Tetrahedron Letters 54 (2013) 3371–3373

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The Michael addition of 1,2-cyclohexanedione to β-nitrostyrenes (I): the synthesis of 3-aryl-5,6-dihydrobenzofuran-7(4*H*)-ones

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ARTICLE INFO

Article history:
Received 26 March 2013
Revised 12 April 2013
Accepted 15 April 2013
Available online 24 April 2013

Keywords:
1,2-Cyclohexanedione
β-Nitrostyrenes
Michael addition
3-Aryl-5,6-dihydrobenzofuran-7(4*H*)-ones

ABSTRACT

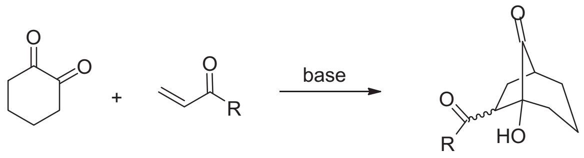
The reaction of β-nitrostyrenes with 1,2-cyclohexanedione using K_2CO_3 as a base results in the formation of 3-aryl-5,6-dihydrobenzofuran-7(4*H*)-ones in good yields. A putative reaction mechanism involves an initial Michael addition of the dione C-enolate to the β-nitro-styrene, followed by intramolecular cyclization of the resulting O-enolate anion, elimination of nitrite ion, and air oxidation. Product formation is highly dependent on base stoichiometry.

The use of cyclohexanediones in organic synthesis has been firmly established.[1,2] While the 1,3-cyclohexanedione system has been widely studied, the chemistry of the 1,2-cyclohexanedione system by comparison has only recently been investigated. The first thorough study of the Michael reaction of 1,2-cyclohexanedione, which focused on the development of optimal conditions for conjugate addition chemistry with simple Michael acceptors, was reported in 1985.[3] During the course of this study, it was found that intramolecular cyclizations could occur through carbonyl trapping of the intermediate anion from the addition of the enolate to the Michael acceptor to afford bicyclo[3,2,1]octan-8-one ring systems (Scheme 1).

In a related study, Ding and co-workers have utilized the Michael reaction properties of 1,2-cyclohexanedione to prepare 2-amino-8-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles (**5**).[4] More recently, Ding et al. have shown that bicycle[3,2,1]octan-8-ones (**7a** and **b**) may be prepared with a high degree of enantioselectivity by using catalytic quantities of chiral bases and β-nitrostyrenes as the Michael acceptor system (Scheme 2).[5]

Based on our long-standing interest in the Michael chemistry of β-nitrostyrenes[6] and the chemistry of 1,2-cyclohexanedione,[7] we initiated a study of the reaction between these substrates with a variety of base systems. We found that the use of greater than stoichiometric quantities of a relatively strong base (K_2CO_3) in the reaction afforded 3-aryl-5,6-dihydrobenzofuran-7(4*H*)-ones in good yields (Scheme 3).[8] While 2-aryl substituted 4,5-dihydro-7(6*H*)-benzofuranone derivatives have been prepared through the reaction of 1,2-cyclohexanedione with electron rich olefins under free-radical conditions,[9] preparation of the corresponding 3-aryl systems is unknown.

Reactions using a K_2CO_3:substrate stoichiometry ratio of 10:1 provided the desired product cleanly by GC/mass spectrometry (Table 1). Preliminary studies indicate that fewer than 10 equiv of K_2CO_3 resulted in significantly lower yields of product with concomitant impurity formation. Studies regarding this observation and the determination of the identity of the impurities are continuing and will be described in due course. A possible reaction mechanism involves an initial Michael addition of the dione C-enolate to the β-nitrostyrene, followed by intramolecular cyclization of the resulting O-enolate anion, elimination of nitrite ion, and air oxidation (Scheme 4). The primary difference in product outcome observed between Ding's work[5] and this work can be attributed to



1 2 3

Scheme 1.

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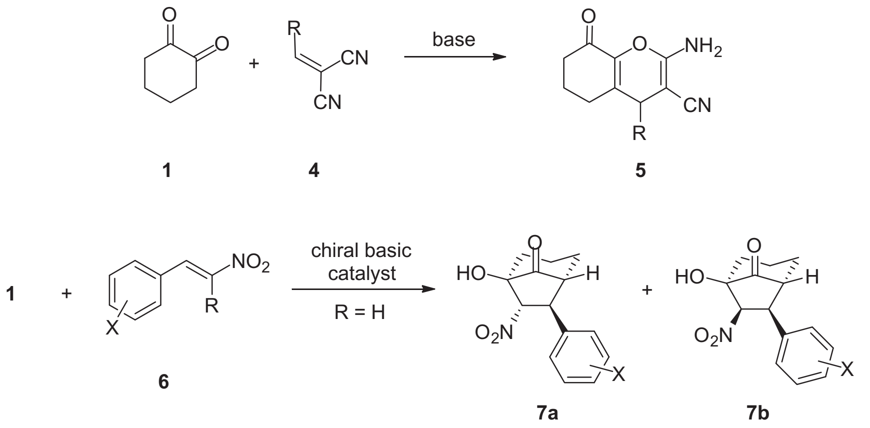
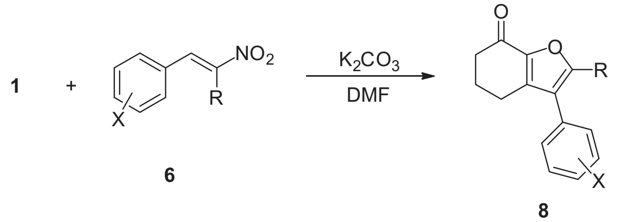
http://dx.doi.org/10.1016/j.tetlet.2013.04.053



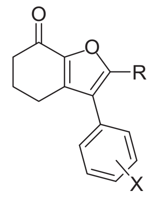
Scheme 2.



Scheme 3. Synthesis of **8**.

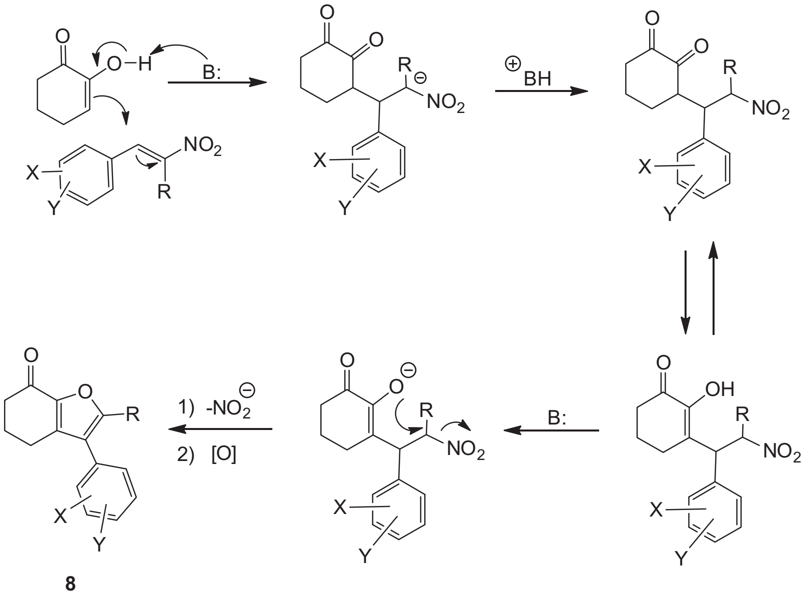
the strength of the base system employed. Maintaining a high concentration of relatively strong base in the system insures the formation of a high concentration of enolate relative to the catalytic method described by Deng.

Table 1



8

Compound	R	X	Yield (%)
8a	–H	–H	61
8b	–H	4–Cl	40
8c	$-CH_3$	–H	63
8d	$-CH_3$	4–Br	67
8e	$-CH_3$	$4-OCH_3$	84
8f	$-CH_2CH_3$	–H	60
8g	$-CH_2CH_3$	4–CN	73
8h	$-CH_2CH_3$	$3-OCH_3$	79



Scheme 4. Proposed mechanism for the formation of **8**.

Acknowledgments

The authors wish to thank The College of New Jersey for their support of this work through the auspices of a MUSE Grant to C.S. We also wish to thank The University of California, Riverside High Resolution Mass Spectrometry Facility for high resolution mass spectral data and Dr. Benny Chan of TCNJ for the x-ray crystal structure determination.

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8. *General procedure for synthesis of 3-aryl-5,6-dihydrobenzofuran-7(4H)-ones. 2-Methyl-3-phenyl-5,6-dihydrobenzofuran-7(4H)-one (***8c***).*
   To a 100 mL round bottomed flask equipped with a magnetic stirrer and reflux condenser was added 1,2-cyclohexanedione (1.00 g; 8.92 mmol), β-methyl β-nitrostyrene[10] (1.46 g; 8.92 mmol), DMF (30 mL), and K_2CO_3 (12.33 g; 89.21 mmol). The reaction was heated to 80 °C using an oil bath for a period of 4 h during which time the reaction mixture changed in color from water white/pale yellow to brown. The mixture was then allowed to cool to room temperature. Dichloromethane (30 mL) and deionized H_2O (100 mL) were added to the reaction mixture and the solution was brought to neutral pH with 10% HCl. The resulting mixture was transferred to a separatory addition funnel and the organic layer removed. After dichloromethane washes (2 × 30 mL), the organic layers were combined and washed with H_2O (3 × 100 mL). The organic layer was dried over anhydrous $MgSO_4$ and the dichloromethane was removed *in vacuo* to provide the crude product which was purified by flash chromatography on silica gel eluting with hexanes/EtOAc to afford **9c** as a white crystalline solid, mp 105–108 °C (1.28 g, 63.2% yield). The structure was supported by X-ray crystallography. ^{1}H NMR δ 7.29–7.06 (m, 5H), 2.55 (t, J = 6.0 Hz, 2H), 2.40 (t, J = 6.0 Hz, 2H), 2.26 (s, 3H), 1.95 (p, J = 6.0 Hz, 2H). ^{13}C NMR δ 185.9, 155.2, 146.0, 140.5, 131.7, 128.8, 127.5, 122.8, 38.1, 24.5, 22.6, 13.1. IR 167, 1424, 1252 cm^{-1}. HRMS: Calcd for $(C_{15}H_{15}O_2)H^+$ 227.1067; found 227.1075.
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