian Liang for his helpful discussion to this work.

References:

1. Dimitriadis G.O.; Tessar; p.; Go V. L. W.; and Gerich J. E., Metabolism, 1985, 34, 261

2. Humphries M.J.; Matsumoto K.; white, S.L.; and Olden K. Cancer Res., 1986, 46,

5215;

3. Winchester, B and Fleet, G.W.J. Glycobiology, 1992, 2, 199;

4. Reese E.T.; parrish F.W. and Ettlinger M. Carbohydr. Res., 1971,18,381;

5. Leaback D. H. Biochem. & Biophys. Res. Commun. 1968, 32(6), 1025;

6. El Khadem H. S.; Arthur Crossman Jr.; Debra Bensen and Andrew Allen J. Org. Chem., 1991, 56, 6944;

(Received in the UK 28 July 1997)