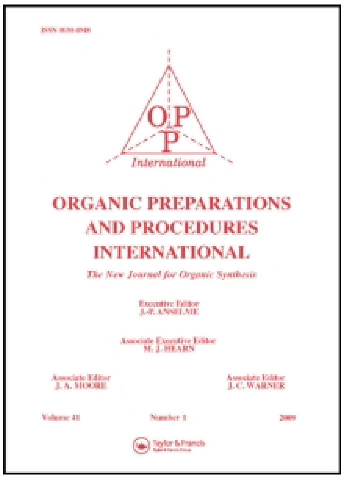

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SYNTHESIS OF DISULFIDES BY THE OXIDATIVE COUPLING OF THIOLS WITH CALCIUM HYPOCHLORITE AND SILICA GEL IN HEXANE

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SYNTHESIS OF DISULFIDES BY THE OXIDATIVE COUPLING OF THIOLS WITH CALCIUM HYPOCHLORITE AND SILICA GEL IN HEXANE

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Thiols (R-SH, **2**) and disulfides (RS-SR, **3**) occur in nature and reversible reactions between them constitute important biological processes such as in the interconversion of cysteine-cystine.[1] Oxidative coupling of **2** to **3** using laboratory chemical reagents[2,3] has been achieved very easily even with atmospheric oxygen (and alumina as the solid base) under mild conditions.[4] We have recently reported in this Journal a convenient oxidation of sulfides[5a] and dethioacetalization of S,S-acetals[5b] with *in situ* generated ferric nitrate supported on silica gel. As a part of our recent interest in the chemistry of sulfur compounds,[5] a new inquiry into the selective oxidation of thiols to disulfides is now proposed using stable, inexpensive, and environmentally friendly reagent, calcium hypochlorite [$Ca(OCl)_2$, **1**], by taking advantages of solid-solution biphasic systems.[5,6]

As demonstrated previously,[5] the *in situ* procedure is straightforward. Thus, the oxidation of **2** can be achieved simply by efficient stirring of a suspension of silica gel, calcium hypochlorite, and the thiol in an organic solvent at 20°. In order to optimize conditions, reaction parameters were first examined using benzenethiol **2a** as the test substrate. We have experienced that efficiency of supported reagent systems is highly dependent on the choice of support, solvent, and presence of water.[5] For example, a small but definite amount of water is essential to effect the reaction. Indeed, attempted reactions of **2a** in hexane using commercial (Fuji-Silysia BW-300), moist (*vide infra*), and precalcinated (500°, 6 h) silica gels gave diphenyl disulfide **3a** in 87, 96 (Entry 1), and 35% yield, respectively, after 20 min. Moreover, use of silica gels with a smaller or a larger water content led to decreased yields. Comparative runs using various commercial silica gels (*vide infra*) exhibited no appreciable difference in the yields of **3a**. On the other hand, when no silica gel was added, the reaction was slow, and **1** and/or its degradation product(s) adhered to the walls of the reaction vessel, which made the work-up very troublesome and led to erratic results. Further studies showed that hexane is superior to other solvents (CH_2Cl_2, $CHCl_3$, CCl_4, acetone, AcOEt, ether, benzene) in terms of conversion of **2a** and yield of **3a**. Even though the reaction in ethanol gave **3a** in 98% yield (GC)

$$\underset{(\mathbf{2})}{\mathbf{2\ R\text{-}SH}} \xrightarrow[\text{Hexane, }20^\circ]{Ca(OCl)_2\ (\mathbf{1})\text{, moist Silica gel}} \underset{(\mathbf{3})}{\mathbf{R\text{-}S\text{-}S\text{-}R}}$$

a) $R = Ph$
b) $R = 4\text{-}MeOC_6H_4$
c) $R = 2\text{-}MeC_6H_4$
d) $R = 3\text{-}MeC_6H_4$
e) $R = 4\text{-}MeC_6H_4$
f) $R = 4\text{-}BrC_6H_4$
g) $R = 4\text{-}ClC_6H_4$
h) $R = 4\text{-}O_2NC_6H_4$
i) $R = PhCH_2$
j) $R = n\text{-}C_6H_{13}$
k) $R = n\text{-}C_8H_{17}$
l) $R = n\text{-}C_{10}H_{21}$
m) $R = n\text{-}C_{14}H_{29}$
n) $R = c\text{-}C_5H_9$
o) $R = c\text{-}C_6H_{11}$

under comparable conditions, contamination of **3a** with oxidant residues made its purification somewhat tedious. Thus, hexane is the solvent of choice for the present reaction and, in addition, its lower toxicity and low cost favorably meet practical, environmental, and economic requirements.

Based on the preliminary results, oxidative coupling of a variety of thiols was performed with a $Ca(OCl)_2$/moist silica gel system in hexane at 20°. Thus, benzenethiols **2a-h** gave the corresponding disulfides **3a-h** in excellent to quantitative yields within reasonable periods of time, irrespective of the electronic properties of the substituents (Entries 1, 2, 5-8) and/or their positions on the benzene-ring (Entries 3-5). It may be emphasized that although the reaction of a deactivated aromatic thiol such as **2h** with *Clayfen* (Montmorillonite K10 doped with ferric nitrate), known as a potent and versatile oxidizing agent,[7a] afforded **3h** in only 58% yield,[7b] the present procedure proceeded quantitatively (Entry 8). The utility of $Ca(OCl)_2$/moist silica gel system for oxidation of aliphatic thiols bearing medium to long alkyl chains (Entries 10-13) and alicyclic thiols (Entries 14,15) is also apparent. It is noteworthy that a large scale synthesis of **3a** from **2a** can be successfully achieved without any difficulty (*vide infra*).

In summary, the $Ca(OCl)_2$/moist silica gel system provides a practical (*viz*., inexpensive, simple, mild, fast, high-yielding) procedure for disulfide synthesis from a variety of thiols.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded with a JEOL PMX-60 (60 MHz) spectrometer for solutions in deuteriochloroform using TMS as an internal standard. Analytical gas chromatography was performed on a Shimadzu GC-4CM or GC-14B instrument with a 2 mx5mm0 glass column packed with 3% Silicone OV-17 on Uniport HP or 5% PEG-20M on Chromosorb WAW-DMCS and interfaced with a Shimadzu Chromatopac C-R6A integrator, with temperature programming. Melting points were determined on a Yanagimoto MP-S3 melting point apparatus and were uncorrected. Thiols **2a-o** and calcium hypochlorite (Kokusan Chemical Works; available chlorine 65% by iodometry) were commercial chemicals and were used as received. Addition of deionized water (0.1 g) to Fuji-Silysia Silica Gel BW-300 (1 g) in portions followed by vigorous shaking of the mixture for a few minutes upon every addition afforded a free-flowing powder (moist silica gel; water content 9 wt-%), 1 g of which was immediately used for the oxidation. Fuji-Silysia Silica Gel BW-127ZH, Merck Silica Gel 60, and Wakogel C-200 were preloaded with deionized water as above. Solvents were dried, distilled, and stored over molecular sieves.

Oxidation Procedure.- A 30 mL two-necked round-bottom flask, equipped with a Teflon-coated stirrer bar, a reflux condenser and a glass gas-inlet tubing connected to an argon-filled balloon, was arranged for conducting the reaction under inert atmosphere by connecting the top of the condenser to a liquid paraffin trap *via* a flexible silicone rubber tubing. The flask was charged with **2a** (0.110 g, 1 mmol), hexane (10 mL), $Ca(OCl)_2$ powder (0.066 g, 0.3 mmol as available chlorine), and freshly prepared moist silica gel (1 g). A gentle stream of dry argon was passed through the reaction system. The resultant heterogeneous mixture was vigorously stirred at 20° for 20 min; care was taken in maintaining efficient stirring during the reaction to ensure efficient contact and to attain reproducible results. The reaction mixture was filtered through a sintered glass funnel and the filter cake was washed thoroughly with portions of ether (total 50 mL). Removal of the solvent on a rotary evaporator, followed by chromatography on silica gel (hexane-ethyl acetate), gave pure diphenyl disulfide **3a** (0.105 g, 96%; mp 60-61°, reported mp[8] 62-63°: ^{1}H NMR, GC, and TLC).

TABLE 1. Oxidative coupling of thiols **2** to the disulfides **3**[a]

Entry No.	Thiol	Ca(OCl)$_2$ (mmol)	Time (min)	Disulfide **3** (%)[b]	mp. (°C) or	bp. (°C/torr)
					Found	Reported
1	**2a**	0.3	20	96	60-61	62-63[c]
2	**2b**	0.35	20	quant.	42-44	44-45[c]
3	**2c**	0.3	30	94	37-38	38-39[c]
4	**2d**	0.3	20	98	181-183/5	177/3[c]
5	**2e**	0.3	20	96	47-48	48[c]
6	**2f**	0.3	20	92	93-95	92-94[c]
7	**2g**	0.3	30	99	69-70	70[c]
8	**2h**	0.35	30	quant.	182-183	182[c]
9	**2i**	0.5	30	94	70-71	71-72[c]
10	**2j**	0.5	30	94	177-179/18	181-182/21[d]
11	**2k**	0.5	30	91	197-199/10	199-200/10[e]
12	**2l**	0.5	30	90	208-209/6	210-212/7[f]
13	**2m**	0.5	30	89	47-48	49-50[g]
14	**2n**	0.5	30	87	129-130/5	130.5-131/5[h]
15	**2o**	0.5	30	93	147-149/4	153-156/5[i]

a) At 20°, under argon; thiol 1.0 mmol, hexane 10 mL, moist silica gel 1.0 g (1.5 g for Entries10-15). b) Isolated yield based on starting **2**. c) *Ref.* 8. d) *Beilstein*, **1**, IV, 1707. e) *Beilstein*, **1**, IV, 1769. f) *Beilstein*, **1**, IV, 1823. g) *Beilstein*, **1**, III, 1806. h) *Beilstein*, **6**, IV, 17. i) *Beilstein*, **6**, IV, 81.

A gram scale synthetic reaction carried out with **1** (9 mmol, 1.98 g), **2a** (30 mmol, 3.30 g), and moist silica gel (12 g) in hexane (40 mL) in a 100 mL round-bottom three necked flask, fitted with the same equipment as those employed in the small scale experiments gave 3.11 g of **3a** (95%) after 30 min.

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NEW SPIROPYRAN-4-YLINDOLIDINE DERIVATIVES FROM THE REACTION OF 2-OXO-3-CYANOMETHYLIDENE-2,3-DIHYDROINDOLES WITH CYCLOHEXANEDIONES AND PHENOLS

Submitted by
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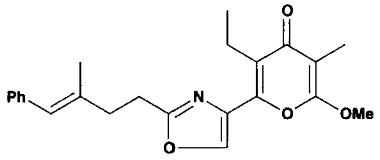
The activity of phenoxan (**1**) and 6-aryl-4-hydroxy-3-methyl-2H-mercapto-2-pyranone (**2**) as anti HIV agent has stimulated recent interest in chemistry of 4-H-pyrans.[1,2] As indolenine **3** has also been reported to possess antibacterial and anti-inflammatory activity,[3-6] the synthesis of compounds having both indolidenene and 4-H-pyran rings seemed of value.



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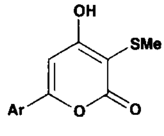

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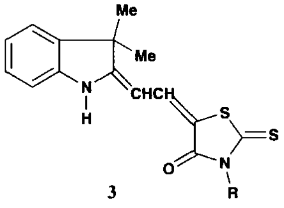

3

The synthesis of 2-amino-3-substituted-4H-pyrans *via* addition of active methylene ketones, naphthols and phenols to ylidene malononitriles in ethanolic piperidine has been extensively utilized in the literature.[7-9] Attempted addition of **4a,b** to 1,3-cyclohexanedione (**5**) under similar conditions led to self-condensation of the dione.[8] On the other hand, treatment of **4a,b** with **5** in refluxing acetic