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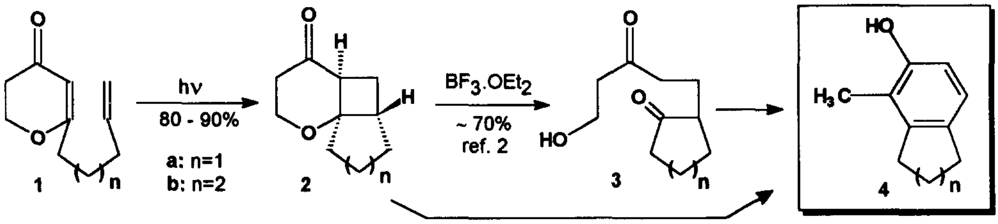
Synthesis of Substituted Phenols *Via* Photoaddition-Fragmentation-Aromatic Annelation Sequence[§]

Nizar Haddad* **and Irina Kuzmenkov**

Department of Chemistry, Technion, Israel Institute of Technology, Haifa 32000, Israel.

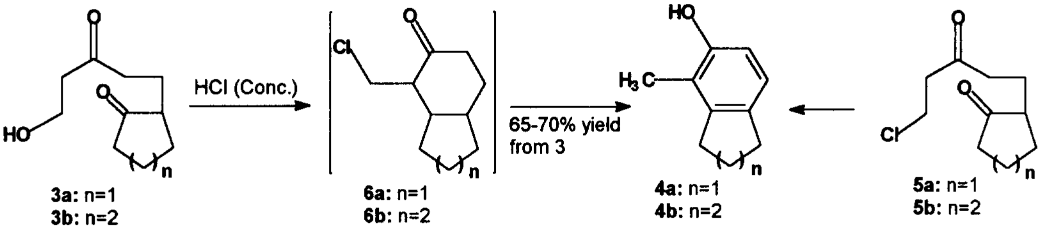
Abstract**:** Intramolecular photocycloaddition reaction of dihyro-4-pyrones to alkenes (**1**), followed by fragmentation then subsequent aromatic annelation, carried out by two alternative methods, has been performed efficiently. The sequence provides a convenient method for the construction of substituted phenols fused to aliphatic ring (**4**).

The synthesis of substituted phenols, fused to aliphatic ring(s) usually starts with the aromatic unit, followed by construction of the remaining aliphatic part. Alternative approaches are based on subsequent construction of the aromatic part *via* intermolecular annelation on substituted cyclic ketones[1]. Most of the approaches derived from both strategies suffer from limitations associated with controlling regioselectivity in the preparation of differently substituted systems. During the course of our studies on the synthetic applications of the intramolecular photocycloadditions of dihydro-4-pyrones[2], we have recently introduced an efficient formation of diketo-alcohols **3a** and **3b** in high yields. Further studies on the cyclizations of **3** leading to bicyclic systems have revealed a versatile method for the construction of certain substituted phenols of type **4**.



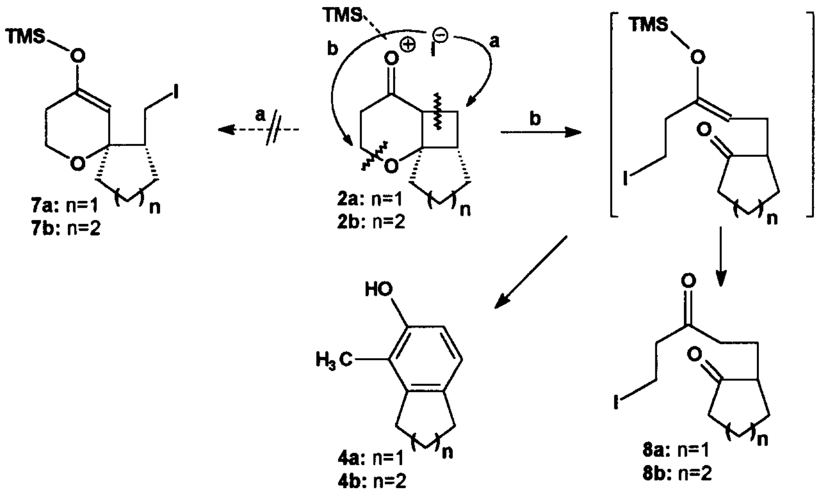
Scheme 1

The 1,5-diketone functionality in **3** is similar to that formed as the common intermediate in the (4 carbon + 2 carbon) Robinson annelation of cyclic ketones with vinyl ketones[3]. The β-hydroxy ketone functionality prohibits intramolecular aldol condensation under basic conditions since dehydration followed by unselective subsequent cyclization might be expected. Indeed, treatment of **3** under different basic conditions (K_2CO_3/MeOH, K_2CO_3/H_2O; KOH/MeOH; MeONa/MeOH; KOH/H_2O) led to the formation of undefined complex mixture of products. On the other hand, treatment of **3a** with hydrochloric acid (2 N, r.t., 24 hr) afforded chloride **5a** as the major product. Treatment of diketo-alcohol **3a** or its corresponding chloride **5a** with concentrated hydrochloric acid afforded by rapid and clean conversion a single compound in over 70% isolated yield. All spectroscopic data[4] are in full agreement with the phenolic structure **4a** (n=1), produced presumably *via* intermediate **6a** (scheme 2). The chloride in **6** is required for providing the desired leaving group in the elimination sequence leading to the phenolic product. Similarly **3b** formed the corresponding phenol **4b** in 78% yield. Interestingly, the photoproducts **2** (n=1, 2) found to be stable under these acidic conditions.



Scheme 2

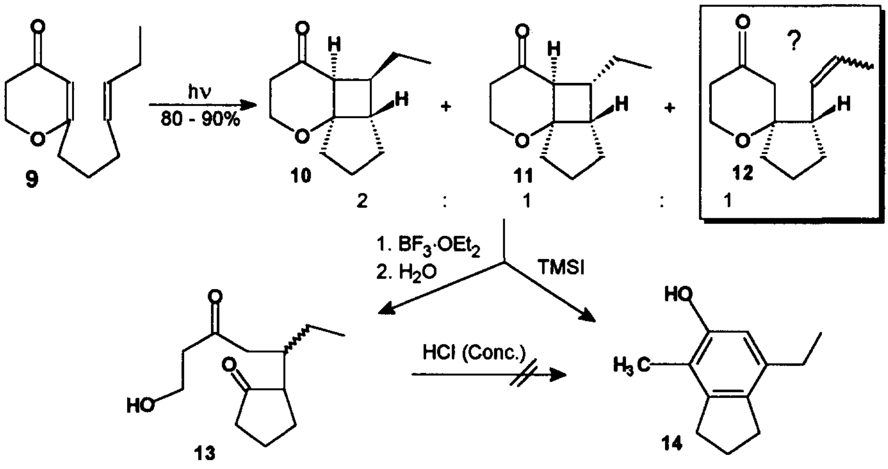
Alternatively, rapid cleavage of the cyclobutyl ring in the photoproducts could be expected upon treatment with trimethylsilyliodide[5] (TMSI), Two possible ring opening pathways a and b could be expected as described in scheme 3. Treatment of the photoadduct **2a** with TMSI (2 equivalents) afforded the diketo-iodide **8** in a mixture with the corresponding phenolic product **4a** in ca. 1 : 1 ratio, both products formed *via* the alternative cleavage b. However, treatment of **2a** with 1 equivalent of TMSI afforded the phenolic product **4a** as the major product in 70% isolated yield, similarly photoproduct **2b** was converted to the corresponding phenolic product **4b** in 74% yield.



Scheme 3

The position of substituents on the aromatic and/or the aliphatic ring(s) might be defined by their position at the pyrone photosubstrate. The sequence thus enables complete control of regioselectivity. As an example for preliminary examination of the possible generality of the title sequence and demonstrating the control in the regioselectivity, we have examined the sequence on compound **9**, possessing ethyl substituent at the vinylic position of the alkenyl side chain[6].

Irradiation of **9** under the normal conditions[7] afforded mixture of four isomers **10**, **11** and **12** (mixture) in a 2:1:1 ratio respectively. The major isomers **10** and **11** were separated and their structures were defined by NMR[4]. The structure of the minor isomers were not fully determined, however, the ^{1}H-NMR of their mixture shows resonances at the vinylic region which might correspond to the expected structures **12**. Treatment of the photoproduced mixture with $BF_3 \cdot OEt_2$ afforded diketoalcohols **13** in 40% yield. Surprisingly, **13** did not succeeded in cyclizing to the corresponding phenolic product upon treatment with HCl (Conc.) under various temperatures and reaction time. However, treatment of the photoproducts mixture with TMSI, in the presence of hexadecane as internal standard, have shown disappearance of the major photoproducts **10** and **11**; and afforded the corresponding substituted phenolic product **14** in 48% yield. This example demonstrates the possibility of introducing further substitution on the produced phenolic ring and, on the other hand, indicates some limitations obtained in the unsuccessful attempts to cyclize **13** upon treatment with HCl under the usual conditions.



Scheme 4

In summary, a highly efficient and selective cleavage of the photoproduced cyclobutane could be achieved upon treatment with either of $BF_3 \cdot OEt_2$ or TMSI. The high yield formation of substituted phenol systems from the readily prepared dihydropyrones **1** and **9**, demonstrates the utility of the Photoaddition-Fragmentation-Aromatic annelation sequence in the preparation of substituted phenols fused to aliphatic ring, the sequence is highly regioselective since the position of the substituents on the aliphatic and/or the phenolic ring can be defined by their position on the alkenyl side chain. Further studies on examining the scope and limitations of the sequence are currently underway in our laboratory.

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References and Notes

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3) For reviews see: Gawley, R. E. *Synthesis* **1976**, *777*. Jung, M. E. *Tetrahedron* **1976**, *32*, 3.
4) All new compounds were characterized by full spectroscopic data, yields refer to chromatographed materials with purity of >95%. ^{1}H-NMR spectra of: **4a:** δ 6.95 (d, 1H), 6.60 (d, 1H), 4.50 (s, 1H), 2.65 (q, 4H), 2.15 (s, 3H), 2.05 (m, 2H); **4b:** δ 6.80 (d, 1H), 6.60 (d, 1H), 4.50 (s, 1H), 2.65 (m, 4H), 2.15 (s, 3H), 1.75 (m, 4H); **14:** δ 6.0 (s, 1H), 4.30 (s, 1H), 2.7 (m, 2H), 2.3 (m, 2H), 2.1 (m, 5H), 1.6 (m, 2H), 0.9 (t, 3H).
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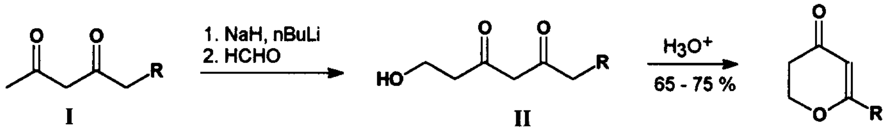
6) The photosubstrates **1** and **9** prepared following either of our previously presented sequence[2] or the following alternative method based on intramolecular cyclization of the corresponding β-diketo-β'-alcohols under acidic conditions[6a], starting by dianion alkylation of acetyl acetone with the corresponding alkenyl halide R-X following Ishida's procedure[6b], then dianion condensation of the produced diketone I with formaldehyde to afford the corresponding β-diketo-β'-alcohol II, which was cyclized spontaneously under the acidic workup conditions revealing the desired dihydropyrones in good yields.



(a) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585. For alternative methods see: Oppolzer, W.; Rodriguez, I. *Helv. Chim. Acta.* **1993**, *76*, 1282 and references cited therein. (b) Ishida, T.; Wada, K. *J. Chem. Soc., Perkin I* **1979**, 323.

7) Irradiations were carried out in acetonitrile solutions at 0 °C, using a 80-W Hanau mercury vapor lamp (Q-81) *via* a Pyrex glass filter.

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