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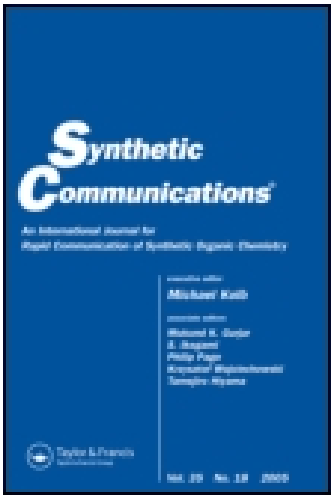

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of 2-Tert-butylimino-3-hepta-O-benzoyl-β-D-lactosylimino-4-S-benzyl-6-arylimino-2,3-dihydro-1,3,5-thiadiazines

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Published online: 27 Dec 2013.

To cite this article: Kavita Manoj Heda & Shirish Panjabrao Deshmukh (2014) Synthesis of 2-Tert-butylimino-3-hepta-O-benzoyl-β-D-lactosylimino-4-S-benzyl-6-arylimino-2,3-dihydro-1,3,5-thiadiazines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:4, 488-492, DOI: 10.1080/00397911.2013.815214

To link to this article: http://dx.doi.org/10.1080/00397911.2013.815214

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Synthetic Communications®, 44: 488–492, 2014
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ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2013.815214

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SYNTHESIS OF 2-*TERT*-BUTYLIMINO-3-HEPTA-O-BENZOYL-β-D-LACTOSYLIMINO-4-S-BENZYL-6-ARYLIMINO-2,3-DIHYDRO-1,3,5-THIADIAZINES

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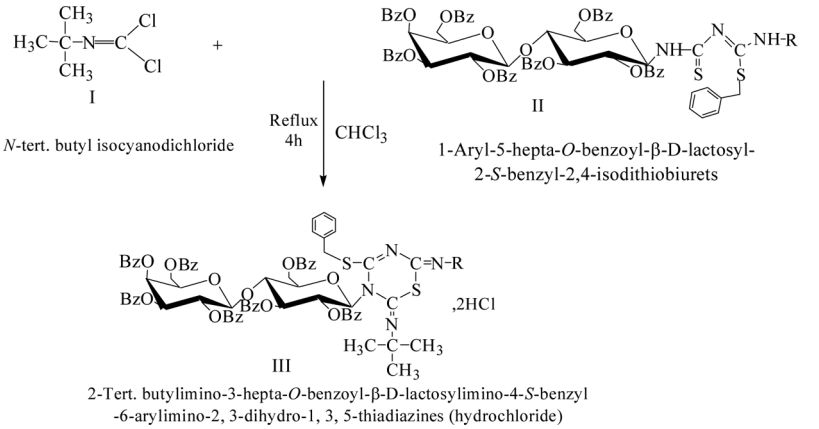
GRAPHICAL ABSTRACT



Abstract *A new series of synthesis of 2-*tert*-butylimino-3-hepta-*O*-benzoyl-β-D-lactosylimino-4-*S*-benzyl-6-arylimino-2,3-dihydro-1,3,5-thiadiazines (hydrochloride) were synthesized by the interaction of 1-aryl-5-hepta-*O*-benzoyl-β-D-lactosyl-2-*S*-benzyl-2,4-isodithiobiurets with* tert*-butyl isocyanodichloride. The identities of these newly synthesized* N*-lactosides have been established on the basis of usual chemical transformations and infrared, ^{1}H NMR, and mass spectral analysis.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords -2,4-isodithiobiurets; *tert*-butyl isocyanodichloride; -1,3,5-thiadiazines

Received March 11, 2013.

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INTRODUCTION

Thiadiazines and their derivatives are important biologically active precursors in the field of medicinal chemistry. Thiazine, thiazole, and thiadiazines have been explored to the maximum extent owing to their pharmacological activities and uses, such as development of new fungicides against rice blast disease, *Magnaporthe grisea*.[1] Some amino derivatives of thiadiazines show antiviral, anesthetic, cardiovascular, and hypometabolic activities.[2,3] Some 1,3,5-thiadiazines are found to possess antifungal, anti-inflammatory, and analgesic activities.[4] A variety of 1,3,5-thiadiazines and 1,3,5-triazines have been prepared by the interaction of phenyl isocyanodichloride and several thioamido group containing compounds.[5–8] The chemistry of organo-sulfur system[9,10] prompted us to extend our work into a series of lactosyl-1,3,5-thiadiazines hydrochlorides. Herein we synthesize several *N*-lactosylated-1,3,5-thiadiazines hydrochlorides by the interaction of *tert*-butyl isocyanodichloride with 1-aryl-5-hepta-*O*-benzoyl-β-D-lactosyl-2-*S*-benzyl-2, 4-isodithiobiurets. The required 1-aryl-5-hepta-*O*-benzoyl-β-D-lactosyl-2-*S*-benzyl-2,4-isodithiobiurets were obtained by the reaction of 1-aryl-*S*-benzyl isothiocarbamides with hepta-*O*-benzoyl-β-D-lactosylisothiocyanate.

RESULTS AND DISCUSSION

A solution of 1-aryl-5-hepta-*O*-benzoyl-β-D-lactosyl-2-*S*-benzyl-2,4-isodithiobiuret (**Ia**) was added to a solution of *tert*-butyl isocyanodichloride and the reaction mixture was refluxed for 3 h. A brisk reaction with evolution of hydrogenchloridegas was noticed. Afterward, the solvent was distilled off to obtain a sticky residue. This residue was triturated with petroleum ether (60–80 °C) to afford a pale yellow solid (**IIIa**). The product was purified by chloroform–petroleum ether.

The specific rotation was measured in chloroform. In spectral analysis[11–13] IR spectra of product showed characteristic absorption of the lactose unit in the ranges of 900–910 and 1000–1100 cm^{-1}. ^1H NMR spectra of product distinctly displayed signals due to aromatic protons and lactose ring protons. The mass spectra of product were also evaluated.

When the interaction of 1-aryl-5-hepta-*O*-benzoyl-β-D-lactosyl-2-*S*-benzyl-2, 4-isodithiobiurets (**Ib–l**) was extended to *tert*-butyl isocyanodichloride, the resepective products of 2-*tert*-butylimino-3-hepta-O-benzoyl-β-D-lactosylimino-4-S-benzyl-6-arylimino-2,3-dihydro-1,3,5-thiadiazines (**IIIb–l**) were isolated.

EXPERIMENTAL

All chemicals were research grade. Melting points were taken in open capillary tubes and are uncorrected. Infrared (IR) spectra were recorded in Nujol, KBr on a FT-IR Perkin-Elmer RXI (4000–450 cm^{-1}) spectrophotometer. ^1H NMR measurement were performed on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal reference. The mass spectra were recorded on a Make-Waters Model-QToF Micro Source-ESI mass spectrometer. Optical rotation $[\alpha]_D^{31}$ was measured on a Equip-Tronics Digital Polarimeter EQ-800 at 31 °C in $CHCl_3$. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapor.

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Starting Materials

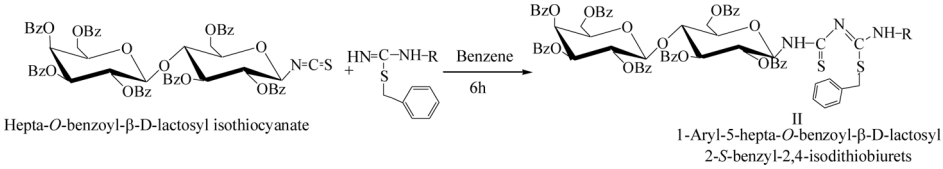
1-Aryl-5-hepta-*O*-benzoyl-β-D-lactosyl-2-*S*-benzyl-2,4-isodithiobiurets (ia–l). 1-Aryl-5-hepta-*O*-benzoyl-β-D-lactosyl-2-*S*-benzyl-2, 4-isodithiobiurets have been prepared by the interaction of hepta-*O*-benzoyl-β-D-lactosylisothiocyanate and 1-aryl-2-*S*-benzyl isothiocarbamides. Hepta-*O*-benzoyl-β-D-lactosylisothiocyanate was added to a benzene solution of 1-phenyl-2-*S*-benzyl isothiocarbamide. The reaction mixture was then refluxed over a boiling water bath for 6 h. After heating, solvent benzene was distilled off and the sticky mass was obtained as residue. This residue was triturated several times with petroleum ether, and a white product separated out. It was crystallized from ethanol (**Ia**, Scheme 1). Compound **Ia**: White powder, yield: 75%, mp 140 °C, $[\alpha]^{29}_{D} + 120°$ (c, 0.15, $CHCl_3$), R_f 0.68 (CCl_4–EtOAc, 3:2). Anal. calcd. for $C_{76}H_{63}O_{17}N_3S_2$; C, 67.40; H, 4.65; N, 3.10; S, 4.73. Found: C, 67.36; H, 4.61; N, 3.14; S, 4.70.

***Tert*-butyl-isocyanodichloride (II).** Through a chloroformic solution of *tert*-butyl isothiocyanate, pure and dry chlorine gas (generated from 15 g $KMnO_4$ and 35 ml conc. HCl) was bubbled, maintaining the temperature of the system below 10 °C. After the addition of excess of chlorine was completed, the yellow reaction mixture was diluted with 10–15 ml dry petroleum ether (60–80 °C). The solvent was then removed by distillation under vacuum. The whole operation was repeated several times with petroleum ether. A pale yellow liquid (**II**) was obtained (Scheme 2).

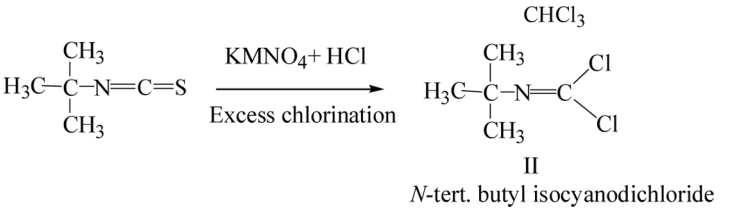
General Procedure for Synthesis of 2-*Tert*-butylimino-3-hepta-*O*-benzoyl-β-D-lactosylimino-4-*S*-benzyl-6-phenylimino-2,3-dihydro-1,3,5-thiadiazines (IIIa)

A solution of *tert*-butyl isocyanodichloride (0.001 M, 0.15 g in 15 ml $CHCl_3$) was added to a solution of 1-phenyl-5-hepta-*O*-benzoyl-β-D-lactosyl-2-*S*-benzyl-2,4-isodithiobiurets (0.001 M, 1.35 g 15 ml $CHCl_3$) (**Ia**) and the reaction mixture was refluxed for 4 h. A brisk reaction with evolution of hydrogenchloride gas was noticed. Afterward, the solvent was distilled off to obtain a sticky residue. This residue was triturated with petroleum ether (60–80 °C) to afford a pale yellow solid (**IIIa**). The product was purified by chloroform–petroleum ether (Scheme 3).

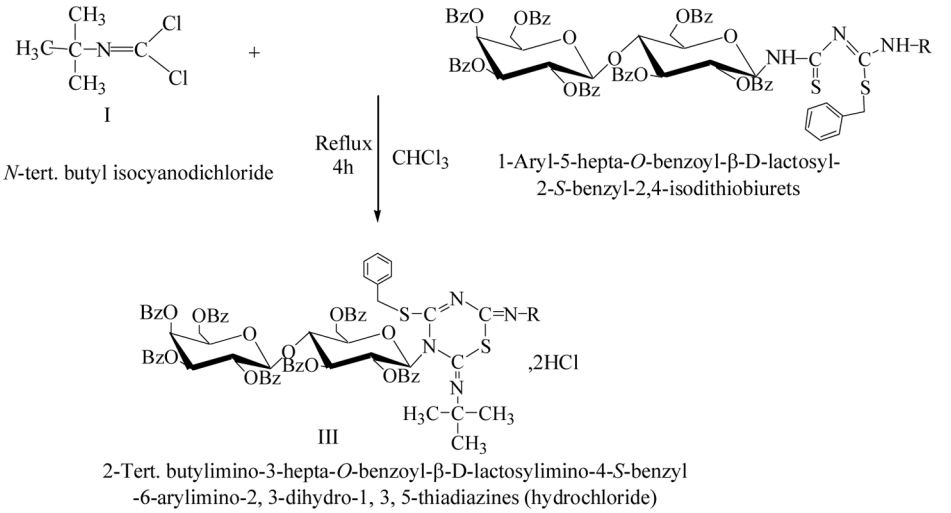
On the basis of elemental analysis and IR, ^{1}H NMR, and mass spectral studies, the product with mp 145 °C was assigned the structure 2-*tert*-butylimino-3-hepta-*O*-benzoyl-β-D-lactosylimino-4-*S*-benzyl-6-phenylimino-2,3-dihydro-1,3,5-thiadiazine (hydrochloride) (**IIIa**). Compound **IIIa**: Pale yellow powder, yield: 85%, mp 145 °C,



Scheme 1. Synthesis of 1-aryl-5-hepta-*O*-benzoyl-*β*-D-lactosyl-2-*S*-benzyl-2,4-isodithiobiurets.



Scheme 2. Synthesis of *N-tert*-butyl isocyanodichloride.



Scheme 3. OBz = Benzoyl; R = (a) Phenyl, (b) *o*-Cl-phenyl, (c) *m*-Cl-phenyl, (d) *p*-Cl-phenyl, (e) *o*-tolyl, (f) *p*-tolyl, (g) *o*-hydroxy-phenyl, (h) *m*-hydroxy-phenyl, (i) *p*-hydroxy-phenyl, (j) *o*-methoxy phenyl, (k) *m*-methoxy-phenyl, (l) *p*-methoxy-phenyl.

$[\alpha]^{29}_{D}-50.36°$ (c, 0.11, $CHCl_3$), R_f 0.65 (pet. ether–EtOAc, 7:3) IR (KBr): υ 3062, 2976, 1730, 1600, 1492, 1315, 1267, 1026, 935, 709, cm^{-1}; ^1H NMR (δ in ppm, $CDCl_3$) δ8.04–7.21 (45H, m, $7C_6H_5CO$, $2C_6H_5$), 6.43–3.72 (16H, m, lactose ring protons, S-CH_2), δ2.17–1.25 (9H, $3CH_3$); mass(*m*/*z*): 1494 ($M^+ + 1$), 1456(M^+-HCl), 1410 (M^+-C_5H_9N), 1356 (M^+-$C_8H_9O_2$), 1053 (HBL^+), 579 (TBG^+), 353 (TBG^+-$C_{14}H_{10}O_3$), 335 (TBG^+-$C_{14}H_{12}O_4$), 231($C_{13}H_{11}O_4$), 136 ($C_6H_5CH_2COOH$), 105 (C_6H_5CO). $C_{81}H_{70}O_{17}N_4S_2$ 2HCl: C, 64.49; H, 4.64; N, 3.71; S, 4.24%. Found: C, 64.45; H, 4.62; N, 3.68; S, 4.20%

ACKNOWLEDGMENTS

Authors thank the Sophisticated Analytical Instrumentation Facility, Panjab University, Chandigarh, for providing spectral data. They are also thankful to S. G. Bhadange for encouragement and necessary facilities.

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