Synthesis of Aryl-Substituted 1,4-Benzoquinone *via* Water-Promoted and In(OTf)₃-Catalyzed *in situ* Conjugate Addition-Dehydrogenation of Aromatic Compounds to 1,4-Benzoquinone in Water

Hai-Bo Zhang,^a Li Liu,^a Yong-Jun Chen,^a Dong Wang,^{a,*} Chao-Jun Li^{b,*}

^a Center for Molecular Science, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, People's Republic of China

Fax: (+86)-10-6255-4449, e-mail: dwang210@iccas.ac.cn

^b Department of Chemistry, McGill University, 801 Sherbrooke St. West, Montreal, Quebec, Canada H3A2K6 Fax: (+1)-514-398-3797, e-mail: cj.li@mcgill.ca

Received: June 16, 2005; Accepted: November 4, 2005

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Mono- and diaryl-substituted 1,4-quinones were synthesized by the $In(OTf)_3$ -catalyzed conjugate addition of aromatic *C*-nucleophiles to 1,4-quinone derivatives followed by *in situ* dehydrogenation in water. Water was found to be beneficial to the reaction.

Introduction

Substituted 1,4-benzoquinone derivatives exist widely in nature and exhibit various important biological activities,^[1] including antitumor and antibiotic activities,^[2] inhibition of HIV-1 reverse transcriptase,^[3] antidiabetic activities,^[4] and others. Among these derivatives, arvlsubstituted 1,4-quinones are found in many natural products. For example, belamcandaquinones A and B isolated from the seed of a medicinal plant, Belamcanda chinests, were used as a specific cyclooxygenase inhibitor.^[5] Common synthetic methods for aryl-substituted 1,4-quinone compounds include the Meerwein arylation reaction of quinone with diazonium salts,^[6] oxidation of aromatic compounds,^[7] transition metal-catalyzed coupling reactions,^[8] and photochemical reactions of acetylenes with Fe(CO)₅.^[9] All these methods have certain limitations, such as the need for precious metals to act as catalysts, the use of a great amount of reagents, or polymerizations and low yields as a result of performing the reaction under intensive reaction conditions. Recently, it was reported by Yadav^[10] and Pirrung^[11] that a Lewis acid can catalyze the conjugate addition reaction of indole compounds with 1,4-benzoquinone to give 3indolylquinone compounds. Such a reaction can also be catalyzed by some Brønsted acids.^[12] On the other The regioselectivity of the addition reaction in water was also examined.

Keywords: arylation; benzoquinone; C–C bond formation; homogeneous catalysis; indium; water as solvent

hand, Chan and co-workers^[13] reported the synthesis of 4-hydroxycoumarin derivatives by the reaction of 4hydroxycoumarins with p-benzoquinone. Although conjugate additions of simple non-conjugated carbonyl compounds by using aromatic compounds as C-nucleophiles have been studied extensively, there were few examples of conjugate addition of aromatic C-nucleophiles to benzoquinones for the synthesis of aryl-substituted benzoquinone compounds.^[14] Recently, aqueous organic reactions have received considerable attention in view of their synthetic efficiency and environmental friendliness.^[15] As part of our continuing interest in performing In(OTf)₃-catalyzed addition reactions of aromatic C-nucleophiles in water,^[16] herein we report an In(OTf)₃-catalyzed conjugate addition of aromatic compounds to 1,4-benzoquinones followed by in situ dehydrogenation in water to give aryl-substituted benzoquinone compounds.

Results and Discussion

When 3-methoxy-*N*,*N*-dimethylaniline (**1a**) was reacted with 1,4-benzoquinone (**2a**) (1a/2a = 1:2) in the presence of a catalytic amount of In(OTf)₃ (5 mol %) in organic solvents such as CH₃CN, CH₂Cl₂ or THF, the yields



Entry	1a:2a	Catalyst ^[a]	Solvent	Reaction time [h]	Yield [%] ^[b]	
					3 a	4a
1	1:2	$In(OTf)_3$	H ₂ O	2	93	trace
2	1:2	$In(OTf)_3$	CH ₃ CN	24	25	_
3	1:2	$In(OTf)_3$	$CH_{3}CN/H_{2}O(2:1)$	24	37	_
4	1:2	$In(OTf)_3$	CH ₂ Cl ₂	24	10	_
5	1:2	$In(OTf)_3$	THF	24	7	_
6	1:2	$In(OTf)_3$	THF/H ₂ O $(1:4)$	24	Trace	_
7	1:2	HOT	H ₂ O	2	86	_
8	1:2	_[c]	H ₂ O	2	31	_
9	1:1	$In(OTf)_3$	H ₂ O	24	8	79
10	1:1	$In(OTf)_3$	CH ₃ CN	24	10	_
11	1:1	$In(OTf)_3$	CH ₂ Cl ₂	24	12	_
12	1:1	$In(OTf)_3$	THF	24	4	_
13	1:1	HOT	H_2O	24	52	-

Table 1. $In(OTf)_3$ -catalyzed reactions of 1a with 2a in various solvents.

^[a] Catalyst loading: 5 mol %.

^[b] Isolated yield.

^[c] Without using catalyst.

of the product **3a** were poor (trace -25%) (Scheme 1, Table 1). Several reports have shown that, aside from potential environmental benefit, the use of water as a reaction medium sometimes provides special effects for chemical reactions.^[17] In a mixed solvent, CH₃CN/H₂O (2:1), the reaction yield increased to 37% (entry 3); however, the use of aqueous THF as reaction media did not improve the yield at all (entry 6). Interestingly, if the reaction of 1a with 2a was carried out at room temperature in air and water, the reaction time was shortened from 24 h to 2 h and the yield of 3a increased remarkably to 93% (entry 1). When the ratio of 1a/2a was changed to 1:1, the solvent effect was more obvious: the aqueous reaction gave diaryl-substituted benzoquinone (4a) in 79% yield (yield is based on the aromatic starting material, entry 9), while the reaction in organic solvent did not produce 4a at all (entries 10-12). Although trifluoromethanesulfonic acid (HOTf) could also catalyze the reaction (entry 7), no diaryl-substituted product 4a was detected in the product mixture (with 1a/2a = 1:1) (entry 13). [Note: similarly, the reaction between 1,3-dimethoxybenzene (1f) and 2a (1:1) did not afford diaryl-substituted quinone (4 h) at all in the presence of HOTf; whereas by using In(OTf)₃ as a catalyst, **4 h** was obtained in 79% yield (Table 3, entry 8)]. In the absence of a catalyst, **3a** was obtained in 31% yield when the reaction was carried out in water (Table 1, entry 8).

Subsequently, various aniline derivatives 1a-d were used in the reaction with 1,4-benzoquinone compounds 2a-c in water and in the presence of catalyst In(OTf)₃. The reactions were carried out under the same conditions, giving the aryl-substituted benzoquinone products 3a-f in good to high yields (Table 2). All the products exhibited a *para*-amino-arylbenzoquinone structure, re-



Scheme 1.

sulting from the aromatic C-nucleophilic attack on the α,β -unsaturated carbonyl unit of 1,4-benzoquinone. However, when methylaniline (1e) was used, an N-nucleophilic addition product 3g was obtained in 63% yield (Table 2, entry 8). Oxygen-containing aromatic compounds 1f and 1g were also effective as aromatic C-nucleophiles in the reaction. The reaction of 1,3-dimethoxybenzene (1f) produced a mixture of mono-substituted (3h) and di-substituted benzoquinone derivatives 4h, while the use of 2-methylfuran (1g) generated product **3j** in 64% yield (Table 2, entry 9), with the 5-position of furyl group linked to the benzoquinone moiety. On the other hand, 45% of the starting material 1,4-benzoquinone (2a) was recovered from the reaction of 1a with 2a (1a/2a = 1:2) after the reaction had gone to completion. In the reactions of both 1d with 2a and 1a with 2c (Table 2, entries 4 and 6), aryl-substituted 1,4-hydroquinone compounds could be obtained. When the reaction time was prolonged to 24 h, the ratio of benzoquinone (3f) to hydrobenzoquinone 3f-1 increased noticeably (Table 2, entry 7). Based on these results, the mecha-



Scheme 2.

nism of the reaction can be hypothesized^[18] as follows: at first, the conjugate addition of the aromatic nucleophile to 1,4-benzoquinone produced a mono-aryl-substituted hydroquinone intermediate 5. Then one half of 1,4-benzoquinone 2a was incorporated into the product and the other half of 2a oxidized the 1,4-hydroquinone intermediate 5 into the mono-substituted 1,4-benzoquinone 3. At the same time, 2a was re-generated by the oxidation of the 1,4-hydrobenzoquinone 6 under an air atmosphere in water. In the case of **1a**, due to the high reactivity in water during the course of the reaction (1a/2a)1:1), it could react with the mono-substituted benzoquinone 3 (generated *in situ*) to produce diaryl-substituted hydrobenzoquinone 7, which was oxidized to give the final product, diaryl-substituted 1,4-benzoquinone (4a) (Scheme 2).

When mono-substituted benzoquinone was used as a substrate in this reaction, there was an issue of regioselectivity: the addition could occur at either the 5- or 6position of 1,4-benzoquinone, leading to 2,5- or 2,6-regioisomers, respectively (Scheme 3). The regioselectivity was found to be highly dependent upon the substituent on the 1,4-benzoquinone ring. As shown in Table 3, for 2-methoxy-1,4-benzoquinone (**2d**), (2,5)-addition products **4b**-**e** were obtained exclusively in 76–89% yields, either through *C*-nucleophilic (Table 3, entries 1-3) or *N*-nucleophilic additions (entry 4). The struc-



Scheme 3.

Adv. Synth. Catal. 2006, 348, 229-235

© 2006 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

X-ray analyses of the single crystals of (2,5)-4c and (2,5)-4e. For the amino-substituted 1,4-benzoquinone, the conjugate addition of 2-arylamino-1,4-quinone 3g with C-nucleophile 1a also exhibited exclusive 2,5-selectivity (entry 12). However, when 2-methyl-1,4-benzoquinone (2e) was used, very poor regioselectivity (2,5-/ 2,6-=1:1.1) was observed by ¹H NMR of the product mixture (entry 5).^[19] Changing the methyl group to a *t*butyl group (2f) increased the 2,6-selectivity (2,6-/2.5isomer = 7.3:1 (entry 6).^[20] 2,6-Regioselectivity was observed in a one-pot reaction of aromatic compounds 1a or 1f with quinone (2a). When the ratio of 1a or 1f to 2a was 1:1, (2,6)-substituted 1,4-benzoquinones (2,6)-4a and 4h were obtained exclusively in 79% yield (Table 3, entries 7 and 8). The 2,6-selectivity was also confirmed by the X-ray analysis of the single crystals of (2,6)-4a and 4h. In terms of the mechanism of the one-pot reaction, it can be hypothesized that the mono-substituted benzoquinone **3a** or **3h**, generated *in* situ from the initial reaction, underwent a subsequent reaction with the same aromatic C-nucleophile to give the homo-(2,6)-diaryl-substituted benzoquinones. This hypothesis was confirmed by stepwise experiments in which the reaction of preformed 3a with 1a also gave the identical homo-diaryl-substituted 1,4-quinone, (2,6)-4a, in 64% yield (Table 3, entry 9). In contrast, when N-methylaniline 1e was reacted with 2a (1e/2a = 1:1), (2,5)-homo-diarylamino-substituted benzoquinone (2,5)-4i was obtained in 65% yield (Table 3, entry 10). The stepwise reaction could be used to generate the cross-2,6-diaryl-substituted 1,4-quinone (2,6)-4j (Table 3, entry 11). In the case of an N-nucleophile, which is more reactive than aromatic C-nucleophiles, (2,6)-selectivity was also observed (Table 3, entry 13). By using the stepwise reactions two isomers, (2,6)-4k

tures of the 2,5-addition products were confirmed by

Entry		Ar-H ^[b]	Quinone ^[b]	Time [h]	Product	Yield ^[c]
1	1a	NMe ₂	2a O	2	3a NMe ₂ OMe	93
2	1b	NMe ₂	2a	24	3b NMe ₂	84
3	1c	NMe ₂	2a	24	3c NMe ₂	69
4	1d	NMe ₂ Me	2a	24	3d NMe ₂ 3d-1 OH NM OMe + OMe OH	le ₂ 33+56
5	1a		2b O O	12	3e O O Me	86
6	1a			2	$\begin{array}{c} O \\ 3f \\ Cl \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	NMe ₂ 40+55
7	1a		2c	24	3f + 3f-1	65+28
8	1e	NHMe	2a	2	³ g O Me	63
9	1f	OMe OMe	2a	24	3h OMe + (2,6)-4h ^[d]	60+17
10	1f		2b	24	3i OMe OMe	78
11	1g	O Me	2a	24	3j Me	64

Table 2. Reactions of Ar–H with quinones catalyzed by $In(OTf)_3^{[a]}$ in water.

^[a] Catalyst loading: 5 mol %. ^[b] Ar-H/quinine=1:2.

^[c] Isolated yield.

^[d] Di-substituted quinine **4h**, see Table 3, entry 8.

Entry	/	Ar-H	Qui	none	ArH/Q	Time	Product	Yield (2,5-/2	(%) ^{[b}} 2,6-) ^[c]
1	1a		2d	MeO	1 : 2	2 h	(2,5)- 4b	MeO OMe	85 (1: 0)
2	1b	NMe ₂	2d	Ö	1 : 2	24 h	(2,5)- 4c	MeO	76 (1: 0)
3	1d	NMe ₂	2d		1:2	24 h	(2,5)- 4d	Ö V NMe2 O MeO Me	81 (1: 0)
4	1e	NHMe	2d		1 : 2	40 min	(2,5)- 4e	MeO NMe2	89 (1: 0)
5	1b		2e	Me O	1:2	24 h	(2,5) -4f	Me + (2,6)-4f NMe ₂	76 (1: 1.1)
6	1a		2f	o o	1:2	24 h	(2,5) -4g	(2,6)-4g O	38 (1: 7.3)
7	1a		2a		1:1	24 h	(2,6)- 4a		79 (0: 1)
8	1f	OMe OMe	2a		1 : 1	24 h	(2,6)- 4h		79 ^[d] (0: 1)
9	1a		3a	Me ₂ N OMe	1 : 2	24 h	(2,6)- 4a	0	64 (0: 1)
10	1e		2a	0	1:1	2 h	(2,5)- 4i	Me O N N N	65 (1: 0)
11	1a		3h (MeO OMe	1 : 2	24 h	(2,6)- 4 j		65 (0: 1)
12	1a		3g [Me O N O	1 : 2	2 h	(2,5)- 4k		71 (1: 0)
13	1	e	3a		1:2	12 h	(2,5) -4k	+ (2,6)-4k Me O NMe ₂	83 (1: 3.2)

Table 3. Regioselectivity of the $In(OTf)_3$ -catalyzed^[a] reactions of Ar-H with quinones in water.

[a] Catalyst loading: 5 mol %.
 [b] Isolated yield.

 $^{[c]}$ Determined by ¹H and ¹³C NMR of the product mixture. $^{[d]}$ With mono-substituted product **3h** (13% yield).





and (2,5)-**4k**, could be obtained respectively (entries 12 and 13).

The regioselectivities are attributed to the different coordinating sites of benzoquinones to In(OTf)₃ (Figure 1). For 2-methoxy-1,4-benzoquinone, a chelation between In(III) with oxygen atoms in the methoxy and 1-carbonyl groups (A) would occur during the reaction, which resulted in the 2,5-selectivity; whereas in the case of the alkyl substituents (R = methyl and *t*-butyl), no chelation was possible and both carbonyl groups of 1,4-benzoquinone ring could coordinate with the Lewis acid, depending on the steric effect of the R group. The smaller methyl group led to the coordination of a Lewis acid to both carbonyl groups with no significant selectivity (a mixture of almost equal amounts of B and B') of the addition reaction; however, the bulky *t*-butyl group prevented the coordination of its neighboring carbonyl and favored the B' coordination mode, resulting in the 2,6-selectivity predominantly. In the case of heteroaromatic-substituted 1,4-benzoquinones (such as 3a and **3b**), although nitrogen- and oxygen-containing groups were present on the phenyl ring, no chelation between $In(OTf)_3$ and the carbonyl group occurred. Thus, the B' coordination mode was also predominant, resulting in the 2,6-regioselectivity.

Conclusion

A convenient and efficient method for the synthesis of aryl-substituted 1,4-quinones through a $In(OTf)_3$ -catalyzed conjugate addition reaction followed by an *in situ* dehydrogenation was developed in water. Water not only serves as the reaction media but also promotes the reaction. (2,6)-Regioselectivity was observed for the bis-arylation reaction and the regioselectivity was confirmed in the reactions of mono-substituted 1,4-quinones without the chelating group, by using either a *C*-nucleophile or *N*-nucleophile.

Experimental Section

General Remarks

IR spectra were recorded on a Bruker Tensor 27 infra-red spectrometer. ¹H and ¹³C NMR spectra were measured on a Bruker AV-300 spectrometer in CDCl₃ with tetramethylsilane as an internal standard. Mass spectra were recorded on a GCT-MS Micromass spectrometer. Elemental analyses were performed on a Carlo Flash 1112 Element Analysis instrument. Melting points were measured by a Beijing-Tike X-4 apparatus and are uncorrected. The X-ray crystal structures were measured on Rigaku R-axis RAPID IP. Common reagents and materials were purchased from commercial sources and purified before used.

Typical Experimental Procedure

A mixture of *N*,*N*-dimethyl-3-methoxyaniline (**1a**, 15.1 mg, 0.1 mmol), 1,4-benzoquinone (**2a**, 21.6 mg, 0.2 mmol), and $In(OTf)_3$ (2.8 mg, 0.005 mmol) in water (2 mL) was stirred at room temperature. The reaction was monitored by TLC. After **1a** had disappeared, the reaction mixture was extracted with dichloromethane (10 mL × 3). The combined organic layer was dried over Na₂SO₄ and evaporated to remove the solvent. The crude product was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 6:1) to give **3a** as a blue solid; yield: 24 mg (93%).

Synthesis of Diaryl-Substituted 1,4-Quinones with a One-Pot Reaction

A mixture of **1a** (30.2 mg, 0.2 mmol), **2a** (21.6 mg, 0.2 mmol) and In(OTf)₃ (5.6 mg, 0.01 mmol) in water (2 mL) was stirred at room temperature for 24 h. The reaction was monitored by TLC. After **1a** had disappeared, the reaction mixture was extracted by dichloromethane (6 mL × 3). The combined organic layer was dried over Na₂SO₄ and evaporated to remove the solvent. The crude product was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 6:1) to give (2,6)-**4a** as a red solid; yield: 32 mg (79%).

Characterization data for all products can be found in the Supporting Information file. Crystallographic data (excluding structure factors) for **4a**, **4c**, **4e**, and **4 h** have been deposited with the Cambridge Crystallographic Data Centre with the following supplementary publication nos.: (2,6)-**4a**: CCDC 288003, (2,5)-**4c**: CCDC 288004, (2,5)-**4e**: CCDC 288005, (2,6)-**4 h**: CCDC 288006. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax.: (internat.) + 44 1223/336-033; email: deposit@ccdc.cam.ac.uk].

Acknowledgements

We thank the National Natural Science Foundation of China and The Chinese Academy of Sciences for financial support.

References and Notes

- [1] R. H. Thomson, *Naturally Occurring Quinones IV*, Blackie Academic & Professional, London, **1997**.
- [2] For example, see: a) R. S. Coleman, F.-X. Felpin, W. Chen, J. Org. Chem. 2004, 69, 7309; b) W. T. Bradner, Cancer Treat. Rev. 2001, 27, 35; c) W. Wang, T. Li, R. Milburn, J. Yates, E. Hinnant, M. J. Luzzio, S. A. Noble, G. Attardo, Bioorg. Med. Chem. Lett. 1998, 8, 1579.
- [3] a) K. Arai, S. Shimizu, Y. Taguchi, Y. Yamamoto, *Chem. Pharm. Bull.* **1981**, *29*, 991; b) S. Shimizu, Y. Yamamoto, S. Koshimura, *Chem. Pharm. Bull.* **1982**, *30*, 1896; c) A. Kaji, R. Saito, Y. Hata, N. Kiriyama, S. Wakusawa, K. Miyamoto, *Chem. Pharm. Bull.* **1994**, *42*, 1682.
- [4] B. Zhang, G. Salituro, D. Szalkowski, Z. Li, Y. Zhang, I. Royo, D. Vitella, M. T. Diez, F. Pelaez, C. Ruby, R. L. Kendall, X. Mao, P. Griffin, J. Calaycay, J. R. Zierath, J. V. Heck, R. G. Smith, D. E. Moller, *Science*, **1999**, 284, 974.
- [5] a) Y. Fukuyama, J. Okino, M. Kodama, *Chem. Pharm. Bull.* **1991**, *39*, 1877; b) Y. Fukuyama, Y. Kiriyama, J. Okino, M. Kodama, *Tetrahedron Lett.* **1993**, *34*, 7633.
- [6] a) D. E. Kvalnes, J. Am. Chem. Soc. 1934, 56, 2478; b) I. Takahashi, O. Muramatsu, J. Fukuhara, H. Kitajima, Chem. Lett. 1994, 465.
- [7] a) B. Errazuriz, R. Tapia, J. A. Valderrama, *Tetrahedron Lett.* 1985, 26, 819; b) T. Higuchi, C. Satake, M. Hirobe, *J. Am. Chem. Soc.* 1995, *117*, 8879.
- [8] a) T. Itahara, J. Org. Chem. 1985, 50, 5546; b) P. K. Singh,
 B. K. Rohtagi, R. N. Khanna, Synth. Commun. 1992, 22, 987; c) L. S. Liebeskind, S. W. Riesinger, J. Org. Chem. 1993, 58, 408; d) R. A. Oliveira, F. Carazza, M. O. Pereira, Synth. Commun. 2000, 30, 4563.
- [9] K. Maruyama, T. Shio, Y. Yamamoto, Bull. Chem. Soc. Jpn. 1979, 52, 1877.

- [10] a) J. S.Yadav, B. V. S. Reddy, T. Swamy, *Tetrahedron Lett.* **2003**, 44, 9121; b) J. S. Yadav, B. V. S. Reddy, R. T. Swamy, *Synthesis* **2004**, 106.
- [11] M. C. Pirrung, Y. Liu, L. Deng, D. K. Halstead, Z. Li, J. F. May, M. Wedel, D. A. Austin, N. J. G. Webster, J. Am. Chem. Soc. 2005, 127, 4609.
- [12] a) M. C. Pirrung, K. Park, Z. Li, Org. Lett. 2001, 3, 365;
 b) M. C. Pirrung, L. Deng, Z. Li, K. Park, J. Org. Chem. 2002, 67, 8374.
- [13] S.-L. Zhang, Z.-S. Huang, L.-K. An, X.-Z. Bu, L. Ma, Y.-M. Li, A. S. C. Chan, L.-Q. Gu, *Org. Lett.* **2004**, *6*, 4853.
- [14] Conjugate addition reactions of aromatic C-nucleophiles to α,β-unsaturated carbonyl compounds, see: K. B. Jensen, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, Angew. Chem. Int. Ed. 2001, 40, 160.
- [15] a) C. J. Li, T. H. Chan, Organic Reactions in Aqueous Media, John Wiley, New York, 1997; b) Organic Synthesis in Water; (Ed.: P. A. Grieco), Blackie Academic and Professional, London, 1998; c) A. Lubineau, J. Auge, in: Modern Solvent in Organic Synthesis, (Ed.: P. Knochel), Springer Verlag, Berlin, 1999; d) C. J. Li, Chem. Rev. 2005, 105, 3095; e) C. J. Li, Chem. Rev. 1993, 93, 2023.
- [16] R. Ding, H. B. Zhang, Y. J. Chen, L. Liu, D. Wang, C.-J. Li, Synlett 2004, 555.
- [17] a) U. M. Lindstrom, Chem. Rev. 2002, 102, 2751; b) C. J. Li; D. Wang, CHEMTRACTS Org. Chem. 2003, 16, 59.
- [18] Regarding the mechanism of the Lewis acid-catalyzed reaction of *C*-nucleophiles to benzoquinone, see ref.^[10]
- [19] The ratio of 2,5- to 2,6-isomers was determined by the ratio of the ¹H NMR peaks of the reaction mixture at δ = 2.12 and 2.08 ppm.
- [20] The ratio of 2,5- to 2,6-isomers was determined by the ratio of the ¹H NMR peaks of the reaction mixture at δ = 6.57, 6.68 and 6.64, 6.71 ppm.