ORGANIC LETTERS

2007
Vol. 9, No. 23
4721−4723

Trapping of Oxonium Ylide with Isatins: Efficient and Stereoselective Construction of Adjacent Quaternary Carbon Centers

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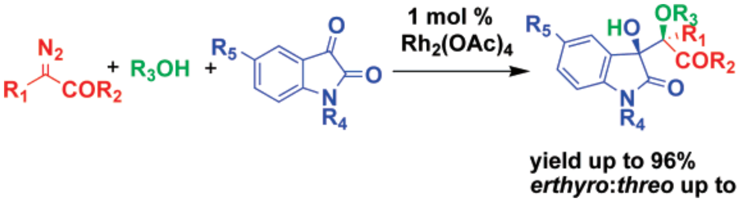
Received August 14, 2007

ABSTRACT



The 3-substituted 3-hydroxyindolin-2-ones with adjacent quaternary stereocenters were constructed in a single step via an efficient and stereoselective trapping of oxonium ylide with isatins. This reaction proceeds well in supercritical CO$_2$ and is an example of the ability to use green approaches to efficiently construct polyfunctional molecules.

Oxindole derivatives are common structural motifs found in a vast array of natural products and medicinal agents.[1] In particular, the 3-substituted 3-hydroxyindolin-2-one moiety is present in a number of biologically active alkaloids such as TMC-95s (Figure 1),[2] welwitindolinone C,[3] celogentin K,[4] convolutamydines,[5] and SM-130686.[6] Most of the currently available methods for the construction of 3-substituted 3-hydroxyindolin-2-ones via nucleophilic addition to isatins[7] generate only one stereocenter and involve stepwise construction of structures with adjacent stereocenters.[8] There is clearly a demand for novel strategies to efficiently construct this important class of polyfunctional substance with multi-stereocenters.

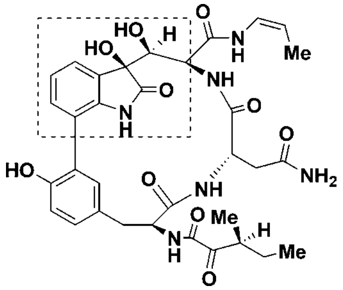


Figure 1. Structure of TMC-95C.

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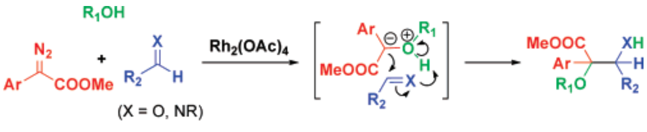
10.1021/ol7019857 CCC: $37.00

An “ideal synthesis” should be a process to give a desired product in as few steps as possible, in good overall yield, and by using environmentally compatible reagents and solvents.[9a] In addition, for polyfunctionally complex molecules, the ideal synthesis should be highly chemo- and stereoselective. Multicomponent reactions (MCRs) are flexible, selective, convergent, and atom-efficient processes that facilitate the construction of complex molecules in a single step. As such, MCRs closely approach the “ideal synthesis”.[9b] The rich chemistry of transformations through onium ylides has been widely studied and utilized in organic synthesis.[10] We recently reported a three-component, C−C-bond-forming reaction in which in-situ generated ammonium/oxonium ylides were trapped with imines and aldehydes (Scheme 1);[11] however, the chemo- and stereoselectivities of these reactions were generally poor to moderate. For example, the Rh(II) catalyzed aldol-type three-component reaction of methyl phenyldiazoacetate with benzyl acohol and *p*-nitrobenzaldehyde gave corresponding α,*β*-dihydroxylacid derivative, methyl 2-(benzyloxy)-3-hydroxy-3-(4-nitrophenyl)-2-phenylpropanoate, in 70% yield with threo/erytheo ratio of 43:57. In addition, extension of the reaction to electron rich aryl aldehydes resulted in a dominant O−H insertion side reaction.[11d] The challenge in the reaction was to identify matched systems in which high chemo-/stereo-selectivities can be realized with a broad scope of substrates. Herein, in a continuation of our efforts involving the ylide-trapping processes, we describe a highly chemo- and stereoselective three-component reaction of a diazoacetate, an alcohol, and an isatin, from which highly functionalized 3-substituted 3-hydroxyindolin-2-ones with two vicinal quaternary stereocenters are constructed in just a single operation.

Scheme 1. Trapping of Oxonium Ylides with Aldehydes and Imines



Initially, the rhodium-acetate-catalyzed decomposition of methyl phenyldiazoacetate (**1a**) in the presence of benzyl alcohol (**2a**) and N-methylisatin (**3a**) was analyzed. Product **4a** was isolated as an erthyro isomer (erthyro/threo = 98:2) in 93% yield [eq 1], and the O−H insertion side product derived from **2a** and **1a** was entirely suppressed. It is suggested that high electrophilicity and rigid cyclic conformation of the isatin account for such a high chemo- and stereoselectivity. Similar results were obtained with other dirhodium catalysts, such as $Rh_2(TFA)_4$ and $Rh_2(S\text{-}MEOX)_4$. No enantioselectivity was observed with the use of the later chiral catalyst.

A number of substituted isatins were then employed in the reaction with methyl phenyldiazoacetate (**1a**) and benzyl alcohol (**2a**). The reaction proceeded smoothly to give the three-component products **4** with N-protected or unprotected isatins in high yields together with excellent diastereoselectivities (Table 1, entries 1−3). Good yields of **4** were also obtained with 5-substituted NH isatins (Table 1, entries 4−6), allowing further derivation on the nitrogen atom. The relative stereochemistry of **4** was established through single-crystal X-ray analysis of *erthyro*-**4d** (Figure 2).

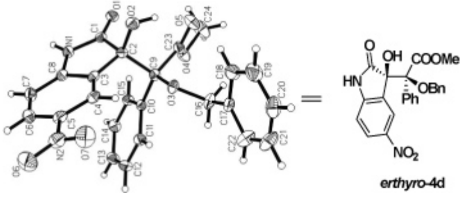


Figure 2. ORTEP representation of the crystal structure of *erthyro*-**4d**.

This transformation was extended to other alcohols and diazo compounds. The results showed that the chemo- and

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Table 1. Addition of Hydroxyl Oxonium Ylide to Isatins

1a: R_1 = Ph, R_2 = OMe
1b: R_1 = 4-MeOC$_6$H$_4$, R_2 = OMe
1c: R_1 = 4-ClC$_6$H$_4$, R_2 = OMe
1d: R_1 = 3-ClC$_6$H$_4$, R_2 = OMe
1e: R_1 = 2-ClC$_6$H$_4$, R_2 = OMe
1f: R_1 = H, R_2 = OEt
1e: R_1 = H, R_2 = Ph

2a: R_3 = Bn
2b: R_3 = Me
2c: R_3 = *i*-Pr
2d: R_3 = *t*-Bu
2e: R_3 = H

3a: R_4 = Me, R_5 = H
3b: R_4 = Ph, R_5 = H
3c: R_4 = R_5 = H
3d: R_4 = H, R_5 = NO$_2$
3e: R_4 = H, R_5 = Cl
3f: R_4 = H, R_5 = Br

entry	1	2	3	4	yield (%)[a]	dr (erthyro/threo)[b]
1	**1a**	**2a**	**3a**	**4a**	93	98:2
2	**1a**	**2a**	**3b**	**4b**	95	>99:1
3	**1a**	**2a**	**3c**	**4c**	90	96:4
4	**1a**	**2a**	**3d**	**4d**	81	96:4
5	**1a**	**2a**	**3e**	**4e**	85	96:4
6	**1a**	**2a**	**3f**	**4f**	82	92:8
7	**1a**	**2b**	**3a**	**4g**	79	97:3
8	**1a**	**2c**	**3a**	**4h**	81	99:1
9	**1a**	**2d**	**3a**	**4i**	72	98:2
10	**1a**	**2e**	**3a**	**4j**	96	63:37
11	**1b**	**2a**	**3a**	**4k**	80	>99:1
12	**1c**	**2a**	**3a**	**4l**	84	98:2
13	**1d**	**2a**	**3a**	**4m**	82	95:5
14	**1e**	**2a**	**3a**	**4n**	24	52:48
15[c]	**1f**	**2a**	**3a**	**4o**	89	54:46
16[c]	**1g**	**2a**	**3a**	**4p**	88	60:40

[a] Isolated yield after column chromatography purification. [b] Determined by ^{1}HNMR of the crude reaction mixtures. [c] **1:2:3** = 1.2:1.5:1.

stereo-selectivities of the reaction were only slightly affected by steric hindrance of the alcohols used. Accordingly, aliphatic alcohols, such as methanol, isopropyl alcohol, and *tert*-butyl alcohol, gave a similar high level of diastereoselectivity for the corresponding products **4h**−**j** in good yields (Table 1, entries 7−9). Interestingly, water also served as a highly active hydroxyl donor, efficiently affording unprotected α,*β*-dihydroxy product **4g** in 96% isolated yield (Table 1, entry 10). The reaction even proceeded well in a biphasetic system in which an excess of water was used, facilitating the recycling of the rhodium catalyst. Low diastereoselectivity (erthyro/threo = 63/37) of the reaction is probably due to higher reactivity of the oxonium ylide derived from water.

The chemo- and stereo-selectivities of the reaction were found to be more or less dependent on the electronic and steric features of the diazo compounds (Table 1, entries 11−16). The reaction proceeded well with 4- and 3-substituted phenyldiazoacetates (Table 1, entries 11−13). However the reaction with 2-Cl-phenyldiazoacetate **1e** gave mainly the O−H insertion side product and therefore resulted in a low yield of **4n** (Table 1, entry 14). We were pleased to find that this reaction can be extended to simpler unsubstituted α-diazocarbonyl compounds, as was the case with ethyl diazoacetate and 2-diazo-1-phenylethanone, which afforded products **4o** and **4p** in 89% and 88% yields, respectively, though with poor diastereoselectivity (Table 1, entries 15, 16). Such diazo compounds fail to afford the desired three-component product in the reaction with aldehydes as electrophiles.

An effort was also made to replace the CH$_2$Cl$_2$ solvent with an environmentally friendly reaction medium. The use of supercritical CO$_2$ (scCO$_2$) as the reaction medium offered the opportunity to replace conventional organic solvents.[12] Several reports have shown that scCO$_2$ can successfully replace organic solvents in a variety of transformations, such as free-radical reactions, polymerizations, and homogeneous catalytic reactions.[13] In particularly, Jessop reported that rhodium-catalyzed asymmetric cyclopropanation of methyl phenyldiazoacetate with styrene gave similar good results in scCO$_2$ and in liquid solvents.[14] The successful diazo-decomposition in scCO$_2$ encouraged us to use scCO2 in the current three-component reaction. Thus, the reaction was carried out in scCO$_2$ by charging a cylindrical stainless-steel reactor with Rh$_2$(OAc)$_4$ catalyst, benzyl alcohol, and isatin **3a**, followed by pressurization with CO$_2$ (15.2 MPa) and cooling in an ice-bath. After the reactor had been warmed to 40 °C, a supercritical phase was produced (19.4 MPa total pressure, 40 °C). Liquid methyl phenyldiazoacetate was then pumped into the reactor, and the resulting scCO$_2$ phase (19.8 MPa pressure, 40 °C) was stirred for 10 min. Release of the pressure allowed scCO$_2$ to be easily removed and the crude product, which was left behind as a yellow solid, was later isolated in 95% yield with 99:1 diastereoselectivity.

In conclusion, the efficient three-component reaction described here affords 3-substituted 3-hydroxyindolin-2-one derivatives with two adjacent tetrasubstituted carbon centers in high yield and excellent chemo- and diastereo-selectivities. Supercritical CO$_2$ successfully replaced the traditional dichloromethane solvent. The current reaction is an example of the ability to use green approaches to efficiently construct polyfunctional molecules. Further investigations to apply chiral catalysts for the catalytic asymmetric three-component reaction is currently in progress in our laboratory.

Acknowledgment. We are grateful for financial support from the Chinese Academy of Sciences and the National Science Foundation of China (Grant No. 20472080). We thank Prof. Kaibei Yu of Chengdu Institute of Organic Chemistry for X-ray measurements and Dr Tao Liu from State Key Laboratory of Chemical Engineering, East China University of Science and Technology for assistance with scCO$_2$ experiments.

Supporting Information Available: Crystallographic data of *erthyro*-**4d** (cif) and experimental procedures and charecterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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