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Synthesis of 2-Mercaptobenzaldehyde, 2-Mercaptocyclohex-1-enecarboxaldehydes and 3-Mercaptoacrylaldehydes

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A novel one-pot approach for the preparation of 2-mercaptobenzaldehyde, 2-mercaptocyclohex-1-enecarboxaldehydes and 3-mercaptoacrylaldehydes [(*Z*)-3-mercapto-2-methyl-3-phenylacrylaldehyde, 3-mercapto-3-(*o*-tolyl)-acrylaldehyde)] starting from *ortho*-bromobenzaldehyde, 2-chlorocyclohex-1-enecarbaldehydes, (*Z*)-3-chloro-2-methyl-3-phenylacrylaldehyde and 3-chloro-3-(*o*-tolyl)acrylaldehyde is reported. The reaction of sulfur with the Grignard reagent of the acetal for the protection of the aldehyde group affords the title compounds through hydrolysis with dilute hydrochloric acid in high yields.

Keywords 2-mercaptobenzaldehyde, 2-mercaptocyclohex-1-enecarboxaldehydes, 3-mercaptoacrylaldehydes, Grignard reagent, sulfur, aldehyde

Introduction

Sulfur-containing heterocycles have a wide range of biological activities which usually exist in proteins, enzyme, coenzyme, and so on. The S-ligation molecules and pharmaceuticals such as thiochromanes[1-9] are reported to exhibit anti-inflammatory, anti-bacteria, anti-psychiatric, anti-hyperplasia, anti-cancer, and analgesic activities.[10-15] The synthesis of the substituted thiochromanes can be conducted by using a cupreine-catalyzed reaction from Zhao's group[16,17] or by using an enantioselective domino-Michael aldol reaction from Wang's group.[18-20] In all these reactions thiosalicylaldehydes serve as starting materials.

In organometallics, the chemistry of thiosalicylaldehydes attracts much attention of researchers through the replacement of the oxygen atom in salicylaldehydes by a sulfur atom which has good coordination abilities with several kinds of transition metal centers which have been widely investigated in syntheses, mechanisms, and catalytics.[21-27]

The literature methods for the preparation of 2-mercaptobenzaldehyde are shown in Scheme 1.

A derivative of 2-mercaptobenzaldehyde was prepared from the corresponding salicylaldehyde in three steps with a total yield of about 40%.[28] 2-Mercaptobenzaldehydes could be obtained in yields of 37%—43% by trapping organolithium intermediates, formed by directed ortho-lithiation of the precursors.[29] Pardoe reported a synthetic method for substituted 2-mercaptobenzaldehydes from substituted aldehydes by successive action of *n*-butyllithium, sulfur and hydrochloric acid with yields of 72%—94% arriving at moderate levels of purities (79%—94%). Due to lack of crystallization the crude products proved difficult to purify.[30] Pariza released a complicated process for the synthesis of 2-mercaptobenzaldehydes from *ortho*-halogeno benzaldehydes[31] similar to that of a Japanese patent.[32] A Chinese patent gives a preparation of 5-nitro-2-mercaptobenzaldehyde from 5-nitro-salicyl-aldehyde which is not reproducable.[33] However, these syntheses are obviously accompanied by poor yields, strict operations, vigorous reaction conditions, long reaction time, undesired side products, difficult purifications and tedious work-up. Furthermore, some of these methods are associated with the use of hazardous phosphine ligands, the use of sulfur-containing reagents such as benzenethiols which generally have such a strong, foul smell that working with them can be extremely unpleasant and in some cases the poor reproducibility of the yields.

2-Mercaptocyclohex-1-enecarbaldehyde was prepared by treating 2-cholrocyclohex-1-enecarbaldehyde with NaSH or from 2-thiocyanatocyclohex-1-enecarbaldehyde in the yield of 40%—65%.[34] (*Z*)-3-Mercapto-2-methyl-3-phenylacrylaldehyde was prepared by treating (*Z*)-3-chloro-2-methyl-3-phenylacrylaldehyde with Na_2S which is not reproducible.[35]

As a consequence, the introduction of new methods and/or further work on technical improvements to

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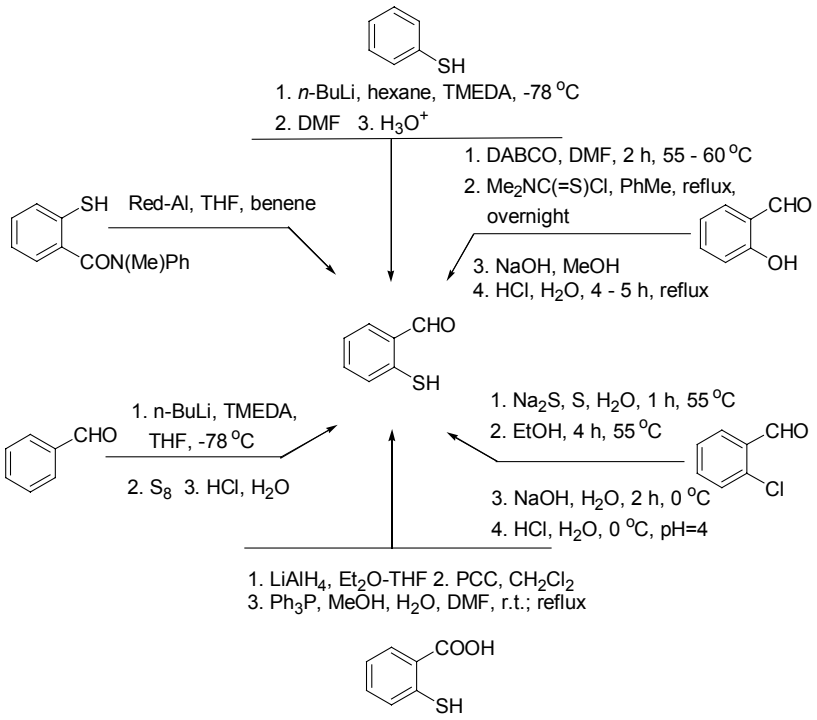
Scheme 1 Literature methods for preparation of 2-mercaptobenzaldehyde



overcome the limitations is still an important experimental challenge. Herein, we have presented our new strategy, a novel procedure for the first time that the reaction of sulfur with the Grignard reagent of the acetal for the protection of the aldehyde group affords the title compounds through hydrolysis with dilute hydrochloric acid in high yields.

Experimental

General procedures and materials

Standard vacuum techniques were used in manipulations of volatile and air-sensitive materials. Infrared spectra (4000—400 cm^{-1}), as obtained from Nujol mulls between KBr disks, were recorded on an ALPHA FT-IR Spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer. Melting points were measured in capillaries and are uncorrected. MS were obtained from Agilent 6510 Accurate-Mass Q-TOF LC/MS system.

2-Chlorocyclohex-1-enecarbaldehyde[36] (**1b**) from cyclohexanone, 2-chloro-5-methylcyclohex-1-enecarbaldehyde[37] (**1c**) from 4-methylcyclohexanone, 5-(*tert*-butyl)-2-chlorocyclohex-1-enecarbaldehyde[38] (**1d**) from 4-(*tert*-butyl)mcyclohexanone, (*Z*)-3-chloro-2-methyl-3-phenylacrylaldehyde[39] (**1e**) from propiophenone and 3-chloro-3-(*o*-tolyl)acrylaldehyde[40] (**1f**) from 1-(*o*-tolyl)methanone were synthesized according to the literature.

2-(2-Chlorocyolohex-1-en-1-yl)-1,3-dioxolane (2b) In a 250 mL one-necked round-bottomed flask, a solution of 2-chlorocyclohex-1-enecarbaldehyde (**1b**) (22.0 g, 0.15 mol) in 40 mL of toluene was added in one portion anhydrous ethylene glycol (12.4 g, 0.20 mol) and *p*-toluenesulfonic acid (258 mg, 1.50 mmol). The resulting solution mixture was refluxed until the theoretical yield of water had been collected in a Dean-Stark trap. After 6 h the mixture was cooled, washed with 10% aqueous sodium hydroxide (30 mL×2), followed by deionized water (30 mL×2), brine (30 mL×1) and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give 24.4 g (86%) of a colorless oil, 2-(2-chlorocyolohex-1-en-1-yl)-1,3-dioxolane (**2b**). m.p. 8.2—9.0 ℃; b.p. 78 ℃/9 mbar; IR (KBr) *v*: 1668, 1442, 1389, 1216, 1127, 1057, 952, 819 cm^{-1}; ^1H NMR (300 MHz, 295 K, C_6D_6) δ: 6.08 (s, 1H), 3.61—3.79 (m, 2H), 3.45—3.58 (m, 2H), 2.18—2.24 (m, 4H), 1.33—1.43 (m, 4H); ^{13}C NMR (75 MHz, 297 K, C_6D_6) δ: 132.8, 130.7, 101.4, 65.1, 34.3, 23.5, 21.5; HRMS calcld for $C_9H_{13}ClO_2$: 189.0638, found 189.0677.

2-(2-Chloro-5-methylcyclohex-1-en-1-yl)-1,3-dioxolane (2c) In a 250 mL one-necked round-bottomed flask, a solution of 2-chloro-5-methylcyclohex-1-enecarbaldehyde (**1c**) (23.8 g, 0.15 mol) in 40 mL of toluene was added in one portion anhydrous ethylene glycol (12.4 g, 0.20 mol) and *p*-toluenesulfonic acid (258 mg, 1.50 mmol). The resulting solution mixture was refluxed until the theoretical yield of water had been collected in a Dean-Stark trap. After 6.5 h, the mixture was cooled, washed with 10% aqueous sodium hydroxide (30 mL×2), followed by deionized water (30 mL×2), brine (30 mL×1) and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give 25.5 g (84%) of a colorless liquid, 2-(2-chloro-5-methylcyclohex-1-en-1-yl)-1,3-dioxolane (**2c**).

m.p. 18.5—19.0 ℃; b.p. 106 ℃/14 mbar; IR (KBr) *v*: 2951, 2924, 1666, 1455, 1433, 1382, 1347, 1304, 1214, 1126, 1050, 1028, 1012, 946, 905, 877, 799, 711, 640, 554 cm^{-1}; ^1H NMR (300 MHz, C_6D_6, 295 K) δ: 6.07 (s, 1H), 3.48—3.54 (m, 2H), 3.32—3.47 (m, 2H), 2.38—2.43 (m, 1H), 2.14—2.37 (m, 2H), 1.79—1.88 (m, 1H), 1.20—1.40 (m, 2H), 0.89—0.99 (m, 1H), 0.75 (d, J=6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, C_6D_6, 297 K) δ: 132.2, 129.5, 100.9, 64.6, 33.9, 31.9, 30.8, 27.2, 20.5; HRMS calcld for $C_{10}H_{15}ClO_2$: 203.0794, found 203.0838.

2-(5-(*tert*-Butyl)-2-chlorocyclohex-1-en-1-yl)-1,3-dioxolane (2d) In a 250 mL one-necked round-bottomed flask, a solution of 5-(*tert*-butyl)-2-chlorocyclohex-1-enecarbaldehyde (**1d**) (30.0 g, 0.15 mol) in 40 mL of toluene was added in one portion anhydrous ethylene glycol (12.4 g, 0.20 mol) and *p*-toluenesulfonic acid (258 mg, 1.50 mmol). The resulting solution mixture was refluxed until the theoretical yield of water had been collected in a Dean-Stark trap. After 7 h, the mixture was cooled, washed with 10% aqueous sodium hydroxide (30 mL×2), followed by deionized water (30 mL×2), brine (30 mL×1) and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give 30.4 g (83%) of a colorless liquid, 2-(5-(*tert*-butyl)-2-chlorocyclohex-1-en-1-yl)-1,3-dioxolane (**2d**). m.p. 23.8—25 ℃; b.p. 125 ℃/12 mbar; IR (KBr) *v*: 2956, 1714, 1675, 1626, 1469, 1388, 1305, 1219, 1130, 1082, 1023, 954, 889, 822, 766, 719, 549, 439 cm^{-1}; ^1H NMR (300 MHz, C_6D_6, 295 K) δ: 6.07 (s, 1H), 3.49—3.58 (m, 2H), 3.34—3.43 (m, 2H), 2.40—2.47 (m, 1H), 1.95—2.19 (m, 3H), 1.35—1.39 (m, 1H), 0.86—1.06 (m, 2H) 0.73 (s, 9H, $3CH_3$); ^{13}C NMR (75 MHz, C_6D_6, 297 K) δ: 132.4, 129.8, 101.1, 64.5, 42.4, 35.0, 31.3, 26.5, 24.5, 24.2; HRMS calcld for $C_{13}H_{21}ClO_2$: 245.1264, found 245.1324.

(*Z*)-2-(1-Chloro-1-phenylprop-1-en-2-yl)-1,3-dioxolane (2e) In a 250 mL one-necked round-bottomed flask, a solution of (*Z*)-3-chloro-2-methyl-3-phenylacrylaldehyde (**1e**) (27.1 g, 0.15 mol) in 40 mL of toluene was added in one portion anhydrous ethylene glycol (12.4 g, 0.20 mol) and *p*-toluenesulfonic acid (258 mg, 1.50 mmol). The resulting solution mixture was refluxed until the theoretical yield of water had been collected in a Dean-Stark trap. After 5.5 h, the mixture was cooled, washed with 10% aqueous sodium hydroxide (30 mL×2), followed by deionized water (30 mL×2), brine (30 mL×1) and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give 29.3 g (87%) of light yellow liquid, (*Z*)-2-(1-chloro-1-phenylprop-1-en-2-yl)-1,3-dioxolane (**2e**). m.p. 6.8—7.3 ℃; b.p. 110 ℃/16 mbar; IR (KBr) *v*: 2954, 2887, 1673, 1650, 1487, 1442, 1390, 1256, 1216, 1100, 1027, 993, 945, 894, 764, 700, 625, 517 cm^{-1}; ^1H NMR (300 MHz, C_6D_6, 295 K) δ: 7.51 (q, J=9 Hz, 2H), 7.09 (q, J=13.5 Hz, 3H), 5.40 (s, 1H), 3.53 (q, J=7.5 Hz, 2H), 3.24 (t, J=6 Hz, 2H), 2.21 (s, 3H, CH_3); ^{13}C NMR (75 MHz, C_6D_6, 297 K) δ:137.4, 134.4, 131.8, 128.5, 128.1, 129.0, 101.3, 64.7, 13.1; HRMS calcd for $C_{12}H_{13}ClO_2$: 225.0638, found 225.0690.

2-(2-Chloro-2-(*o*-tolyl)vinyl)-1,3-dioxolane (2f) In a 250 mL one-necked round-bottomed flask, a solution of 3-chloro-3-(*o*-tolyl)acrylaldehyde (**1f**) (27.1 g, 0.15 mol) in 40 mL of toluene was added in one portion anhydrous ethylene glycol (12.4 g, 0.20 mol) and *p*-toluenesulfonic acid (258 mg, 1.50 mmol). The resulting solution mixture was refluxed until the theoretical yield of water had been collected in a Dean-Stark trap. After 5 h, the mixture was cooled, washed with 10% aqueous sodium hydroxide (30 mL×2), followed by deionized water (30 mL×2), brine (30 mL×1) and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the residue distilled (b.p.: 168 ℃/19 mbar) to give the product (30.0 g, 89%) as a pale-yellow oil as a 22∶78 mixture (by ^1H NMR analysis) of *E/Z* isomers, 2-(2-chloro-2-(*o*-tolyl)vinyl)-1,3-dioxolane (**2f**). b.p.: 168 ℃/19 mbar; IR (KBr) *v*: 2955, 2886, 1656, 1599, 1485, 1456, 1386, 1285, 1228, 1148, 1071, 1027, 944, 876, 762, 726, 665, 606, 520, 449 cm^{-1}; ^1H NMR (300 MHz, C_6D_6, 295 K) *E* isomer δ: 7.31 (d, J=7.5 Hz, 1H), 7.08—7.00 (m, 3H), 6.29 (q, J=4 Hz, 1H), 5.10 (q, J=6 Hz, 1H), 3.66 (d, J=3 Hz, 1H), 3.60 (d, J=2.1 Hz, 1H), 3.21 (d, J=7.2 Hz, 2H), 2.41 (s, 3H, CH_3); *Z* isomer δ: 7.19—7.24 (m, 1H), 6.93—7.03 (m, 3H), 6.08 (q, J=6.8 Hz, 1H), 5.89 (q, J=6.8 Hz, 1H), 3.59—3.66 (m, 2H), 3.45 (d, J=2.1 Hz, 2H), 2.32 (s, 3H, CH_3); ^{13}C NMR (75 MHz, C_6D_6, 297 K) δ: 139.1, 138.1, 136.4, 130.9, 129.6, 129.5, 128.1, 126.3, 100.9, 65.3, 19.9; HRMS calcld for $C_{12}H_{13}ClO_2$: 225.0638, found 225.0670.

2-Mercaptobenzaldehyde (5a) A 500 mL three-necked flask was charged with magnesium (2.6 g, 0.11 mol) and 100 mL of anhydrous THF. 2-(2-bromophenyl)-1,3-dioxolane (**2a**)[41] (22.9 g, 0.10 mol) was added dropwise at 0 ℃. The mixture was allowed to warm to ambient temperature and refluxed for 1 h. At 0 ℃ sublimed sulfur (3.2 g, 0.10 mol) was added to the mixture. The solution was stirred overnight at room temperature. 1 mol/L of HCl was used to quench the reaction until the mixture was acidic. After refluxing for 2 h the mixture was extracted with diethyl ether (50 mL×3) and the organic phase was dried over anhydrous Na_2SO_4. After filtration and concentration to 50 mL product **5a** was obtained at −30 ℃ as bright yellow solid (12.6 g, yield 91%). m.p.: 43—44 ℃; IR (KBr) *v*: 1690 (s, C=O), 2561 (m, S—H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 295 K) δ: 10.05 (s, 1H), 7.72 (dd, J=7.2, 1.2 Hz, 1H), 7.27—7.32 (m, 2H), 7.36—7.42 (m, 1H), 5.52 (s, 1H, SH); ^{13}C NMR (75 MHz, $CDCl_3$, 297 K) δ: 192.8, 137.9, 136.1, 133.4, 131.3, 131.1, 125.0.

2-Mercaptocyclohex-1-enecarbaldehyde[34] (5b) A 500 mL three-necked round-bottomed flask was charged with magnesium (1.6 g, 0.066 mol) and 100 mL of anhydrous THF. 2-(2-Chlorocyclohex-1-en-1-yl)-1,3-dioxolane (**2b**) (11.9 g, 0.063 mol) was added dropwise at 0 ℃. The mixture was allowed to warm to ambient

temperature and refluxed for 2 h. At 0 ℃ sublimed sulfur (2.0 g, 0.063 mol) was added to the mixture and stirred for 1 h. The solution was stirred overnight at room temperature. At 0 ℃ 1 mol/L of HCl was used to quench the reaction, then the solution was stirred for 2 h until the mixture was acidic. Then the mixture was extracted with diethyl ether (50 mL×3) and the organic phase was dried over anhydrous Na_2SO_4. After filtration and concentration 2-mercaptocyclohex-1-enecarbaldehyde (**5b**) was obtained at −20 ℃ as yellow needle crystal (8.6 g, yield 96%). m.p.: 7.8—8.2 ℃; IR (KBr) *v*: 1679 (s, C=O), 1623 (s, C=C) cm^{-1}; ^1H NMR (300 MHz, 295 K, $CDCl_3$) *δ*: 10.20 (s, 1H), 2.57 (t, *J*=6, 3 Hz, 2H), 2.28 (t, *J*=6 Hz, 2H), 1.75 (t, *J*=12, 3 Hz, 2H), 1.66 (t, *J*=12, 3 Hz, 2H), 1.58 (s, 1H, SH); ^{13}C NMR (75 MHz, $CDCl_3$, 297 K) *δ*: 190.5, 150.8, 132.9, 35.3, 23.2, 22.7, 20.5; HRMS calcld for $C_7H_{10}OS$: 143.0486, found 143.0629.

2-Mercapto-5-methylcyclohex-1-enecarbaldehyde (5c) A 500 mL three-necked flask was charged with magnesium (2.6 g, 0.11 mol) and 100 mL of anhydrous THF. 2-(2-Chloro-5-methylcyclohex-1-en-1-yl)-1,3-dioxolane **2c** (20.3 g, 0.10 mol) was added dropwise at 0 ℃. The mixture was allowed to warm to ambient temperature and refluxed for 2 h. At 0 ℃ sublimed sulfur (3.2 g, 0.10 mol) was added to the mixture. The solution was stirred overnight at room temperature. 1 mol/L of HCl was used to quench the reaction until the mixture was acidic. After refluxing for 2 h the mixture was extracted with diethyl ether (50 mL×3) and the organic phase was dried over anhydrous Na_2SO_4. After filtration and concentration 2-mercapto-5-methylcyclohex-1-enecarbaldehyde (**5c**) was obtained at −20 ℃ as yellow tidy crystal (13.8 g, yield 88%). m.p.: 13.8—15.0 ℃; IR (KBr) *v*: 3334 (w, C=O(H)), 1677 (s, C=O), 1622 (s, C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 295 K) *δ*: 10.19 (s, 1H), 2.60—2.66 (m, 2H), 2.50—2.59 (m, 1H), 1.69—1.85 (m, 3H), 1.39—1.43 (m, 1H), 1.25 (s, 1H, SH), 1.02 (d, *J*=6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 297 K) *δ*: 191.6, 151.6, 133.4, 36.3, 32.2, 31.6, 27.9, 21.4; HRMS calcld for $C_8H_{12}OS$: 157.0642, found 157.0866.

5-(*tert*-Butyl)-2-mercaptocyclohex-1-enecarbaldehyde (5d) A 500 mL three-necked flask was charged with magnesium (2.6 g, 0.11 mol) and 100 mL of anhydrous THF. 2-(5-(*tert*-Butyl)-2-chlorocyclohex-1-en-1-yl)-1,3-dioxolane (**2d**) (24.5 g, 0.10 mol) was added dropwise at 0 ℃. The mixture was allowed to warm to ambient temperature and refluxed for 2 h. At 0 ℃ sublimed sulfur (3.2 g, 0.10 mol) was added to the mixture. The solution was stirred overnight at room temperature. 1 mol/L of HCl was used to quench the reaction until the mixture was acidic. After refluxing for 2 h the mixture was extracted with diethyl ether (50 mL×3) and the organic phase was dried over anhydrous Na_2SO_4. After filtration and concentration 5-(*tert*-butyl)-2-mercaptocyclohex-1-enecarbaldehyd-e (**5d**) was obtained at −20 ℃ as yellow tidy crystal (17.2 g, yield 87%). m.p.: 14.6—16.8 ℃; IR (KBr) *v*: 3337 (w, C=O(H)), 1678 (s, C=O), 1625 (s, C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 295 K) *δ*: 10.18 (s, 1H), 2.60 (q, *J*=22.1 Hz, 2H), 1.18—1.95 (m, 2H), 0.91—1.42 (m, 3H), 0.91 (s, 9H, 3×CH_3), 0.88 (s, 1H, SH); ^{13}C NMR (75 MHz, $CDCl_3$, 297 K) *δ*: 191.7, 151.7, 133.8, 43.4, 37.5, 32.7, 27.6, 25.8, 25.0; HRMS calcld for $C_{11}H_{18}OS$: 199.1112, found 199.2176.

(*Z*)-3-Mercapto-2-methyl-3-phenylacrylaldehyde (5e) A 500 mL three-necked flask was charged with magnesium (2.6 g, 0.11 mol) and 100 mL of anhydrous THF. (*Z*)-2-(1-Chloro-1-phenylprop-1-en-2-yl)-1,3-dioxolane (**2e**) (22.5 g, 0.10 mol) was added dropwise at 0 ℃. The mixture was allowed to warm to ambient temperature and refluxed for 4 h. At 0 ℃ sublimed sulfur (3.2 g, 0.10 mol) was added to the mixture. The solution was stirred overnight at room temperature. 1 mol/L of HCl was used to quench the reaction until the mixture was acidic. After refluxing for 2 h the mixture was extracted with diethyl ether (50 mL×3) and the organic phase was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the yellow oil was purified by chromatography using petroleum ether/ethyl acetate (25∶1) as eluent to afford the product (*Z*)-3-mercapto-2-methyl-3-phenylacrylaldehyde (**5e**) (15.3 g, yield 86%) as a pale-yellow oil. IR (KBr) *v*: 3329 (w, C=O(H)), 1674 (s, C=O), 1608 (s, C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 295 K) *δ*: 9.48 (s, 1H), 7.48—7.40 (m, 5H), 2.09 (s, 3H, CH_3) 1.85 (s, 1H, SH); ^{13}C NMR (75 MHz, $CDCl_3$, 297 K) *δ*: 198.8, 153.9, 153.8, 135.3, 129.9, 129.6, 127.9, 12.8; HRMS calcld for $C_{10}H_{10}OS$, 179.0486, found 179.0681.

3-Mercapto-3-(*o*-tolyl)acrylaldehyde (5f) A 500 mL three-necked flask was charged with magnesium (2.6 g, 0.11 mol) and 100 mL of anhydrous THF. 2-(2-Chloro-2-(*o*-tolyl)vinyl)-1,3-dioxolane (**2f**) (22.5 g, 0.10 mol) was added dropwise at 0 ℃. The mixture was allowed to warm to ambient temperature and refluxed for 4 h. At 0 ℃ sublimed sulfur (3.2 g, 0.10 mol) was added to the mixture. The solution was stirred overnight at room temperature. 1 mol/L of HCl was used to quench the reaction until the mixture was acidic. After refluxing for 2 h the mixture was extracted with diethyl ether (50 mL×3) and the organic phase was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the yellow oil was purified by chromatography using petroleum ether/ethyl acetate (25∶1) as eluent to afford the product (15.8 g, yield 89%) as a pale-yellow oil as a 40∶60 mixture (by ^1H NMR analysis) of *E/Z* isomers. IR (KBr) *v*: 3342 (w, C=O(H)), 1681 (s, C=O), 1613 (s, C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 295 K) *E* isomer *δ*: 10.20 (d, *J*=9 Hz, 1H), 7.35—7.25 (m, 4H), 6.25 (d, *J*=6 Hz, 1H), 2.42 (s, 3H, CH_3),1.59 (s, 1H, SH); *Z* isomer *δ*: 9.21 (d, *J*=9 Hz, 1H), 7.35—7.25 (m, 4H), 6.55 (d, *J*=9 Hz, 1H), 2.38 (s, 3H, CH_3), 1.25 (s, 1H, SH); ^{13}C NMR (75 MHz, $CDCl_3$, 297 K) *E* isomer *δ*: 190.3, 158.4, 136.6, 135.0, 132.0, 131.3, 130.9, 129.9, 126.5, 19.9; *Z* isomer

δ: 191.4, 153.0, 137.8, 135.1, 131.5, 130.8, 129.2, 128.9, 126.6, 20.5; HRMS calcld for $C_{10}H_{10}OS$: 179.0486, found 179.0683.

Results and Discussion

Our strategy for developing a convenient one-pot synthesis of 2-mercaptobenzaldehyde **5a**, 2-mercaptocyclohex-1-enecarbaldehyde **5b**, 2-mercapto-5-methylcyclohex-1-enecarbaldehyde **5c**, 5-(*tert*-butyl)-2-mercaptocyclohex-1-enecarbaldehyde **5d**, (*Z*)-3-mercapto-2-methyl-3-phenylacrylaldehyde **5e** and 3-mercapto-3-(*o*-tolyl)acrylaldehyde **5f** can be illustrated in Scheme 2.

The corresponding novel intermediates (**2b—2f**) and the title compounds (**5a—5f**) were isolated in high yields (Tables 1 and 2).

At first the aldehyde group of *ortho*-bromobenzaldehyde **1a**, 2-chlorocyclohex-1-enecarbaldehyde **1b**, 2-chloro-5-methylcyclohex-1-enecarbaldehyde **1c**, 5-(*tert*-butyl)-2-chlorocyclohex-1-enecarbaldehyde **1d**, (*Z*)-3-chloro-2-methyl-3-phenylacrylaldehyde **1e** or 3-chloro-3-(*o*-tolyl)acrylaldehyde **1f** is protected from the attack of the basic Grignard reagent by conversion to the acetal **2** with *p*-toluenesulfonic acid (PTSA) as catalyst.[13] Acetal **2** transforms to the Grignard compound **3** in THF. The reaction of Grignard reagent **3** with sulfur gives rise to the magnesium halide **4**. The acetal and the SMgX groups of compound **4** can be simultaneously hydrolyzed by treatment with acid to form the corresponding expected compounds **5a**, **5b**, **5c**, **5d**, **5e** and **5f**. In order to get high yields in this acidification refluxing for at least 2 h is necessary until the acetal was completely hydrolyzed. Comparing with the literature methods, however, there are several remarkable advantages of this novel method. First, the transformation from the acetal **2** to the end product **5** is a convenient one-pot reaction whereby **5a** can be obtained in a reproducible high yield of 91% (for **5b**: 96%, **5c**: 88%, **5d**: 87%, **5e**: 86%, **5f**: 89%). As the second improvement no column chromatography for the purification of the crude products as described in the literature is necessary because the pure product **5a**, **5b**, **5c** or **5d** is conveniently obtained as bright yellow solid by crystallization from diethyl ether while this procedure made hardly damage to the environment and easy work-up. Furthermore, we have been successfully involved in a program aimed at the use of odorless starting materials which can substitute for malodorous reagents such as benzenethiol, and other sulfur-containing reagents, however, this feature has greatly improved the environmental working conditions.

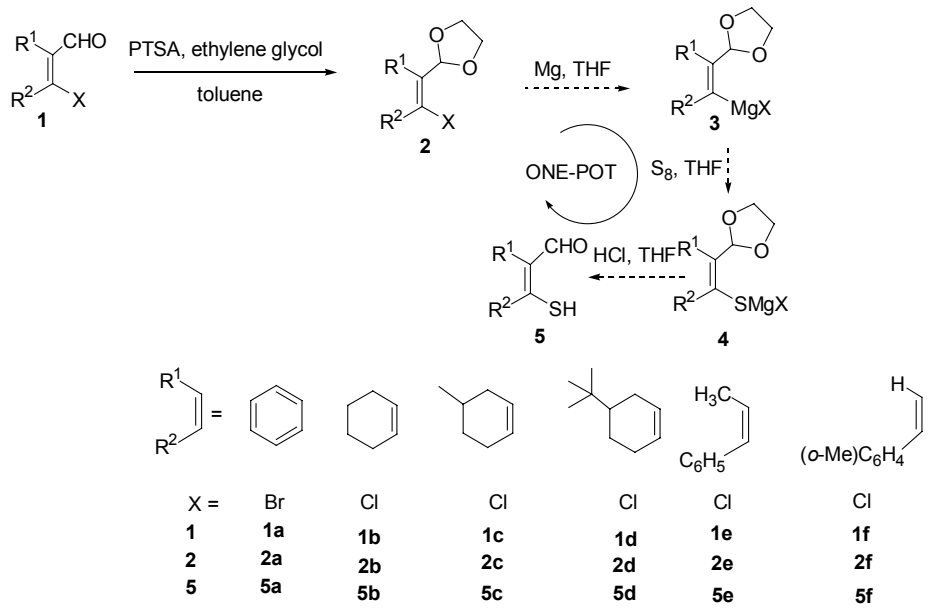
Table 1 Yields for novel intermediates **2b—2f**

Novel intermediates **2b—2f**	Yield of **2b—2f**/%
2b	86
2c	84
2d	83
2e	87
2f	89

Table 2 Yields for the title compounds **2b—2f**

Title compounds **5a**—5**f**	Yield of **5a—5f**/%
5a	91
5b	96
5c	88
5d	87
5e	86
5f	89

Scheme 2 Our strategy for the synthetic route



Conclusions

In summary, we have demonstrated the remarkable effect of one-pot approach for the first time for the preparation of 2-mercaptobenzaldehyde (**5a**), 2-mercaptocyclohex-1-enecarbaldehydes (**5b** — **5d**) and 3-mercaptoacrylaldehydes (**5e**—**5f**) starting from *ortho*-bromobenzaldehyde (**1a**), the derivatives (**1b**—**1d**) of 2-chlorocyclohex-1-enecarbaldehydes, and the derivatives (**1e**—**1f**) of acrylaldehydes. The reaction of sulfur with the Grignard reagent of the acetal for the protection of the aldehyde group afforded the title compounds in high yields of 86%—96% through hydrolysis with dilute hydrochloric acid that is facile, efficient, and highly selective. Surprisingly, the pure products **5a, 5b, 5c** and **5d** are conveniently isolated as bright yellow microcrystals. The novel procedure showed high yields of the desired products, easy work-up, short reaction time, no catalyst, no hazardous phosphine ligands, no strong and foul smell sulfur-containing reagents, no environmental problem and mild reaction conditions in comparison with other methods, which are the strong points of the present procedure.

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