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Regio- and stereoselective acylation of saturated carbocycles via Norrish–Yang photocyclization

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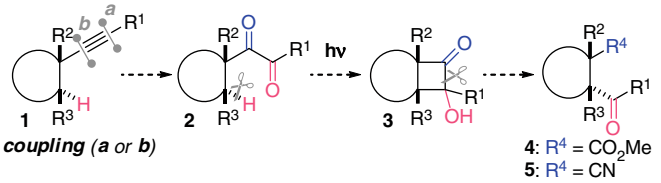
ABSTRACT

A regio- and stereoselective acylation of saturated carbocycles has been achieved through two-step reactions involving the Norrish–Yang photocyclization of 1,2-diketones and subsequent ring opening of the α-hydroxy-cyclobutanones. The C–H activation of the carbocycle proceeds regioselectively at vicinal to the diketone moiety resulting in stereoselective formation of *cis*-fused bicycles. The following C–C cleavage affords vicinally *cis*-acylated carbocycles. Predictability, generality, and practicality of the present strategy have been demonstrated using variously modified saturated carbocycles.

The demand for more efficient ways to construct complex chemical structures from simple precursors continues unabated. A very attractive way to meet this demand would be through selective C–C bond formation from sp^3-hybridized carbon–hydrogen bonds of saturated carbocycles.[1,2] The successful development of such C–H functionalizations would greatly simplify the strategies available for the synthesis of natural products and pharmaceuticals, because they enable C–C bond formations at any desired position starting from inert but readily available carbon frameworks. However, the ubiquitousness of sp^3 C–H bonds in organic molecules and the highly reactive agents necessary for cleavage of strong C–H bonds make selective and controllable reactions very challenging. Herein we report a general strategy for regio- and stereoselective C–H functionalization of saturated carbocycles by applying photocyclization and subsequent ring-cleavage reaction.

We planned to employ an intramolecular C–H activation of carbocycles, since spatial proximity between the reactive moiety and the sp^3 C–H bond might accelerate the desired transformation at a specific position in a predictable manner. In this context, Norrish–Yang photocyclization[3,4] of 1,2-diketone **2** was selected (Scheme 1).[5] Photoactivation would convert the C–H bond of carbocycle **2** into the C–C bond of **3** with simultaneous formation of the four-membered ring. The 1,2-diketone of **2** has advantageous features for controlling both reaction pathways and functional group selectivity:[6] (1) 1,2-diketones generally prefer Norrish–Yang cyclization over competing unproductive Norrish type-II fragmentation; (2) the long excitation wavelength of the 1,2-diketone (λ_{max} = approximately 450 nm) allows its selective activation over other photochemically excitable groups. Moreover, for application to the assembly of complex molecules, it would seem expedient that 1,2-diketone **2** can be readily prepared from fragments in several transformations, for example, sp^3-sp or sp^2-sp fragment coupling at either bond ***a*** or bond ***b*** in **1** followed by one-step RuO_2-catalyzed oxidation.[7] The cyclized **3** would be then transformed into acylated carbocycles (**4** and **5**) by inducing C–C bond rupture of the cyclobutanone structure. Overall, these mild two-step reactions would enable unique acylation of carbocycles, which is otherwise a difficult task. To test the scope and limitations of the methodology, we systematically investigated the structural elements influencing the regio- and stereoselectivity of the Norrish–Yang reaction using variously modified carbocycles.

At the outset, we designed and synthesized 1,2-diketone **2a**,[8] which possesses the saturated carbocycle and the carbon chain (Scheme 2). Excitation of diketone **2a** would generate a biradical, represented as two resonance structures **6a** and **7a**, each of which could abstract hydrogens from proximal sites, potentially leading to numerous products. Despite this situation, the irradiation of **2a** in benzene using a medium-pressure mercury lamp in the presence of benzophenone at room temperature[9] resulted in selective activation of the carbocycle over the carbon chain, leading to *cis*-fused bicyclo[4.2.0]octanone **3a** as the sole isomer. This remarkable regio- and stereoselectivity was further confirmed by running the reaction using acetoxy-diketone **2b** under the same conditions (**2b**→**3b**). Since only the radical abstraction of the methylene C–H bond vicinal to the 1,2-diketone group (colored in circle) (**7**→**8**)



Scheme 1. Plan for acylation of carbocycles.

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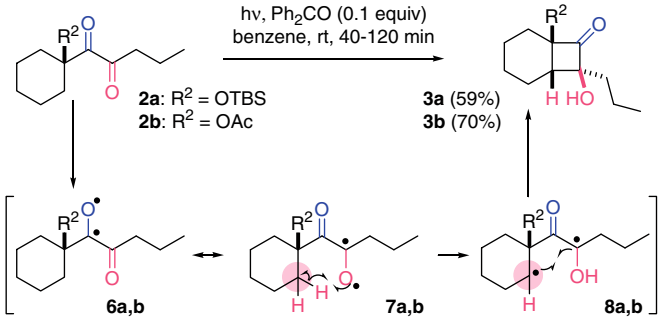
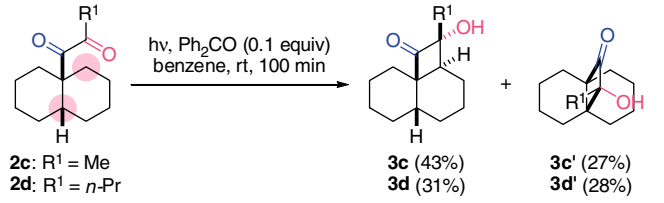


Scheme 2. Cyclization of geminally substituted carbocycles.

goes through the unstrained bicyclo[4.4.0]decane-like transition state without the large conformational reorganization, the regioselectivity would be explained by the preorganized nature of the abstracted C–H bond in comparison with the C–H bonds of the other sites. On the other hand, the exclusive stereoselectivity (**8**→**3**) should originate from the lower strain energy of the 6/4-*cis*-fused system compared to that of the highly strained *trans*-fused counterpart.

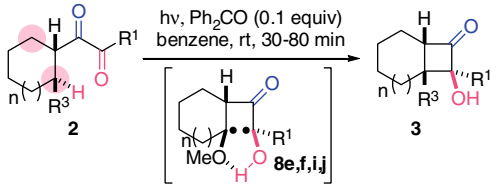
We next examined the reactions of the *cis*-decalin skeleton attached to the 1,2-diketone structure (Scheme 3). Irradiation of methyl diketone **2c** activated both the methylene and methine C–H bonds of the decalin at room temperature giving rise to tricyclic compounds **3c** and **3c**′.[10] Under the same reaction conditions, *n*-propyl diketone **2d** was similarly transformed into **3d** and **3d**′, again showing that the C–H functionalization reaction preferred the carbocycle over the carbon chain. Formation of the three consecutive tetra-substituted carbons of **3c**′ and **3d**′ demonstrated the power of the Norrish–Yang reaction for building sterically congested ring systems. Furthermore, the generation of the two ring isomers suggested that the regioselectivity between the methylene and methine C–H bonds came from a balance between the intrinsic reactivity toward abstraction ($R_3CH > R_2CH_2$) and steric congestion ($R_3CH > R_2CH_2$).

To further clarify the controlling factors of the regioselectivity of the C–H bonds, we utilized mono-carbocycles **2e–j** that possess the 1,2-diketone and the oxygen functionality in a vicinal relationship (Table 1). Intriguingly, the photocyclization of methoxy diketones **2e** (R^1 = Me) and **2f** (R^1 = *n*-Pr) proceeded at the more hindered methine C–H bond to afford cyclobutanones **3e** and **3f**, respectively, in a regio- and stereoselective manner. Even the sterically bulky siloxy group of **2g** promoted the cyclization at the methine site providing **3g** along with its alcohol epimer **3g**′. These results indicated that the electron-rich ether functionalities acted as the effective directing groups of the photocyclization by increasing the reactivity of the C–H bonds. This consideration was corroborated by the lack of selective cyclization from **2h**, which had the electron-withdrawing acetoxy functionality. The generality of the ether-directed photocyclization was further demonstrated using five-membered **2i** and seven-membered **2j**, which gave rise to 5,4- (**3i**) and 7,4-fused bicyclic systems (**3j**), respectively. It is noteworthy that all the newly formed hydroxy groups of **3e**,**f**,**i**,**j** are positioned *syn* to the methyl ethers suggesting that hydrogen bonding fixed the transition state **8e**,**f**,**i**,**j** during cyclization.



Scheme 3. Cyclization of *cis*-decalin derivatives.

Table 1
Cyclization of vicinally substituted carbocycles

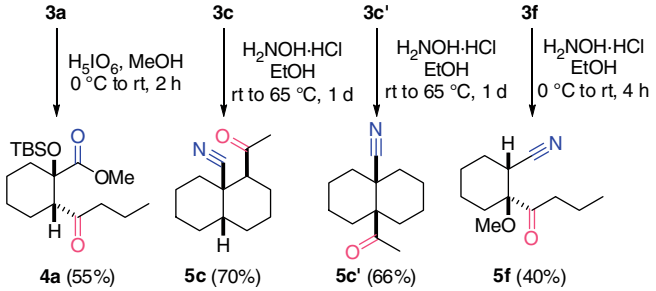


Substrate	*n*	R^1	R^3	Yield
2e	1	Me	OMe	74% (**3e**)
2f	1	*n*-Pr	OMe	70% (**3f**)
2g	1	*n*-Pr	OTBS	71%[a,b] (**3g** + **3g**′)
2h	1	*n*-Pr	OAc	—[c]
2i	0	*n*-Pr	OMe	51% (**3i**)
2j	2	*n*-Pr	OMe	74% (**3j**)

[a] Calculated yield.
[b] **3g** and its epimer **3g**′ at the hydroxylated carbon center were formed (**3g**:**3g**′ = 3.7:1).
[c] Diketone **2h** was consumed within 60 min to give complex mixture.

Having established the regio- and stereoselective C-H functionalization of the carbocycles through Norrish–Yang reaction, the next step was the ring-opening reaction of the α-hydroxy-cyclobutanone structures to build the various acylated carbocycles (Scheme 4). These reactions were realized by either direct oxidative cleavage or hydroxylamine-promoted 1,3-elimination. Oxidation of **3a** with periodic acid in aqueous methanol furnished 1,2-*cis*-substituted ketoester **4a**.[6i] Alternatively, treatment of **3c**, **3c**′, and **3f** with hydroxylamine hydrochloride led to the corresponding β-hydroxy-oximes, which underwent in situ 1,3-elimination through expulsion of water to afford 1,2-*cis*-substituted cyanoketones **5c**, **5c**′, and **5f**, respectively.[11] No epimerizations were observed for the obtained acyl and cyano cyclohexanes under these conditions, thus the stereochemistries of the cyclobutanones were successfully retained.

In conclusion, we have developed an operationally simple and structurally predictable protocol for the regio- and stereoselective acylation of saturated carbocycles using the Norrish–Yang photocyclization of 1,2-diketones in combination with ring-opening reactions. The factors affecting the cyclization selectivity have been examined. Since the generated acyl and carbomethoxy/nitrile groups would function as useful handles for further synthetic transformations, the present acylation of sp^3 C–H bonds should serve as a unique strategy for the construction of structurally complex organic molecules. Further studies along this line are underway in our laboratory.



Scheme 4. Ring-opening reactions of α-hydroxy-cyclobutanones.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.027.

References and notes

1. For recent reviews on direct C–C bond formation from sp^3 C–H bonds, see: (a) *Handbook of C–H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; vols. 1-2, (b) Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393; (c) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795; (d) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439; (e) Davies, H. M.; Manning, J. R. *Nature* **2008**, *451*, 417; (f) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094; (g) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335; (h) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074.
2. In comparison to sp^3 C–H arylation, alkenylation, and alkylation, sp^3 C–H acylation was relatively unexplored. For representative examples, see: (a) Fukunishi, K.; Kohno, A.; Kojo, S. *J. Org. Chem.* **1988**, *53*, 4369; (b) Kishi, A.; Kato, S.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **1999**, 1421; (c) Akhrem, I. S.; Churilova, I. M.; Orlinkov, A. V.; Afanas'eva, L. V.; Vitt, S. V.; Petrovskii, P. V. *Russ. Chem. Bull.* **1998**, *47*, 918; (d) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935; (e) Uenoyama, Y.; Fukuyama, T.; Morimoto, K.; Nobuta, O.; Nagai, H.; Ryu, I. *Helv. Chim. Acta* **2006**, *89*, 2483.
3. Yang, N. C.; Yang, D.-D. H. *J. Am. Chem. Soc.* **1958**, *80*, 2913.
4. For reviews on the Norrish–Yang reaction, see: (a) Wagner, P. J. In *Synthetic Organic Photochemistry*; Griesbeck, A. G., Mattay, J., Eds.; Marcel Dekker: New York, 2005; pp 11–39. Chapter 2; (b) Wessig, P.; Mühling, O. In *Synthetic Organic Photochemistry*; Griesbeck, A. G., Mattay, J., Eds.; Marcel Dekker: New York, 2005; pp 41–87. Chapter 3.
5. For a recent review on applications of photochemistry in organic synthesis, see: Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052.
6. For representative examples of the Norrish–Yang photocyclization of 1,2-diketones, see: (a) Urry, W. H.; Trecker, D. J. *J. Am. Chem. Soc.* **1962**, *84*, 118; (b) Turro, N. J.; Lee, T.-J. *J. Am. Chem. Soc.* **1969**, *91*, 5651; (c) Hirao, K.; Unno, S.; Miura, H.; Yonemitsu, O. *Chem. Pharm. Bull.* **1977**, *25*, 3354; (d) Obayashi, M.; Mizuta, E.; Noguchi, S. *Chem. Pharm. Bull.* **1979**, *27*, 1679; (e) Hamer, N. K. *Tetrahedron Lett.* **1982**, *23*, 473; (f) Sarphatie, L. A.; Verheijdt, P. L.; Cerfontain, H. *J. R. Neth. Chem. Soc.* **1983**, *102*, 9; (g) Hamer, N. K. *Tetrahedron Lett.* **1986**, *27*, 2167; (h) Herrera, A. J.; Rondón, M.; Suárez, E. *Synlett* **2007**, 1851; (i) Herrera, A. J.; Rondón, M.; Suárez, E. *J. Org. Chem.* **2008**, *73*, 3384.
7. (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936; (b) Zibuck, R.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 237.
8. See Supplementary data for preparation of the 1,2-diketones.
9. The yield was lower without using benzophenone as the sensitizer. The reaction was slower when irradiated with sunlight.
10. See Supplementary data for the detailed structure assignments.
11. Zhang, X.; Li, W. Z. *Synth. Commun.* **2006**, *36*, 249.