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# AN EFFICIENT SYNTHESIS OF 6,6-DIMETHYL-2-(4-NITROPHENYL)-1-(R-PHENYL)-4,5,6,7-TETRAHYDRO-1*H*-4-INDOLONES USING A SOLID SULFATED ZIRCONIA AS CATALYST

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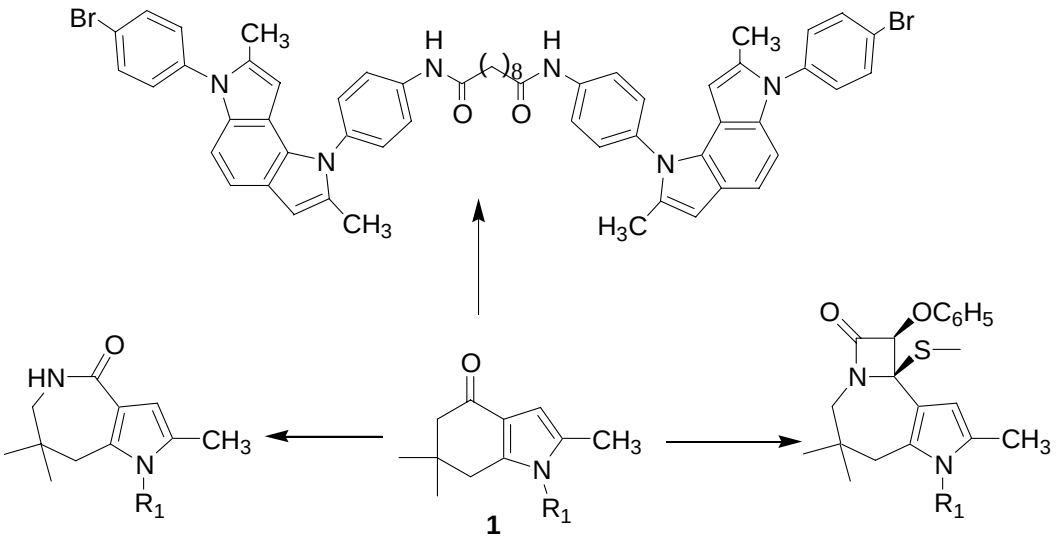
**Abstract** – Sulfated zirconium has been found to be an excellent substitute for conventional acids in the tetrahydroindolone derivatives synthesis, resulting in milder reaction conditions, bringing down reaction temperature and formulating more efficient isolation and purification procedure.

Cancer is one of the main causes of death in the world despite considerable progress in the understanding of its biology and pharmacology. The traditional therapeutic strategies for the treatment of this disease are surgery, radiotherapy, immunotherapy and chemotherapy. For the time being, 50% of the patients diagnosed with cancer are cured either through one of these methods or by a combination of them. For some types of disseminated cancers, chemotherapy is the only effective therapy because it distributes anticancer drugs through the circulatory system.[1]

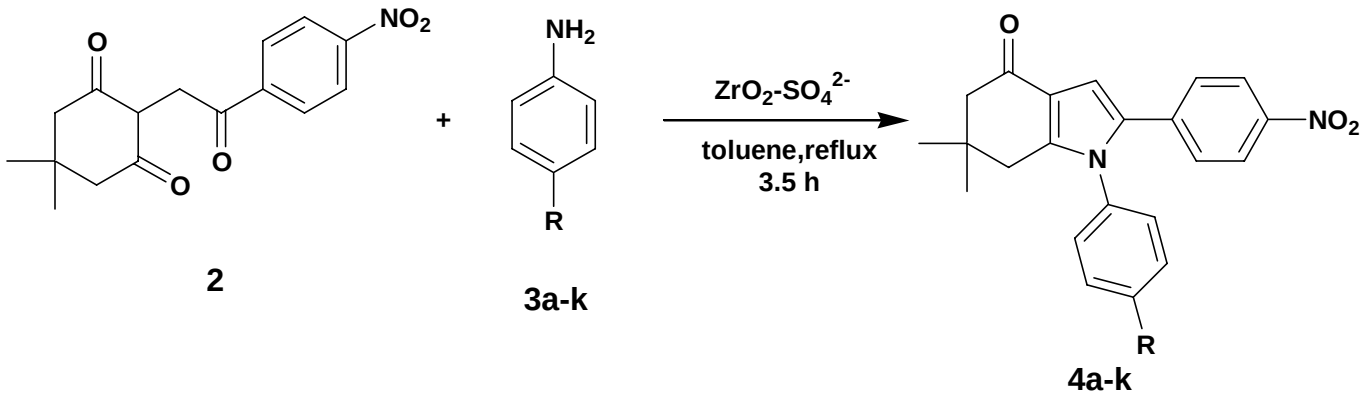
We are currently engaged in a program aimed at synthesizing new heterocyclic compounds that inhibit the growth of cancer cells.[2-5] The synthetic routes used to prepare such compounds have utilized as key intermediate tetrahydroindolones like (**1**) (Scheme 1). The general procedure to prepare pyrrole derivatives uses the reaction of an enolizable 1,4-dicarbonyl compounds with a dehydrating agent ($H_2SO_4$, $P_2O_5$, $ZnCl_2$, etc) ammonia or a primary amine, or an inorganic sulfide (Paal-Knorr reaction).[6] Unfortunately this method still suffered from some disadvantage, such as requiring severe conditions, needing excess of the reagents, using dangerous reagents or working with tedious work up procedures.




Scheme 1

Therefore, it is desirable to use heterogeneous catalysts because of their easy isolation from the products by filtration and the possibility of recycling can results in waste stream reduction for a better preservation of the environment.[7] Zirconia-Sulfate ($ZrO_2$-$SO_4^{2-}$) has been shown to the active for reaction including isomerization of n-butane, cracking , alkylation, and esterification.[8] Recently considerable attention has been devoted to heterogeneous organic transformations utilizing sulfated zirconia as catalyst because of its super-acidity, non-toxicity and low cost.[9] Superacids, defined as materials with an acid strength stronger than 100% sulfuric acid, have many benefits such as the ability to lower reaction temperatures and to form reaction intermediates unattainable with conventional acid catalysts. Most superacids currently in use are homogeneous liquid catalysts, which present many problems. Liquid catalysts are difficult to separate from the product stream. Large amounts of catalyst are usually required, often leading to wasted catalyst. Furthermore, the liquid acids are corrosive to the reactive system and the liquid waste is an environmental hazard.

To explore further applications of Zirconia-Sulfate in organic synthesis, herein we report an efficient unprecedented cyclization of 1,4-dicarbonyl compounds to tetrahydroindolones using a slurry of Zirconia-Sulfate in toluene and substituted anilines. In a typical experiment, treatment of tricarbonyl compound (**2**) with aniline in the presence of a mixture of sulfated zirconia in toluene at reflux by 3.5 h gave the tetrahydroindolone (**4a**) in 80 % yield. Under identical reaction conditions, the substituted anilines (**3b-k**) afforded the corresponding indolones (**4b-k**) in good yields. The ratio of tricarbonyl compound/ catalyst (1:1 wt) proved to be optimal system for prepared the representative set of compounds listed on Table 1. When we used a lesser relation than this ratio the yields and rates of conversion to 4-indolones was poor. So, we hypothesized that the Lewis acid sites of tetragonal zirconium catalyze the reaction instead of usual dehydrating agents. Further studies of catalyst role on the reaction are currently on process.




| | a | b | c | d | e | f | g | h | i | j | k |
|---|---|---|---|---|---|---|---|---|---|---|---|
| R | H | 4-$CH_3$ | 4-$OCH_3$ | 4-F | 4-Cl | 4-Br | 4-I | 4-$NO_2$ | 3-$CH_3$ | 3-Cl | 3-Br |

Scheme 2

**Table 1.** Yields and Physical Data for Tetrahydroindolones(**4a-k**)

| Compound | R | Yield % | Mp $^oC$ | IR $cm^{-1}$ | Ref. |
|---|---|---|---|---|---|
| **4a** | H | 80 | 245-6 | 1667 | 5 |
| **4b** | 4-$CH_3$ | 60 | 260-2 | 1657 | 5 |
| **4c** | 4-$OCH_3$ | 63 | 205-7 | 1657 | 5 |
| **4d** | 4-F | 63 | 265-7 | 1660 | 5 |
| **4e** | 4-Cl | 55 | 246-7 | 1660 | 5 |
| **4f** | 4-Br | 55 | 224-5 | 1659 | 5 |
| **4g** | 4-I | 50 | 130-131 | 1661 | 5 |
| **4h** | 4-$NO_2$ | 50 | 269-70 | 1664 | 5 |
| **4i** | 3-$CH_3$ | 55 | 255-71 | 1657 | 5 |
| **4j** | 3-Cl | 65 | 225-7 | 1661 | 5 |
| **4k** | 3-Br | 50 | 226-7 | 1661 | 5 |

## EXPERIMENTAL

The structure of all compounds were supported by IR, $^1$H-NMR and MS spectral data which are identical to those reported.[5] Preparation of the catalyst: 3.2 mL of sulfuric acid (98 % wt) was mixed with 4 mL of deionized water while 20 mL of zirconium isopropoxide (70% wt in 1-propanol) were diluted with 30.5 mL

of n-propanol. The acid solution was added by drop-wise to the alcoxide under vigorous stirring, until a viscous solution was obtained. The gel was heated at 333 K in order to evaporate excess alcohol. After, the dry gel was calcinated at 873 K for 7 h in air to finally to obtain a white solid. The X-Ray powder diffraction analysis of the sample revealed the presence of tetragonal zirconia sulfate species.[10]

**Synthesis of 6, 6-Dimethyl-2-(4-nitrophenyl)-1-(4-R-phenyl)-4, 5, 6,7-tetraydro-1*H*-4-indolones (4a-k). 6,6-Dimethyl-2-(4-nitrophenyl)-1-phenyl-4,5,6,7-tetraydro-1*H*-4-indolone (4a)**

To a reaction vessel with a reflux condenser were successively added 5,5-Dimethyl-2[2-(4-nitrophenyl)-2-oxoethyl]ciclohexane-1.3-dione(0.060 g, 0.20 mmol), sulfate zirconium (0.080 g), aniline (0.02 mL) and toluene (3mL). After the resulting mixture was stirred at 100 $^{o}$C for 3 h, the sulfate zirconium was separated by filtration. The filtrate was concentrated and subjected to column chromatography on silica gel(3 g) with a mixture of n-hexane and ethyl acetate (3:1), giving **4a** as a colorless solid (0.056 g 80%), mp. 245-246 $^{o}$C ($CH_2Cl_2$/ Hexane); $^1$H-NMR ($CDCl_3$, 200 MHz) δ 1.11 (H-8,8'), 2.43 (H-5), 2.54 (H-7), 6.97 (H-3), 7.16 - 8.01 (Ar-H); Anal. Calcd for $C_{22}H_{20}N_2O_3$: C, 73.31; H, 5.59; N, 7.77. Found: C, 73.38; H, 5.57, N, 7.75.

**Compound** (**4b):** $^1$H-NMR ($CDCl_3$, 200 MHz) δ 1.10 (H-8,8'), 2.42 (4-$CH_3$-Ar), 2.44 (H-5), 2.52 (H-7), 6.96 (H-3), 7.02 - 8.05 (Ar-H). MS: m/z (%) 374 ($M^+$, 100), 318 (55), 290 (30).

**Compound** (**4c):** $^1$H-NMR ($CDCl_3$, 200 MHz) δ 1.11 (H-8,8'), 2.42 (H-5), 2.51 (H-7), 3.78 (4-$OCH_3$-Ar), 6.95 (H-3), 6.94 - 8.05(Ar-H). MS: m/z (%) 390 ($M^+$, 100), 334 (51), 306 (31).

**Compound** (**4d):** $^1$H-NMR ($CDCl_3$, 200 MHz) δ 1.11 (H-8,8'), 2.43 (H-5), 2.51 (H-7), 6.96 (H-3), 7.16 - 8.07 (Ar-H). MS: m/z (%) 378 ($M^+$, 100), 322 (64), 294 (44).

**Compound** (**4e):** $^1$H-NMR ($CDCl_3$, 200 MHz) δ 1.11 (H-8,8'), 2.43 (H-5), 2.53 (H-7), 6.95 (H-3), 7.12 - 8.07 (Ar-H). MS: m/z (%) 396 (/ $M^+$+ 2, 35 ), 394 ($M^+$, 100), 338 (42), 310 (6).

**Compound** (**4f):** $^1$H-NMR ($CDCl_3$, 200 MHz) δ 1.11 (H-8,8'), 2.43 (H-5), 2.51 (H-7), 6.95 (H-3), 7.04 - 8.08 (Ar-H). MS: m/z (%) 440 ($M^+$+ 2, 100 ), 438 ($M^+$, 100), 382 (47), 354 (10).

**Compound** (**4g):** $^1$H-NMR ($CDCl_3$, 200 MHz) δ 1.11 (H-8,8'), 2.43(H-5), 2.52 (H-7), 6.95 (H-3), 7.10-8.05 (Ar-H). MS: m/z (%) 486 ($M^+$, 100). 430 (43), 402 (8).

**Compound** (**4h):** $^1$H-NMR ($CDCl_3$, 200 MHz) δ 1.12 (H-8,8'), 2.45 (H-5), 2.57 (H-7), 6.99 (H-3), 7.18 - 8.36 (Ar-H). MS: m/z (%) 405 ($M^+$, 100), 349 (85), 321 (16).

**Compound** (**4i):** $^1$H-NMR ($CDCl_3$, 200 MHz) δ 1.11 (H-8,8'), 2.43 (H-5), 2.52 (H-7), 6.96 (H-3), 6.96 - 8.05 (Ar-H). MS: m/z (%) 374 ($M^+$, 100), 318 (55), 290 (33).

**Compound** (**4j):** $^1$H-NMR ($CDCl_3$, 200 MHz) δ 1.12 (H-8,8'), 2.43 (H-5), 2.54 (H-7), 6.96 (H-3), 7.04 - 8.08 (Ar-H). MS: m/z (%) 396 ($M^+$+ 2, 35 ), 394 ($M^+$, 100), 338 (49), 310 (11).

**Compound** (**4k**)**:** $^{1}$H-NMR ($CDCl_3$, 200 MHz) δ 1.12 (H-8,8'), 2.43 (H-5), 2.45 (H-7), 6.95 (H-3), 7.09 - 8.08 (Ar-H). MS: m/z (%) 440 ($M^+$+ 2, 100 ), 438 ($M^+$, 100), 382 (54), 354 (15).

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**REFERENCES**

1. S. P. Gupta, *Chem. Rev.*, 1994, **94**, 1507.
2. L. Chacón and R. Martínez, *Eur. J. Med. Chem.*, 2002, **37**, 261.
3. R. Martínez, J. G. Avila, L. G. López, and V. O. Nava, *Heterocycles*, 2000, **53**, 557.
4. R. Martínez, J. G. Avila Z., Ma. E. Duran, Ma. T. Ramírez, and R. Cañas, *Biorg. Med. Chem. Lett.*, 2002, **12**, 1675.
5. R. Martínez, J. G. Avila Z., Ma. E. Duran, Ma. T. Ramírez, A. Ángeles, and A. Pérez, XXV Congreso Latinoamericano de Química, Cancun, Q. Roo, México , 2002.
6. C. Paal, *Ber*., 1884, **17**, 2725; L. Knoor, *ibid*., 1884, **17**, 2863; C. Paal and L. Lederer, *Ber*., 1885, **18**, 2591; W. S. Bishop, *J. Amer. Chem. Soc*., 1945, **67**, 2261;C. A. Haley and P. Maitland, *J. Chem.Soc*., 1951, 3155.
7. P. T. Anastas, L. B. Barlett, M. M. Kirchoff, and T. C. Williamson, *Catal. Today*, 2000, **55**, 11
8. K. Arata, *Adv. Catal*., 1990, **37**, 165.
9. M. R. Benjaram and M. S. Pavani, *Tetrahedron Lett.*, 2003, **44**, 4447, and references cited therein.
10. B. M. Reddy and V. R. Reddy, *Mater. Sci. Lett.*, 2000, **19**, 763; B. M. Reddy, P. M. Sreekanth, Y. Yamada, Q. Xu, and T. Kobayashi, *Appl. Catal. A* : *General* , 2000, **228**, 269; Y. Zhao, W. Li, M. Zhang, and K. Tao, *Cat. Comm*., 2002, **3**, 20039.