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Activation of alcohols to nucleophilic substitution

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***Abstract*. The cyclic thionocarbamate of alaninol undergoes nucleophilic attack at 5-C by sulfur nucleophiles when derivatised on nitrogen with a Boc group, to reduce nitrogen to thione conjugation, to give 2-thioethylamine derivatives. Iodide under microwave conditions causes a rearrangement to the thiazolidinone. "Hard" nucleophiles react at the thione group followed by either C-N or C-O cleavage to yield a variety of product types.**

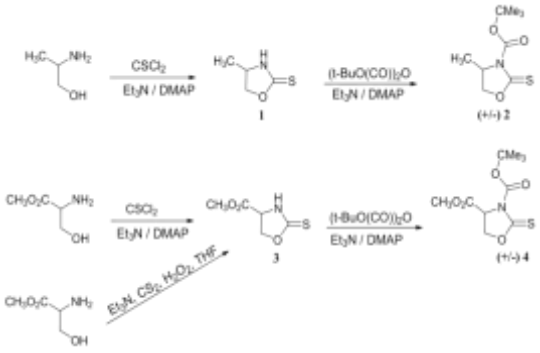
***Keywords:* cyclic thionocarbamate, vic-aminoalcohols, thiophosgene, microwave condition.**

Introduction

This particular project is concerned with the development of new synthetic methods for use in organic chemistry. The replacement of a hydroxyl group with nucleophiles is a useful process, and we are going to investigate methods for doing this in vic-aminoalcohols and vic-diols.[1-3] The aim of this particular part of the project was to study the synthesis of amines and amino acids via cyclic thionocarbamate thus allowing the activation of the oxgen atom by the thiocarbonyl group. The starting compound (+/-)alaninol containing one hydroxyl group and an adjacent amino group, was converted into a cyclic thionocarbamate.[4,5,6] The cyclic thionocarbamate was then targeted by sulphur-containing nucleophiles to assess the conditions in which the carbon - oxygen bond will break.[7,8]

The preparation of cyclic thionocarbamates 2 and 4.

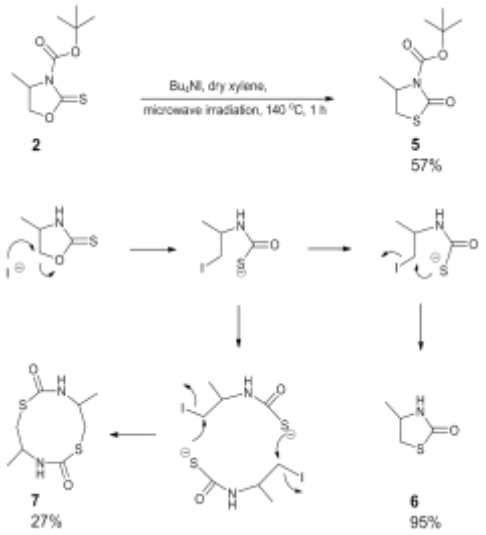
Cyclic thionocarbamates with N‑benzyl groups do not react with nucleophiles at 5-C atom, however, we have found that installation of N-Boc group instead of N-benzyl to give thione 2 and 4 provides sufficient activity for this reaction to take place with thiolates. X-ray evidence shows that in 2 and 4 the Boc group removes electron density from the ring N atom and reduces its conjugation with thiocarbonyl group.The N-Boc thionocarbamates 2 and 4 were made in two steps via ring formation to give compound 1 and 3 in 36% and 66% yield, however, a higher yielding procedure for this transformation was also used. In this case DL-serine methyl ester was reacted with carbon disulfide,[9] Et_3N (2 eq.) and H2O2 in dry THF to give a much cleaner product 3 in 83% yield. followed by the addition of the Boc group.



Scheme 1

Rearrangement reaction with iodide

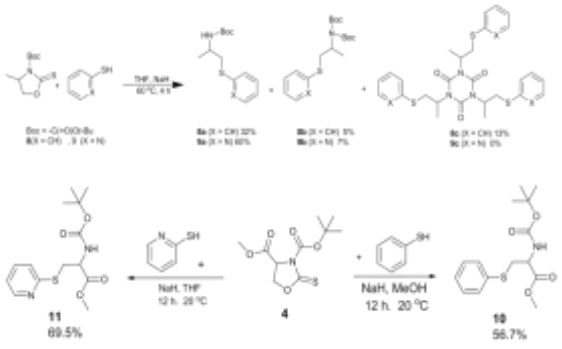
It was interesting to see the reaction of 2 with tetrabutylammonium iodide under refluxing conditions was unsuccessful, but transferring the reaction to microwave conditions using dry xylene as solvent at 145 ^oC for 1 h. gave a 57.0% yield of the thiazolidin-2-one 5 Due to the interest in synthesis under microwave conditions, this reaction was also conducted on compound 1, which is closely related to 2 but does not carry the Boc group thought to be necessary for activation to nucleophilic attack. The product obtained from the rearrangement of rac thione 1 using tetrabutylammonium iodide as the nucleophile was dependent on the precise conditions used. The use of dry xylene (10 ml of xylene per 2.0 mmol of 1) and a lengthy reaction time under microwave irradiation gave the pure rac 4-methyl-1,3-thiazolidine-2-one 6 as a yellow oil in high yield 95%. On the other hand in the same microwave conditions but using very little solvent (2 ml of xylene per 6.0 mmol of 1) the reaction resulted in a dimeric product containing a ten membered ring 7 as pale brown oil in 27% yield.



Scheme 2.

Reactions with soft nucleophiles

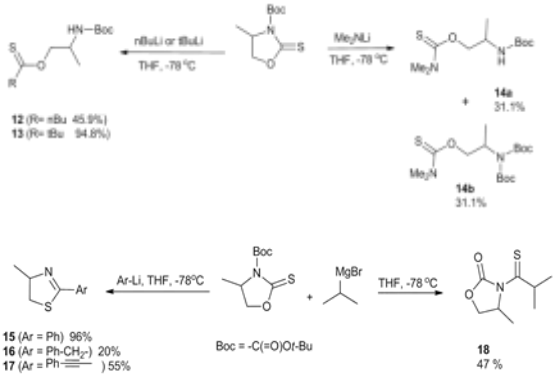
From measurements of the structures of 2 and 4 it appears that acylation of the nitrogen atom has had the desired effect of increasing the interaction of the thiocarbonyl group with the ring oxygen atom, and thus improving the leaving group characteristic of this oxygen at 5-C of the ring system. Thus, some preliminary investigations of the reactions of cyclic thionocarbamates 2 and 4 with nucleophiles have been made, and indicate some successful ring openings by breaking of the ring sp3 C-O bond at carbon. Initial experiments have involved reaction of 2 with e.g. thiophenolate and pyridine-2-thiolate, to give 8a, 8b, 9a, and 9b. Interestingly the former reaction also led to production of a tris-N-substituted cyanuric acid derivative 8c. Several reactions of the thionocarbamate 4 carrying an ester group at the 4-C position were investigated. Reaction with sulfur nucleophiles such as phenylthiolate and 2-pyridinethniolate gave the products 10 and 11 arising from attack at the 5-C, in 69.5 and 56.7% yield.



Scheme. 3 and 4.

Reactions with hard nucleophiles

The reaction with “harder” organolithium and organomagnesium nucleophiles presented a different picture. Their reactions start by attack of the organometallic on the thione group, but the precise product formed depends on the subsequent reactions of this addition product. Thus, n-butyl lithium, t-butyl lithium and lithium dimethylamide were reacted with thione 2. Analysis of the products showed that the organometallic adds to the thione group, the tetrahedral intermediate collapses with breakage of the ring C-N bond to give 12, 13 and (14a + 14b) as main products in yields of 45.9, 94.8 and (31.1 + 30.9%). Interestingly, the reaction with aromatic lithium or aromatic magnesium Grignard or isopropylmagnesium bromide in the same conditions react at the thiocarbonyl group to give one of several producats, e.g. , 15, 16, 17 and 1 8, depending on which organometallic reagent is used, and whether the N-C or O-C bond is broken.



Scheme. 5 and 6.

Conclusion

The “soft” polarisable sulphur nucleophiles such as phenylthiolate and 2-pyridine-thiolate and potassium thioacetate have been reacted successfully at the 5-C of cyclic thionocarbamate. Also, under microwave conditions there was a successful rearrangement reaction of thionocarbamate catalysed by iodide to obtain the corresponding thiazolidin-2-one. The "hard” polarised N or C nucleophiles attack the thione group to present a different picture, the precise product produced depends on the subsequent reactions of this addition product, whether the N-C or O-C bond is broken depending on which organometallic reagent is used.

EXPERIMENTAL

Reactions of 2:

(a) with sodium pyridine-2-thiolate

A solution of the sodium salt of 2-mercaptopyridine in dry THF (15 ml), formed from 2-mercaptopyridine (101.4 mg, 0.108 ml, 0.92 mmol) and sodium hydride (60% dispersion in oil, 74 mg, 1.84 mmol), was added to a solution of 2 (200 mg, 0.92 mmol) in dry THF (10 ml). The mixture was stirred and heated to 70 ºC overnight. The pale red solution was left to cool to room temperature, several drops of water were added, and the mixture stirred for 30 min. The solvent was evaporated, and the residue was extracted with dichloromethane (2 x 20 ml) and the extract washed with water (30 ml) and dried with sodium sulfate. The crude product was purified by chromatography using cyclohexane/ethyl acetate (1:1, increasing to 1:4) to give 9a (60.0%) and 9b (6.5%). N-t-Butyloxycarbonyl-1-(pyrid-2'-ylthio)prop-2-ylamine, 9a, pale yellow solid (148 mg, 60.0%); m.p. = 56 ºC. Anal. calcd for $C_{13}H_20N_2O_2S$: C, 58.20; H, 7.46; N, 10.44%; found: C, 58.33; H, 7.41; N, 10.36%; δH (400 MHz): 8.40 (1H, d, J 4.0, 6'-H), 7.46 (1H, m, 4'-H), 7.23 (1H, d, J 8.0, 3'-H), 6.85 (1H, m, 5'-H), 5.49 (1H, s, NH), 3.95 (1H, m, 2-H), 3.30 (2H, m, 1-H2), 1.39 (9H, s, 3 x CH_3), 1.25 (3H, d, J = 6.8, 3-H_3); δC(100 MHz): 155.4 (N-C=O), 158.7, 149.1, 135.9, 122.3 & 119.5 (Ar-C5), 78.8 (C-$(CH_3)_3$), 47.1 (2-C), 36.0 (1-C), 28.3 (3 x CH_3), 20.3 (3-C); vmax: 3359, 2973, 1678, 1581, 1519, 1415, 1167, 1154, 1125, 1059, 1053, 752, 578, 399 cm-1; m/z (ESI) found: 269 [M + H]+, other peaks at 559 [2M+Na]+, 152 ([M – NHBoc]+; HRMS (ESI) calcd for $C_{13}H_20N_2O_2$ + H+: 269.1318; found: 269.1324. N,N-Di(t-butoxycarbonyl)-1-(pyrid-2'-ylthio)propyl-2-amine 9b, pale yellow solid, (22 mg, 6.5%). δH (400 MHz): 8.38 (1H, dd, J 4.0, 6`-H), 7.44 (1H, m, 4'-H), 7.14 (1H, m, 3'-H), 6.99 (1H, m, 5'-H), 4.53 (1H, m, 2-H), 3.52 (2H, m, 1-H2), 1.43 (18H, s, 6 x CH3), 1.39 (3H, d, J 7.2, 3-H3); δC(100 MHz): 157.1 (2 x N-C=O), 159.1, 149.1, 135.7, 122.3 & 119.5 (Ar-C5), 82.0 (2 x C$(CH_3)_3$), 52.2 (2-C), 34.6 (1-C), 27.9 (6 x CH3), 17.9 (3-C); vmax: 3049, 2978, 1942, 1699, 1577, 1553, 1454, 1337, 1212, 1142, 1121, 1039, 985, 752 & 395 cm-1; m/z: (ESI) 369 [M + H]+ other peaks at 759 [2M + Na]+, 269 [M – Boc]+, 213, 152 [M – N(Boc)2]+; HRMS (ESI) calcd for [M + H]+, $C_{18}H_{28}N_2O_4S$ + H+: 369.1843; found: 369.1838.

(b) with sodium phenylthiolate

To a solution of the sodium salt of thiophenol in dry THF (15 ml), formed from thiophenol (101.4 mg, 0.108 ml, 0.92 mmol) and sodium hydride (60% dispersion in oil, 74 mg, 1.84 mmol), was added to a solution of 2 (200 mg, 0.92 mmol) in dry THF (10 ml). The mixture was stirred and heated to 60 ºC for 4 h. After adding some drops of water, the mixture was left stirring for 30 min. The clear solution was diluted with water (30 ml) and extracted with dichloromethane (2 x 20 ml). The organic layer was evaporated, and the crude product was purified by chromatography eluting with cyclohexane/ethyl acetate (10:1). The separation gave three compounds 8a (32.0%), (8b (4.5%) and 8c (38.3%). rac. N-1-t-Butoxycarbonyl-1-phenylthiopropyl-2-amine 8a is a white solid (78 mg, 32.0%), m.p. 63 ºC. Anal. calcd for $C_{14}H_{21}NO_2S$: C, 62.92; H, 7.86; N, 5.24%; Found: C, 63.00; H, 7.96; N, 5.21%; δH (400MHz, CD3OD): 7.37 (2H, d, J 8.0, ortho Ar-H2), 7.27 (2H, t, J 8.0, meta Ar-H_2), 7.15 (1H, t, J 7.2, para Ar-H), 4.86 (1H, s, NH), 3.71 (1H, m, 2-H), 3.09 (1H, br dd, J 6.0 & 13.0, 1-Hα), 2.88 (1H, dd, J 7.2 & 13.0, 1-Hβ), 1.41 (9H, s, 3 x CH_3), 1.18 (3H, d, J 6.8, 3-H3); δC(100 MHz): 157.6 (N-C=O), 137.8, 130.3, 129.9 & 127.0, (Ar-C6), 79.9 (C-(CH3)3), 48.6 (2-C), 40.8 (1-C), 28.8 (3 x CH3), 20.0 (3-C); vmax: 3368, 2976, 1681, 1518, 1244, 1153, 1026, 737, 610, 468 cm-1; m/z: (EI) 290 [M + Na]+, 212 [M+H – C_4H_8]+, 151 [M – NHBoc]+; HRMS (EI) calcd for [M + Na]+, $C_{14}H_{21}NO_2S$ + Na: 290.1185; found: 290.1189.

N,N-Bis(t-butoxycarbonyl)-1-(phenylthio)propyl-2-amine 8b, clear colourless liquid (15 mg, 4.45%). Anal. calcd for $C_{19}H_{29}NO_4S$: C, 62.12; H, 7.90; N, 3.81%; found: C, 62.14; H, 7.83; N, 3.96%; δH (400 MHz): 7.29 (2H, d, J 7.8, ortho Ar-H2), 7.19 (2H, t , J 7.8, meta Ar-H2), 7.10 (1H, t, J 7.2, para Ar-H), 4.33 (1H, m, 2-H), 3.35 (1H, dd, J 8.0 & 13.6, 1-Hα), 3.06 (1H, dd, J 7.2 & 13.6, 1-Hβ), 1.39 (18H, s, 6 x CH_3), 1.30 (3H, d, J 6.8, 3-H3); δC(100 MHz): 152.8 (2 x N-C=O), 135.8, 129.5, 128.8 & 126.1, (Ar-C6), 82.2 (2 x C(CH3)3), 52.2 (2-C), 38.6 (1-C), 27.9 (6 x CH3), 17.6 (CH3); vmax: 2978, 1736, 1699, 1367, 1345, 1273, 1142, 740, 691 cm-1; m/z (ESI): 390 [M + Na]+, other

peaks at 757 [2M+NH4]+, 268 [M – Boc]+, 151 [M – N(Boc)2]+; HRMS (ESI) calcd for [M + H]+ $C_{19}H_{29}NO_4S$ + H: 368.1890; found: 368.1890. rac-R,R,R- and rac-R,R,S-1,3,5-tris(1'-(phenylthio)prop-2'-yl)hexahydro-1,3,5-triazine-2,4,6-trione 8c, clear colourless liquid (68 mg, 12.8%). δH (400 MHz): 7.35 (6H, d, J 7.8, 3 x ortho Ar-H_2), 7.33 (6H, t, J 7.8, 3 x meta Ar-H_2), 7.25 (3H, t, J 7.2, 3 x para Ar-H_1), 4.92 (3H, m, 3 x 2`-H), 3.56 (3H, m, 3 x 1`-Hα), 3.18 (3H, m, 3 x 1`-Hβ), 1.44 (9H, d, J 6.8, 3 x 3`-H_3); δC(100 MHz): 159.4 (3 x N_2-C=O), 135.3, 130.4, 130.2, & 126.8 (3 x Ar-C_6), 51.1 (3 x 2`-C), 37.1 (3 x 1`-C), 17.3 (3 x 3`-C); vmax: 2975, 1683, 1425, 1369, 1024, 762, 734, 689, 421 cm-1; m/z: (EI) 579 ([M]+, 15), 151 ([PhS-CH_2-CH-CH_3]+, 35), 150 ([PhS-CH=CH-CH_3]+, 100); HRMS (ESI) calcd for [M + H]+, $C_{30}H_{33}N_3O_3S_3$ + H: 580.1749; found 580.1749.

(c) with tetrabutylammonium iodide.

Tetrabutylammonium iodide (339 mg, 0.92 mmol) and 2 (200 mg, 0.92 mmol) were dissolved in dry xylene (10 ml) and the mixture was stirred and irradiated in a microwave oven at 145 oC for 1 hr. After cooling to room temperature the reaction mixture was dissolved in dichloromethane (15 ml) and was washed with distilled water (2 x 10 ml). The organic layer was dried over sodium sulfate, and solvent removed in vacuo. The crude residue was purified by chromatography using cyclohexane / ethyl acetate (2:1) as eluent to give N-t-butoxycarbonyl-4-methyl-1,3-thiazolidin-2-one 5 as a white solid (114 mg, 57.0%), which was crystallized from ethyl acetate, m.p. 77-78 ºC; Anal.calcd for $C_9H_{15}NO_3S$: C, 49.7; H, 7.0; N, 6.4%, found: C, 49.7; H, 7.0; N, 6.3 %; δH: 4.53 (1H, m, 4-H), 3.51 (1H, m, 5-Hα), 2.73 (1H, m, 5-Hβ), 1.45 (9H, s, 3 x CH_3), 1.35 (3H, d, J 6.2, 4-CH_3); δc (100 MHz): 169.6 (2-C), 148.5 (N-C=O), 83.3 ($C(CH_3)_3$), 54.6 (4-C), 31.6 (5-C), 27.7 (3 x CH_3), 18.7 (4-CH3); v_{max}: 2977, 1755, 1672, 1369, 1354, 1326, 1278, 1245, 1169, 1147, 942, 859, 768, 672, 548 cm-1; m/z: (ESI) 235 [M + NH4]+, 218 [M + H]+, 162 [M+NH_4 – C_4H_9O], 144; HRMS: calcd for [M + NH_4]+ $C_9H_{15}NO_3S$ + NH_4 requires 235.1111, found: 235.1114.

(d) with n-butyl lithium

n-Butyllithium (0.37 ml, 2.5 M, 0.92 mmol) was added to a stirred solution of 2 (200 mg, 0.92mmol) in anhydrous tetrahydrofuran (20 ml), under a nitrogen atmosphere at -78 ºC. The solution was allowed to warm to 20 oC and was stirred overnight and became yellow. After adding some drops of a mixture of THF and water, and stirring for 30 min, the solvent was evaporated. The residue was extracted with dichloromethane (2 x 20 ml) and the extract was washed with water (30 ml). The organic layer was evaporated and the resulting residue was chromatographed using cyclohexane / ethyl acetate (2:1) to give the product O-(2'-((tert-butoxycarbonyl)amino)propyl) thiopentanoate 12 (116 mg, 45.9%) as a yellow liquid. Anal. calcd for $C_{13}H_{25}NO_3S$: C, 56.72; H, 9.09; N, 5.09%; found: C, 56.68; H, 9.15; N, 5.05%; δH (400 MHz, CD_3OD): 4.85 (1H, s, NH), 4.36 (1H, m, 1'-Hα), 4.25 (1H, m, 1'-Hβ), 4.00 (1H, m, 2'-H), 2.72 (2H, m, 2-CH_2), 1.70 (4H, m, 3-,4-CH_2), 1.41 (9H, s, 3 x CH_3), 1.16 (3H, d, J 6.8, 3'-H_3), 0.90 (3H, t, J 6.8, 5-H_3); δC (100 MHz CD_3OD): 224.18 (C=S), 157.29 (N-C=O), 78.7 ($C(CH_3)_3$), 74.3 (1`-C), 46.78 (2`-C), 45.38 (2-C), 31.74 (3-C), 27.48 (3 x CH_3), 21.61 (4-C), 16.31 (3`-C), 12.85 (5-C); v_{max}: 3328, 2961, 2933, 1683, 1409, 1366, 1248, 1175, 1077, 982, 778 cm-1; m/z: (EI) found 276 [M + H]+, other peaks at 260, 220, 204, 186, 180, 160; HRMS (EI) calcd for [M + H]+ $C_{13}H_{25}NO_3S$ + H+: 276.1629; found: 276.1631.

(e) with t-butyl lithium

Prepared following procedure for 12 above.

(f) with lithium dimethylamide.

Prepared following procedure for 12.

(g) with isopropyl magnesium chloride.

Prepared following the procedure for 12.

Reactions of 4

(a) with pyridine-2-thiolate

A solution of the sodium salt of 2-mercaptopyridine in dry THF (15 ml), formed from 2-mercaptopyridine (122 mg, 1.1 mmol) and sodium hydride (60% dispersion in mineral oil, 71 mg, 1.78 mmol), was added to a solution of thionocarbamate 4 (261 mg, 1.0 mmol). After stirring at room temperature overnight, drops of 20% acetic acid were added, and the mixture left to stir for 30 min. The solvent was evaporated, and

the residue was extracted with dichloromethane (2 x 20ml) and the extract washed with water (30 ml). The crude product was purified by chromatography using cyclohexane/ethyl acetate (1:2), to furnish the final product as a yellow oil rac methyl 2-((tert-butoxycarbonyl)amino)-3-(pyridin-2-ylthio)propanoate 11 (177 mg, 56.7%). Anal. calcd for C14H20N2O4S: C, 53.62; H, 6.45; N, 8.97%, found: C, 53.62; H, 6.47; N, 8.88%. δ_H (400 MHz): 8.32 (1H, d, J = 4.0, 6'-H), 7.41 (1H, m, 4'-H), 7.14 (1H, d, J = 8.0, 3'-H), 6.94 (1H, m, 5'-H), 6.26 (1H, s, NH), 4.50 (1H, m, 2-H), 3.63 (3H, s, OCH_3), 3.55 (2H, m, 3-H2), 1.33 (9H, s, 3 x CH3); δC(400 MHz): 171.4 (1-C), 158.8 (N-C=O), 149.7 (ipso-C), 137.1 (2 x meta-C), 121.9 (2 x ortho-C), 119.5 (para-C), 79.94 (C-$(CH_3)_3$), 54.4 (2-C), 52.2 (OCH_3), 31.9 (3-C), 28.2 (3 x CH_3), v_{max}: 3352, 2961, 1744, 1711, 1578, 1454, 1416, 1365, 1258, 1164, 1017, 797, 761 and 401 cm-1; m/z (EI) found: 312 [M]+, other peaks at 239, 219, 196, 156, 135, 123, 110, 83, 56, and 48; HRMS: m/z (EI) calcd for [M]+ $C_{15}H_{21}NO_4S$: 312.1138, found: 312.1136.

(b) with phenylthiolate.

Sodium hydride (60% dispersion in mineral oil, 71mg, 1.78 mmol) was added to anhydrous methanol (10 ml) and the mixture stirred at room temperature for 30 min. Dry thiophenol (0.28ml, 2.67mmol) was added and the mixture was stirred for a further 30 min after which time thionocarbamate 4 (261 mg, 1.0 mmol) was added. After stirring at room temperature overnight, a few drops of 20% acetic acid were added and the reaction mixture was evaporated. The residue was extracted with diethyl ether, dried and concentrated in vacuo. Final purification was achieved by column chromatography with ethyl acetate as eluent to give the desired product in the second fraction as clear oil rac methyl 2-((tert-butoxycarbonyl)amino)-3-(phenylthio)propanoate 10 (216 mg, 69.5%). Anal. calcd for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50%; found: C, 57.85; H, 6.81; N, 4.41%; δH (400 MHz): 7.39 – 7.15 (Ar-H_5), 5.32 (1H, s, NH), 4.48 (1H, m, 2-H), 3.66 (1H, dd, J = 4.7 , 7.4, 2-H), 3.45 (3H, s, OCH_3), 3.30 (2H, m, 3-H2), 1.43 (9H, s, 3 x CH_3); □C(100 MHz): 170.8 (1-C), 154.8 (N-C=O), 134.81 (ipso-C), 130.51 (2 x meta-C), 129.00 (2 x ortho-C), 126.79 (para-C), 79.94 (C-$(CH_3)_3$), 53.73 (2-C), 52.14 (OCH_3), 37.0 (3-C), 28.2 (3 x CH_3); v_{max}: 3373, 2977, 1746, 1712, 1499, 1438, 1366, 1161, 1053, 1011, 742 and 691 cm-1; m/z (EI) found: 311 [M]+ $C_{15}H_{21}NO_4S$, other peaks at 193, 122, 56; HRMS m/z: (EI) calcd for [M]+ $C_{15}H_{21}NO_4S$: 311.1186, found: 311.1183. Compound 10 has been briefly referred to before.33

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