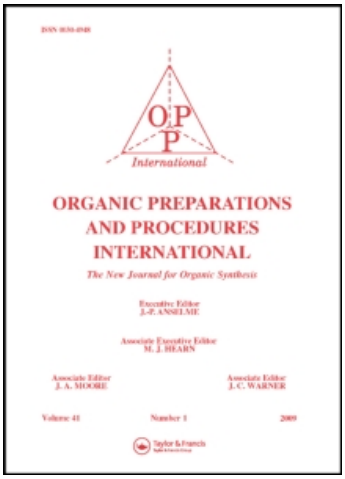

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IMPROVED LARGE SCALE SYNTHESIS OF 2-TRIMETHYLSILOXY-1,3-BUTADIENE

Roy T. Uyeda[a]; Phong Vu[a]; Daniel D. Holsworth[a]
[a] 2325 Camino Vida Roble, Department of Chemistry, Ontogen Corporation, Carlsbad, CA

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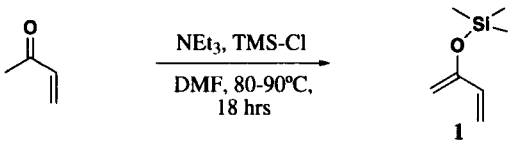
IMPROVED LARGE SCALE SYNTHESIS OF 2-TRIMETHYLSILOXY-1,3-BUTADIENE

Submitted by (09/10/01) Roy T. Uyeda, Phong Vu and Daniel D. Holsworth*

Ontogen Corporation, 2325 Camino Vida Roble
Department of Chemistry, Carlsbad, CA, 92009

We recently required multigram quantities of 2-trimethylsiloxy-1,3-butadiene (**1**), a versatile Diels-Alder reaction component used to synthesize a number of ring systems, including substituted pyranones,[1] pyridones,[2] and cyclohexanones.[1] A number of methods exist for the synthesis of this compound,[3] the procedure outlined by Jung[4] being the most convenient. Although, Jung's procedure

was successfully repeated, the method is both time-consuming and low yielding for large-scale syntheses. In particular, the evaporation of pentane on a 100 g scale required several days and resulted in low yields of diene **1** (~ 25%) due to partial polymerization of the diene during fractional distillation. In pursuit of a cost-effective procedure for synthesizing this important diene, we developed a higher yielding, more convenient method for producing diene **1** on a moderately large-scale (100 g), based on the amount of methyl vinyl ketone.



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In order to expedite the original work-up procedure and overcome the polymerization problems, the development of a more efficient method for the removal of **1** from the reaction mixture was sought. In the original method,[4b] diene **1** was removed by washing with sodium bicarbonate and extraction into pentane, followed by fractional distillation. It was found that simple application of vacuum to the reaction mixture (with no external heat) was sufficient to extract the diene from the reaction mixture without polymerization. The crude diene, contaminated with small amounts of DMF, trimethylsilyl chloride, and triethylamine, was washed three times with water for further purification. Finally, the diene was dried over anhydrous magnesium sulfate and filtered into a flask for storage.

Once a reproducible procedure was developed, the number of equivalents of trimethylsilyl chloride and triethylamine were adjusted in an effort to optimize the yield of diene **1** (**Table 1**). *Entry 1* shows a 52% yield of diene with one equivalent of each reagent, and a 10% yield of the hexamethyldisiloxane by-product.

Table 1. Optimization of 2-Trimethylsiloxy-1,3-Butadiene Synthesis

Entry	MVK[a]	TMS-Cl[b]	TEA[c]	Diene Yield	% TMS-O-TMS	% Yield
1	100g	1.1	1.1	104g	10	52
2	100g	1.0	1.1	120g	5	58
3	100g	1.05	1.05	100g	40	n/a

a) Methyl vinyl ketone; b) Number of equivalents of trimethylsilyl chloride; c) Number of equivalents of triethylamine.

Hexamethyldisiloxane was presumably formed by hydrolysis of excess trimethylsilyl chloride during the washing stage. *Entry 2* displays the best conditions: 1.0 equivalent of trimethylsilyl chloride and 1.1 equivalents of triethylamine. The reaction produced only 5% of the hexamethyldisiloxane by-product. Interestingly, using 1.1 or 1.05 equivalents of each reagent (*Entries 1* and *3*, respectively) resulted in lower yields of diene **1** and higher amounts of TMS ether by-product.

There are several advantages to this method over the original procedure.[4b] It requires no extraction into pentane, the diene is not exposed to a saturated solution of sodium bicarbonate, and no

evaporation of pentane is employed. In addition, there is no distillation of diene **1** conducted with the application of external heat[4b], the yields of diene **1** are much higher, and lastly the work-up can be performed on 100 g scale in an afternoon.

EXPERIMENTAL SECTION

All reagents were purchased from Aldrich and used without further purification. Solvents used were of HPLC grade and used without further purification. ^{1}H NMR were recorded in $CDCl_3$ at 300 MHz, on a Varian Gemini spectrometer and referenced to the solvent.

Procedure.- A 3-neck round bottom flask equipped with a reflux condenser and two addition funnels was charged with triethylamine (218.83 mL, 1.1 eq., 1.57 mol) in DMF (800 mL). One addition funnel was charged with methyl vinyl ketone (100 g, 1.43 mol) in DMF (100 mL), and the other with trimethylsilyl chloride (181.48 mL, 1.0 eq., 1.43 mol) in DMF (100 mL). The vessel was placed in an oil bath pre-heated to 80-90° and the reagents added dropwise simultaneously. After 18 hrs at 80-90°, the reaction mixture was cooled to room temperature, filtered, and placed into a round bottom flask attached to a distillation apparatus. Under a 150 mm-Hg vacuum with no external heat, the diene slowly distilled into a pre-cooled (-78°) receiver flask. Complete distillation of the diene from the reaction mixture required approximately 3 hrs, and then it was rapidly washed with cold water (3 x 25 mL), dried over anhydrous magnesium sulfate, and filtered into a flask for storage. The diene yield was 120 g (58%)[5]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.076 (s, 0.9 H [TMS ether)), 0.24 (s, 9H), 4.36 (d, J = 3.6, 2H), 5.09 (dt, J = 2.1, 9, 1H), 5.48 (dd, J = 2.1, 16.5, 1H), 6.21 (dd, J = 10.5, 17.1, 1H), identical with the data in the literature.[4b]

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* To whom requests for reprints should be addressed: Pfizer Global Research and Development, Department of Chemistry, Bldg. 28-1, 2800 Plymouth Rd, Ann Arbor, MI 48105. E-mail: daniel.holsworth@pfizer.com

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5. Compound **1** was contaminated with 5% of hexamethyldisiloxane (δ 0.076) as based on integration of the ^{1}H NMR spectrum (see Table 1, entry 2). The by-product could not be removed with distillation. The by-product is chemically inert in hetero Diels-Alder reactions conducted at Ontogen Corporation.

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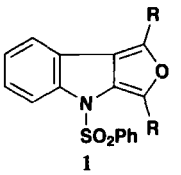
AN EFFICIENT SYNTHESIS OF 1,3-DIMETHYL-4-(PHENYLSULFONYL)-4*H*-FURO[3,4-*b*]INDOLE

Submitted by Jun Jiang and Gordon W. Gribble*
(02/19/02)
Department of Chemistry, Dartmouth College, Hanover, NH 03755

The fused heterocyclic ring system 4*H*-furo[3,4-*b*]indole (**1**) has served admirably over the past 20 years as a stable indole-2,3-quinodimethane (**2**) synthetic analogue in Diels-Alder reactions.[1,2] We have utilized this ring system in syntheses of isomeric benzocarbazoles,[1a,b,f] *bis*(benzo[*b*]carbazoles),[1c] and pyridocarbazoles including the antitumor alkaloid ellipticine (**3**).[1d,e,2h] Our synthesis of ellipticine successfully employed the 1,3-dimethyl analogue **1** (R = Me). Unfortunately, our two original methods for the syntheses of **1** (R = Me) were lengthy. We now describe a very convenient and efficient synthesis of 1,3-dimethyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (**1**, R = Me). Our new method has the advantage over the earlier methods in that oxidation and reduction steps are avoided in the manipulation and formation of the furan ring.



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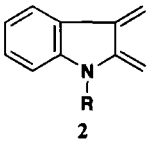

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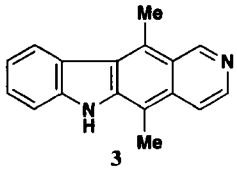

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As we have previously described, indole (**4**) is readily converted in high yield to 3-acetyl-1-(phenylsulfonyl)indole (**6**) *via* 1-(phenylsulfonyl)indole (**5**) (Scheme 1). Treatment of **6** with lithium diisopropylamide (LDA) followed by the addition of *tert*-butyldimethylsilyl triflate (TBSOTf) gives enol ether **7**. Without isolation, **7** was further treated with LDA and then acetaldehyde to afford alcohol **8**. Exposure of **8** to trifluoroacetic acid (TFA) effects hydrolysis of the silyl enol ether and cyclodehydration to give the desired furoindole **9** in 49% yield from **6**. This synthesis of furoindole **9** represents a marked improvement of our two previous methods in terms of efficiency, reproducibility, and length.