# An Improved Synthesis of 2*H*-1,2,6-Thiadiazine 1,1-Dioxides by Condensation of β-Amino and β-Chloro α,β-Unsaturated Ketones with Sulfamides

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Symmetrically substituted β-amino α,β-unsaturated ketones react with sulfamide giving 2*H*-1,2,6-thiadiazine 1,1-dioxides in excellent yields. Unsymmetrically substituted β-amino and β-chloro α,β-unsaturated ketones also react with benzylsulfamide to yield thiadiazine derivatives in good chemical yields and excellent regioselectivity.

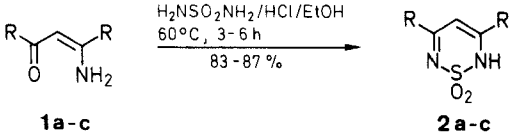
The initial report by Degering[1] on the reaction of 2,4-pentanedione with sulfamide was greatly exploited for the synthesis of simple 1,2,6-thiadiazine 1,1-dioxides,[2-4] and their benzo-homologs.[5] In a conceptually similar approach, the reaction has been extended to some other β-difunctional compounds such as malondiamidine,[6] malononitrile,[7,8] α,β-unsaturated ketones[9] and mono- or diacetals of 1,3-dicarbonyl compounds[10] for the preparation of 3,5-diamino derivatives or dihydro-1,2,6-thiadiazine 1,1-dioxides.

The reaction of sulfamide with symmetrical β-diketones leads to a single product, but with unsymmetrically substituted β-diketones it gives a mixture of tautomers; moreover, on reaction with monosubstituted sulfamides the latter yield a mixture of regioisomers.[2-4]

The reactivity of β-diketones towards sulfamides depends on both the electronic and steric requirements of the substituents in the β-diketone. Thus, 3,5-diphenyl-2*H*-1,2,6-thiadiazine 1,1-dioxide has been obtained in less than 45%, and its 2-butyl derivative in only 39%,[2] while the 3,5-di-*tert*-butyl-1,2,6-thiadiazine 1,1-dioxide has never been synthesized.

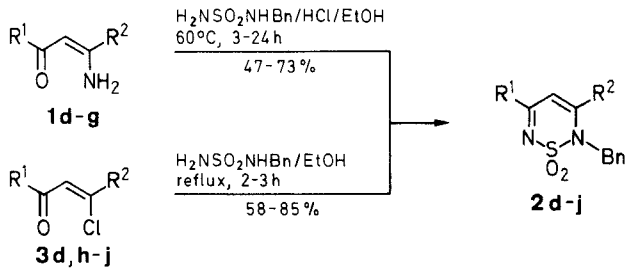
We have recently shown that β-amino α,β-unsaturated ketones are versatile starting compounds in the synthesis of a great variety of heterocycles and are advantageous compared to the corresponding β-diketones;[11-13] herein we report the preparation of 2*H*-1,2,6-thiadiazine 1,1-dioxides by reaction with sulfamides.

The synthesis of symmetrical 3,5-disubstituted 2*H*-1,2,6-thiadiazine 1,1-dioxides was tested by reaction of the β-amino α,β-unsaturated ketones **1a–c** with sulfamide. The reaction was carried out in hydrogen chloride saturated anhydrous ethanol and the results show that 3,5-di-*tert*-butyl- and 3,6-diphenyl derivatives were obtained in excellent yield. The yield for the latter is greatly improved from that previously described for the synthesis from dibenzoylmethane.[2]




| 1,2 | a | b | c |
|---|---|---|---|
| R | Me | Ph | *t*-Bu |

The process was extended to the regioselective preparation of 2*H*-1,2,6-thiadiazine 1,1-dioxides from the β-amino α,β-unsaturated ketones **1d–g** or the β-chloro α,β-unsaturated ketones **3d,h–j** and benzylsulfamide. The reactions of β-amino α,β-unsaturated ketones were carried out at 60°C in hydrogen chloride saturated, anhydrous ethanol leading to **2e** and **2f** as a single product and to mixtures or **2d** and **2g** and their regioisomers (70:30 and 95:5 respectively) as shown by $^1$H-NMR on the reaction mixture; the latter are obtained as pure compounds after recrystallization. The β-chloro α,β-unsaturated ketones **3d,h–j** are more reactive than the β-amino derivatives and they are easily transformed into the 2*H*-1,2,6-thiadiazine 1,1-dioxides **2d,h–j** by refluxing in ethanol with benzylsulfamide; moreover the desired thiadiazines are obtained regiospecifically and in higher yields than from β-diketones or β-amino α,β-unsaturated ketones.




| 1–3 | $R^1$ | $R^2$ | 1–3 | $R^1$ | $R^2$ |
|---|---|---|---|---|---|
| **d** | Et | Me | **h** | Et | H |
| **e** | *i*-Pr | Me | **i** | *i*-Pr | H |
| **f** | $PhCH_2CH_2$ | Me | **j** | 4-$MeOC_6H_4$ | H |
| **g** | Ph | Me | | | |

The results obtained show that β-amino and β-chloro α,β-unsaturated ketones are better starting materials than β-diketones in the synthesis of 1,2,6-thiadiazine 1,1-dioxides, not only giving better chemical yields, but also providing excellent regioselectivity in their reactions with benzylsulfamide.

**Reaction of β-Amino α,β-Unsaturated Ketones with Sulfamides; General Procedure:**

Through a solution of sulfamide (0.96 g, 10 mmol) or benzylsulfamide (1.86 g, 10 mmol) and the corresponding β-amino derivative **1a–g** (10 mmol) in anhydr. EtOH (20 mL) at r.t., is bubbled anhydr. HCl for 15 min. The mixture is heated at 60°C while stirring for the time indicated in the Table and then cooled to r.t. The excess of HCl is evacuated by bubbling $N_2$ for 15 min, and the EtOH is evaporated *in vacuo* (Rotavapor). The residue is recrystallized from the appropriate solvent.

From the reaction mixture of **1d** with benzylsulfamide the compound **2d** is obtained by recrystallization of the residue from EtOH

**Table.** 1,2,6-Thiadizine 1,1-Dioxides **2a–j** Prepared

| Product | Time (h) | Yield[a] (%) | mp (°C)[b] (solvent) | Molecular Formula[c] or Lit. mp (°C) | $^1$H-NMR (solvent[e]/TMS) $\delta$, $J$ (Hz) | MS (70 eV)[d] $m/z$ (%) |
|---|---|---|---|---|---|---|
| **2a** | 3 | 88 | 145–146 ($H_2O$) | 147[1] | 2.15 (s, 6H, Me), 5.80 (s, 1H, H-4), 8.50 (br s, 1H, NH) | 160 (100) |
| **2b** | 6 | 83 | 278–279 (EtOH) | 278–279[5] | 6.82 (s, 1H, H-4), 7.40–8.10 (m, 11H, Ph, NH) | 284 (40), 222 (100) |
| **2c** | 6 | 87 | 244–245 (EtOH) | $C_{11}H_{20}N_2O_2S$ (244.4) | 1.25 (s, 18H, Me), 6.05 (s, 1H, H-4), 8.40 (br s, 1H, NH) | 244 (16), 229 (100) |
| **2d** | 3 | 58 (47)[f] | 56–57 (EtOH) | $C_{13}H_{16}N_2O_2S$ (264.3) | 1.13 (t, 3H, $J$ = 7, $CH_3CH_2$), 2.07 (s, 3H, Me), 2.47 (q, 2H, $J$ = 7, $CH_3CH_2$), 5.07 (s, 2H, $CH_2Ph$), 5.88 (s, 1H, H-4), 7.30 (s, 5H, Ph) | 264 (5), 91 (100) |
| **2e** | 3 | 73 | 122–123 (EtOH) | $C_{14}H_{18}N_2O_2S$ (278.4) | 1.18 (d, 6H, $J$ = 7, $Me_2CH$), 2.20 (s, 3H, Me), 2.70 (m, 1H, $J$ = 7, $Me_2CH$), 5.20 (s, 2H, $CH_2$), 6.03 (s, 1H, H-4), 7.43 (s, 5H, Ph) | 278 (4), 91 (100) |
| **2f** | 3 | 62 | 89–90 (EtOH) | $C_{19}H_{20}N_2O_2S$ (340.4) | 2.03 (s, 3H, Me), 2.85 (m, 4H, $CH_2CH_2$), 5.07 (s, 2H, $CH_2Ph$), 5.83 (s, 1H, H-4), 7.20 (s, 5H, Ph), 7.28 (s, 5H, Ph) | 340 (10), 91 (100) |
| **2g** | 24 | 59 | 119–120 (EtOH) | 119–120[4] | 2.28 (s, 3H, Me), 5.23 (s, 2H, $CH_2$), 6.67 (s, 1H, H-4), 7.33 (s, 5H, $PhCH_2$), 7.75 (m, 5H, Ph) | 312 (6), 91 (100) |
| **2h** | 2 | 64 | 67–68 (EtOH) | $C_{12}H_{14}N_2O_2S$ (250.3) | 1.17 (t, 3H, Me), 2.50 (q, 2H, $J$ = 7, $CH_2Me$), 4.90 (s, 2H, $CH_2Ph$), 5.73 (d, 1H, $J$ = 7, H-4), 7.05 (d, 1H, $J$ = 7, H-3), 7.33 (s, 5H, Ph) | 250 (6), 91 (100) |
| **2i** | 2 | 85 | 69–70 (EtOH) | $C_{13}H_{16}N_2O_2S$ (264.3) | 1.15 (d, 6H, $J$ = 7, Me), 2.67 (m, 1H, $J$ = 7, $CHMe_2$), 4.87 (s, 2H, $CH_2$), 5.75 (d, 1H, $J$ = 7, H-4), 7.08 (d, 1H, $J$ = 7, H-3), 7.35 (s, 5H, Ph) | 264 (5), 91 (100) |
| **2j** | 3 | 58 | 112–113 (EtOH) | $C_{17}H_{16}N_2O_3S$ (328.4) | 3.83 (s, 3H, MeO), 4.95 (s, 2H, $CH_2$), 6.28 (d, 1H, $J$ = 7, H-4), 6.93 (d, 2H, $J$ = 8, $m$-H), 7.18 (d, 1H, $J$ = 7, H-3), 7.38 (s, 5H, Ph), 7.95 (d, 2H, $J$ = 8, $o$-H) | 328 (9), 91 (100) |

[a] Yields refer to pure and isolated compounds.
[b] mp, uncorrected, were measured on capillary tube in a Büchi apparatus.
[c] Satisfactory microanalyses obtained: C ±0.18, H ±0.15, N ±0.19.
[d] Determined on a Hewlett-Packard 5988A mass spectrometer by E.I.
[e] Registered on a Bruker AC80 at 80 MHz. The solvents used were: $CD_3CN$ for **2a, c, d, f**; acetone-$d_6$ for **2b, e, g**; and $CDCl_3$ for **2h, i, j**.
[f] Number in parentheses refers to the yield obtained from **1d**.

(Table). The purification of its regioisomer 2-benzyl-3-ethyl-5-methyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (**2'd**) was unsuccessful (recrystallization or TLC). GC-MS analyses (methyl silicone gum, 12 m × 0.2 mm glass capillary column; He as carrier gas; 0.T. 240 °C) of the mother liquor shows two peaks: **2d** ($t_R$ = 6.63 min, 25%) and **2'd** ($t_R$ = 6.45 min, 75%).

$^1$H-NMR (from the mixture, in $CD_3CN$): $\delta$ = 1.09 (t, 3H, $J$ = 7 Hz, $CH_3CH_2$), 2.29 (s, 3H, $CH_3$), 2.39 (q, 2H, $J$ = 7 Hz, $CH_3CH_2$), 5.06 (s, 2H, $CH_2Ph$), 5.73 (s, 1H, 4-CH), 7.30 (s, 5H, Ph).

MS: $m/z$ (%) = 264 ($M^+$, 4), 91 (100).

**Reaction of β-Chloro α,β-Unsaturated Ketones with Benzylsulfamide; General Procedure:**

A mixture of benzylsulfamide (1.86 g, 10 mmol) and the corresponding β-chloro derivative **3d,h–j** (10 mmol) in anhydr. EtOH (20 mL) is refluxed for the time indicated in the Table. After this period the solution is cooled to r.t. and the EtOH is removed (Rotavapor). The solid residue is recrystallized from the appropriate solvent.

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