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PREPARATION OF PROTECTED 2-HYDROXYMETHYL ISOCYANATES: AN APPLICATION TO AGRICULTURAL SYNTHESIS

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Abstract: The preparation of N-benzyloxymethyl isocyanate (4) and t-butyldiphenylsiloxymethyl isocyanate (9) *via* the diphenylphosphoryl azide modified Curtius rearrangement is described. These isocyanates have been employed in the synthesis of a herbicide metabolite 1, which contains the sensitive N-hydroxymethyl urea functional group.

In the course of large animal metabolism studies of tebuthiuron herbicide, researchers at DowElanco have isolated a polar metabolite from milk. Based on previous metabolism studies[1], N-(5-(2-hydroxy- 1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N-hydroxymethyl-N-methyl urea (1) has been proposed as a potential polar metabolite. This report describes the preparation of protected 2-hydroxymethyl isocyanates and their application to the synthesis of potential metabolite 1.

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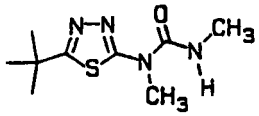
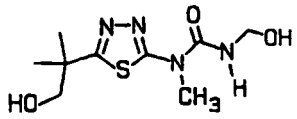


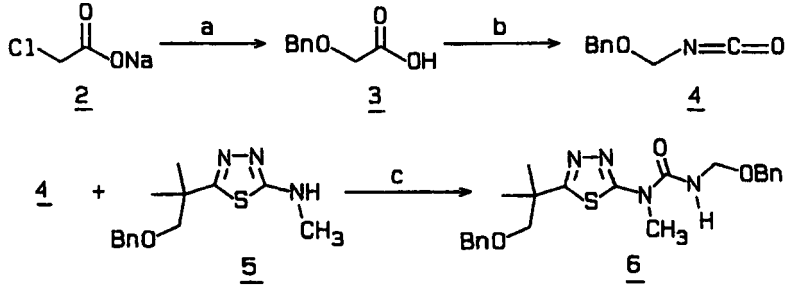
Tebuthiuron



1

In 1968, Balba and coworkers[2] described the synthesis of N-benzyloxymethyl isocyanate (4), which was used to prepare N-hydroxymethyl carbamate insecticide metabolites. Two synthetic routes to 4 were reported: 1) acylazide formation from benzyloxyacetyl chloride followed by thermal Curtius rearrangement and 2) alkylation of silver isocyanate with benzylchloromethyl ether. Unfortunately these procedures suffer from low yields, hazardous reagents and the need to purify the unstable isocyanate 4. We have found that isocyanate 4 can be prepared in excellent yield by application of the diphenylphosphoryl azide (DPPA) modification[3] of the Curtius rearrangement using benzyloxyacetic acid[4] (3) as the substrate. The isocyanate is not isolated, but it is treated *in situ* with the desired nucleophile (5, Scheme I) to provide the protected N-hydroxymethyl urea 6 in good yield.

Scheme I

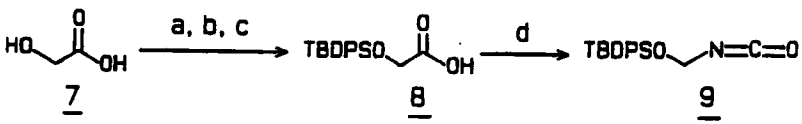


(a) sodium benzylate, BnOH; (b) DPPA, NEt_3, toluene; (c) toluene

Although hydrogenolysis of the benzyl protecting groups of 6 did provide the desired metabolite standard 1, sluggish catalytic reactions coupled with low yields rendered this synthetic route unacceptable for the preparation of multigram quantities of 1.

Due to difficulties encountered in removal of the benzyl protecting groups, we turned our attention to developing a more suitably masked 2-hydroxymethyl isocyanate. We have found that the t-butyldiphenylsilyl (TBDPS) protective group can be conveniently introduced and may be removed under mild conditions that are compatible with the liberated N-hydroxymethyl functional group. Tert-butyldiphenylsiloxymethyl isocyanate (9) is readily prepared as depicted in Scheme II.

Scheme II



7 8 9

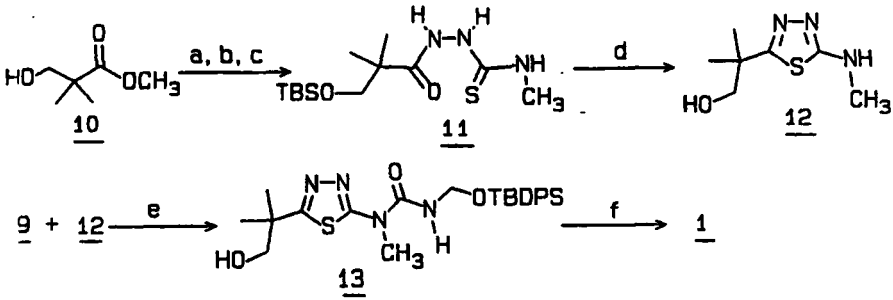
(a)THF, TMSCl, NEt_3, DMAP; (b) NEt_3, TBDPSCl; (c) H_2O, HOAc; (d)DPPA NEt_3, THF

Treatment of a THF solution of glycolic acid (7) with triethylamine and trimethylsilyl chloride, followed by triethylamine and t-butyldiphenylsilyl chloride, and finally acetic acid / water yielded protected glycolic acid 8 in a one pot procedure. Application of the DPPA modified Curtius rearrangement afforded isocyanate 9 which can be isolated via flash chromatography. It is noteworthy that unlike benzyloxymethyl isocyanate (4), the isocyanate 9 is stable for weeks when stored under nitrogen in a freezer.

Our alternate synthesis of 1 was completed as shown in Scheme III. Protection of 10 as its t-butyldimethylsilyl ether (TBS), followed by hydrolysis of

the ester, acid chloride formation, and coupling with 4-methyl-3-thiosemicarbazide provided the acylated thiosemicarbazide 11.

Scheme III



(a) TBSCl, NEt_3, DMAP, CH_2Cl_2; (b) NaOH, H_2O, EtOH; (c) $(COCl)_2$, benzene: 4-methyl-3-thiosemicarbazide, pyridine, CH_2Cl_2; (d) CH_3SO_3H, toluene; (e) THF; (f) $FNBu_4$, THF, HOAc

Cyclodehydration[5] of 11 with concomitant silicon protective group removal gave the desired amine 12, which when treated with one equivalent of isocyanate 9 in refluxing THF provided excellent yield of urea 13. Fluoride mediated removal of the protective group of 13 under mildly acidic conditions gave the desired metabolite standard 1 *via* a synthetic sequence that is amenable to multigram preparations.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. All ^1H NMR spectra were determined on a Varian EM 390 spectrometer and values are reported in ppm (delta scale) from Me_4Si. Mass spectra were obtained using a Finnigan 4615 instrument operated in the positive ion mode or GC/MS was performed using a Hewlett Packard 5971A mass selective detector (70eV). Direct exposure probe mass spectra were obtained

at an ionization potential of 70eV or methane chemical ionization. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. Combustion analyses were performed by Oneida Research Services, Whitesboro, N.Y. Silica gel chromatography was performed on Whatman 60 angstrom, 230-400 mesh silica.

Benzyloxyacetic acid (3)

Sodium metal (50g, 2.17mol, 3-8mm spheres) was dissolved in benzyl alcohol (1000mL) by the addition of 5g quantities over a period of about two hours while maintaining the reaction temperature at 90-100°C. The hydrogen gas thus formed was vented through a bubbler. After all sodium metal had dissolved, chloroacetic acid, sodium salt (230g, 1.98mol) was added in 45g portions maintaining the temperature at 90-110°C. Following complete addition, the mixture was warmed to 165°C and held there for 20 hours. The mixture was cooled and most of the benzyl alcohol removed *via* distillation. Water (1.5L) was added and the aqueous mixture extracted with ether (3 x 300mL), then taken to pH 2 with concentrated HCl (150mL). The mixture was extracted with ether (3 x200mL) and the combined organic extracts dried (Na_2SO_4 /$MgSO_4$) and filtered. After all ether was removed on the rotary-evaporator, the bath was slowly warmed to 40°C (ca. 30 mmHg) to remove the unreacted chloroacetic acid. The residual pale yellow liquid was distilled through a 30cm Snyder column and the product (3) collected as a clear, colorless liquid (216g, 66%): bp 137-139°C / 0.6 mmHg; ^{1}H NMR ($CDCl_3$) 4.1 (s, 2H, CH_2CO_2H), 4.6 (s, 2H, CH_2Ph), 7.3 (s, 5H, ArH's), 10.8 (s, 1H, CO_2H); IR (film) 3700-2800 (b), 1730.

N-(5-(2-Benzyloxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N'-benzyloxymethyl-N-methyl urea (6)

To a stirred mixture of benzyloxyacetic acid (3, 5.58g, 33.6mmol) and triethylamine (9.3mL, 67.2mmol) in toluene (100mL) was added diphenylphosphoryl azide (8.3mL, 38.6mmol). After stirring at room temperature for 0.5 hours, the mixture was warmed to 90°C and held there for 0.5 hours, then allowed to cool to room temperature. The thiadiazolyl amine 5 (5.65g, 20.29mmol) was added and the solution warmed to 50°C for one hour. After cooling to room temperature, the volume of the solution was reduced *in vacuo* and the residue loaded directly onto a silica gel column. Flash chromatography using 1:1 hexane / ethyl acetate provided 6 as a viscous light yellow oil (8.46g, 95%). ^{1}H NMR ($CDCl_3$) 1.5 (s, 6H, $C(CH_3)_2$), 3.5 (s, 3H, NCH_3), 3.55 (s, 2H, $OCH_2C(CH_3)_2$), 4.6 (s, 2H, OCH_2Ph), 4.65 (s, 2H, OCH_2Ph), 4.9 (d, J=6Hz, 2H, $NHCH_2OBn$), 7.3 (s, 10H, ArH's), 9.1 (bt, J=6Hz, 1H, NH); IR (film) 3500-3150, 3150-2800, 1680; MS (CI) 442 (M+1, 17%), 441 (20%), 361 (8%), 334 (17%), 333 (100%); Anal. calcd. for $C_{23}H_{28}N_4O_3S$: C, 62.70; H, 6.41; N, 12.72. Found: C, 62.73; H, 6.37; N, 12.99.

t-Butyldiphenylsiloxyacetic acid (8)

Glycolic acid (7.6g, 100mmol) was dissolved in dry THF (400mL) and treated with 4-dimethylaminopyridine (300mg) and triethylamine (14.7mL, 105mmol). The mixture was cooled to 0°C and treated dropwise over 0.5 hours with trimethylsilyl chloride (12.7mL, 105mmol). The mixture was stirred at 0°C for one hour, then at room temperature for one hour. Triethylamine (14.7mL) was added followed by dropwise addition of t-butyldiphenylsilyl chloride (26.4mL, 101mmol). The thick white mixture was stirred at room temperature for 16 hours and then treated with water (250mL) and HOAc (90mL). After stirring at room

temperature for 1.5 hours, the mixture was extracted with hexane (500mL) and then ether (2 x 200mL). The combined organic extracts were dried (Na_2SO_4 / $MgSO_4$) and the solvents removed *in vacuo*. The residual oil was chromatographed on silica gel (approximately 700g) using a hexane / ether gradient[6] (from 100% hexane to 50% hexane) providing 8 as a viscous oil (22.1g, 70%); ^{1}H NMR ($CDCl_3$) 1.1 (s, 9H, $C(CH_3)_3$), 4.3 (s, 2H, CH_2CO_2H), 7.35 (m, 6H, ArH's), 7.7(m, 4H, ArH's), 9.2 (bs, 1H, CO_2H); IR (film) 3700-2800, 1730, 1430; MS (EI) 315 (M+, 11%), 257 (36%), 199 (55%), 135 (100%), 91 (79%).

t-Butyldiphenylsiloxymethyl isocyanate (9)

To a cooled (0°C) solution of 8 (3.9g, 12.4mmol) in THF (225mL) was added triethylamine (2.1mL, 15.1mmol) followed by dropwise addition of DPPA (3.0mL, 13.9mmol). The mixture was warmed slowly to room temperature and then stirred for 45 minutes. The mixture was then refluxed for 45 minutes and cooled to room temperature . The THF was removed *in vacuo* and the residual oil was dissolved in benzene then flash chromatographed on silica gel (hexane / ethyl acetate, 95:5). The desired product began eluting with the benzene solvent front. Removal of the solvent *in vacuo* provided 9 as a clear colorless oil (2.3g, 61%)[7] which was pure enough (ca. 90%) for further reactions. ^{1}H NMR ($CDCl_3$) 1.1 (s, 9H, $C(CH_3)_3$), 4.9 (s, 2H, CH_2NCO), 7.4 (m, 6H, ArH's), 7.7 (m, 4H, ArH's); IR (film) 3100, 2950, 2880, 2260 (intense), 1110; MS (EI) 311(M+, 0.75%), 282 (M-HCO. 0.7%), 269 (M-NCO, 0.7%), 254 (M-t-Bu, 50%), 244 (100%). A second chromatographic purification can provide material that is essentially pure as determined by ^{1}H NMR.

N-(5-(2-Hydroxy-1,1-dimethyl)-1,3,4-thiadiazol-2-yl)-N'-t-butyldimethylsiloxymethyl-N-methylurea (13)

The amine (12, 3.08g, 16.5mmol) and the isocyanate (9, 5.39g, 17.3mmol) were combined in THF (50mL) and stirred at reflux for 1.5 hours. The mixture was cooled to room temperature and the solvent removed on the rotary evaporator. The resulting oil was dissolved in benzene and flash chromatographed with 3:2 ethyl acetate / hexane. The product was isolated as a white solid (6.79g, 13.63mmol, 83% yield), mp 107-110°C. ^{1}H NMR (DMSO-d6) 1.0 (s, 9H, $C(CH_3)_3$), 1.35 (s, 6H, $C(CH_3)_2$), 3.5 (s, 5H, N-CH_3 and HO-CH_2), 4.95 (m, 3H, OH and HN-CH_2), 7.4 (m, 6H, Ar H's), 7.7 (m, 4H, Ar H's), 8.5 (t, 1H, N-H); IR peaks at 1680, 2870, 2960, 3070, 3340 (b); MS (DCI methane) 499 (M+1, 0.7%), 239 (34%), 199 (23.3%), 179 (100%), 75 (26.3%); Anal. Calcd. for $C_{25}H_{34}N_4SO_3Si$: C, 60.21; H, 6.87; N, 11.23. Found: C, 60.33; H, 6.86; N, 11.19.

N-(5-(2-Hydroxy-1,1-dimethyl)-1,3,4-thiadiazol-2-yl)-N'-hydroxymethyl-N-methylurea (1)

The protected urea (13, 4.0g, 8.0mmol) was dissolved in THF (120mL) and HOAc (2.0mL) and tetrabutylammonium fluoride (24mL, 24mmol) were added. The resulting mixture was stirred at room temperature for 45 minutes; then the solvent was removed on the rotary evaporator. The residue was dissolved in acetone and pre-absorbed onto 25g silica gel, then flash chromatographed on silica gel 60 (230-400 mesh) using 1:1 CH_2Cl_2 / acetone as the eluent. The product was isolated as a white solid (2.0g, 7.7mmol, 96%); m.p. 133-135°C. ^{1}H NMR (DMSO-d6) 1.3 (s, 6H, $C(CH_3)_2$), 3.5 (d, 2H, J=5Hz, HO-CH_2), 3.55 (s,

3H, N-C<u>H</u>$_3$), 4.65 (t, 2H, J=6Hz, NH-C<u>H</u>$_2$), 5.1 (t, 1H, J=5Hz, <u>H</u>O-CH$_2$), 5.7 (t, J=6Hz, HN-CH$_2$-O<u>H</u>), 8.3 (t, 1H, J=6Hz, N-<u>H</u>); IR (KBr) 1665, 2980, 3290 (b); MS (DCI methane) 261 (M+1, 48.3%), 243 (80.4%), 231 (55.2%), 216 (11.7%), 188 (100%).

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References and Notes

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4. Although many preparations of benzyloxyacetic acid have been reported, we have found the procedure described herein to be convenient for large and small scale preparations since it avoids the handling of highly irritating chloro or bromoacetic acid. Selected references to previous preparations are listed: H.O.L. Fischer and B. Gohlke, *Helv. Chim. Acta*, 1933, *16*, 1130; K.M. Hammond, N. Fisher, E.N. Morgan and E.M. Tanner, *J. Chem. Soc.*, 1957, 1062; M.S. Manhas, S.G. Amin, H.P.S. Chawla and A.K. Bose, *J. Heterocyclic Chem.*, 1978, *51*, 601; M.J. Kulka and J.M. Fortunato, *J. Org. Chem.*, 1984, *49*, 5003.
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6. The gradient elution was performed to first elute the bis-t-butyldiphenylsilyl ether/ester of glycolic acid followed by t-butyldiphenylsilanol and finally the desired product 8.
7. Other preparations on this scale provided yields ranging from 55-66%.

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