

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/7938539>

[5 + 1] Annulation: A Synthetic Strategy for Highly Substituted Phenols and Cyclohexenones

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · MAY 2005

Impact Factor: 12.11 · DOI: 10.1021/ja043023c · Source: PubMed

CITATIONS

147

READS

18

6 AUTHORS, INCLUDING:



Xihe Bi

Northeast Normal University

65 PUBLICATIONS 1,160 CITATIONS

SEE PROFILE



Dewen Dong

Chinese Academy of Sciences

136 PUBLICATIONS 1,856 CITATIONS

SEE PROFILE

[5 + 1] Annulation: A Synthetic Strategy for Highly Substituted Phenols and Cyclohexenones

Xihe Bi, Dewen Dong,* Qun Liu,* Wei Pan, Lei Zhao, and Bing Li

Department of Chemistry, Northeast Normal University, Changchun, 130024, P. R. China

Received November 19, 2004; E-mail: dongdw663@nenu.edu.cn

The regiospecific preparation of polyfunctionalized aromatic compounds represents a major challenge in organic synthesis.¹ Classical approaches are established on the modification of given arenes, which rely heavily on the conventional electrophilic or nucleophilic substitutions, catalyzed coupling reactions, and metalation–functionalization reactions. However, these synthetic routes suffer from a long multistep reaction sequence, lower yields of target products, and, in particular, serious regiochemical ambiguities due to the activating/deactivating and orienting effects of the substituents. Alternatively, important modern approaches are developed by the regioselective construction of the aromatic skeleton from acyclic precursors, in which the substitution pattern of the final product is dictated by the structures and functionalities of the precursors. The benzannulation reactions include [3 + 2 + 1] Dötz reaction of Fischer carbene complexes,² Danheiser alkyne–cyclobutanone [4 + 2] cyclization,³ [4 + 2] cycloaddition of metalacyclopentadienes and alkynes,⁴ transition-metal-catalyzed [2 + 2 + 2] and [4 + 2] cycloaddition,⁵ [3 + 3] cyclocondensation of bielelectrophiles with binucleophiles,⁶ and 1,6-electrocyclic reaction.⁷ Some of these methodologies have been applied in the synthesis of natural products and have met with considerable success since the formation of a regioisomeric mixture can be avoided in most cases.⁸ Nonetheless, regiochemistry still challenges the above reactions. In the benzannulation of Fischer carbene complexes, for example, terminal alkynes can be incorporated into the assembled hydroquinone with high regioselectivity, while internal alkynes are prone to much poorer regioselectivity.⁹ The inconvenience and difficulty caused by unsymmetry and the complexity of acyclic substrates limit the further application of these reactions. Conceptually, a [5C + 1C] strategy should be a regiospecific reaction, which may overcome the above drawbacks. So far, to the best of our knowledge, there is no such [5 + 1] benzannulation reaction reported. This stems, at least to some extent, from the fact that the unsaturated degree of aromatization is hard to attain.

Over the past decades, α -oxo ketene-(*S,S*)-acetals are emerging as versatile intermediates in organic synthesis.¹⁰ As three-carbon 1,3-ielectrophilic synthons, α -oxo ketene-(*S,S*)-acetals have found their application in the [3 + 3] strategy for the synthesis of substituted and fused aromatic and heterocyclic structural frameworks by reacting with Grignard reagent, Reformatsky reagent, and 3-trimethylsilylallyllithium.¹¹ Recently, [4 + 2] Robinson aromatic annulation of 4-bis(methylthio)-3-buten-2-one with active methylene ketones to substituted phenols was also achieved.¹²

During the course of our studies on the chemistry of α -oxo ketene-(*S,S*)-acetals,¹³ we investigated the aldol reactions of α -acyl ketene-(*S,S*)-acetals with aromatic aldehydes. It is noted that α -alkenyl ketene-(*S,S*)-acetals **1** generated from the aldol reaction show promising structural feature as novel organic intermediates for their (1) double Michael acceptors serving as five-carbon 1,5-bielelectrophilic species, (2) dense and flexible substitution patterns, and (3) good leaving alkylthio groups subjected to a S_NV -type

Scheme 1. Reaction of α -Alkenyl Ketene-(*S,S*)-Acetals **1** with Nitroalkanes **2**

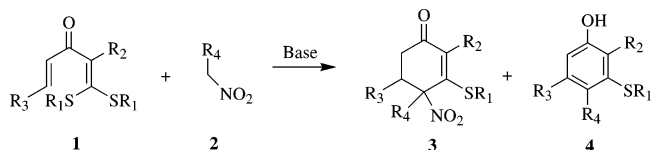


Table 1. Reaction of **1a** with **2a** under Different Conditions

entry ^a	solvent	DBU (equiv)	T (°C)	time (h)	Yield (%) ^c	
					3a	4a
1	THF	1.0	r.t.	10	48	32
2	CH ₃ CN	1.0	r.t.	10	29	40
3	DMF	1.0	r.t.	10	36	48
4	DMF	1.0	r.t.	0.5	88	trace
5	DMF	1.0	r.t. ~ 70 ^b	1.2	10	58
6	DMF	1.5	r.t. ~ 70 ^b	1.0	n.d.	67

^a Three equivalents of C₂H₅NO₂ was used in all the reactions. ^b The reaction mixture was heated to 70 °C after the consumption of **1a** monitored by TLC. ^c Isolated yields.

reaction.¹⁰ These prompted us to explore the feasibility of the construction of a substituted phenolic ring relying upon utilization of **1** as the five-carbon 1,5-bielelectrophilic components in a [5 + 1] annulation with various one-carbon nucleophilic components.

In this communication, nitroalkanes **2** are selected as the one-carbon components since they are well-known carbon nucleophiles, and the nitro group is a good leaving group in the β -elimination reaction.¹⁴

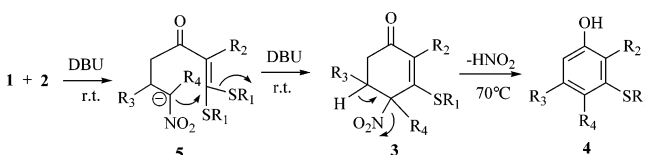
The reaction of 2-[bis(ethylthio)methylene]-*N*-(4-chlorophenyl)-3-oxo-5-*p*-tolylpent-4-enamide **1a** with nitroethane **2a** was investigated in the presence of various bases, such as K₂CO₃, Et₃N, NaH, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). It was observed that both substituted cyclohexenone **3a** and substituted phenol **4a** could be obtained in the presence of the above bases (Scheme 1). Among those examined, DBU proved to be the most efficient base for the good yield to produce **4a**. Obviously, **3a** was a very stable intermediate of the reaction and finally converted into **4a** via an aromatization process. The reaction media and the amount of DBU were then examined; some of the results are listed in Table 1. All of the reactions could proceed to afford **3a** and/or **4a** in the tested solvents, such as THF, acetonitrile, and DMF. By comparison, DMF was a more efficient solvent and was selected for the following investigations. It is worth noting that the reaction could be controlled to exclusively yield **3a** or **4a** by varying the amount of base and the reaction temperature (entries 4 and 6).

Under the conditions described in Table 1, entry 6, a range of reactions were carried out with systematically varied substrates **1** and nitroalkanes **2**, and some results are listed in Table 2 (entries 1–14). It is observed that all of the reactions proceeded smoothly under the essentially mild basic conditions to afford the corresponding substituted phenols **4a–n** in moderate to good yields. The

Table 2. Reactions of α -Alkenoyl Ketene-(*S,S*)-Acetals **1** with Nitroalkanes **2**

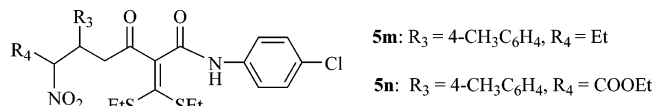
entry ^a	phenols 4	yield (%) ^c	α -Alkenoyl Ketene-(<i>S,S</i>)-Acetals				Nitroalkanes		Cyclohexenones		entry ^b
			1	R ₁	R ₂	R ₃	2	R ₄	3	yield (%) ^c	
1	4a	67	1a	Et	4-ClC ₆ H ₄ NHCO	4-CH ₃ C ₆ H ₄	2a	Me	3a	88	1'
2	4b	72	1b	Et	4-ClC ₆ H ₄ NHCO	3,4-O ₂ CH ₂ C ₆ H ₃	2a	Me	3b	86	2'
3	4c	80	1c	Et	4-ClC ₆ H ₄ NHCO	4-ClC ₆ H ₄	2a	Me	3c	91	3'
4	4d	76	1d	Et	4-ClC ₆ H ₄ NHCO	4-FC ₆ H ₄	2a	Me	3d	90	4'
5	4e	82	1e	Et	4-ClC ₆ H ₄ NHCO	2-thienyl	2a	Me	3e	93	5'
6	4f	75	1f	Et	4-ClC ₆ H ₄ NHCO	2-furyl	2a	Me	3f	88	6'
7	4g	64	1g	Et	4-ClC ₆ H ₄ NHCO	PhCH=CH	2a	Me	3g	82	7'
8	4h	72	1h	Et	2-MeC ₆ H ₄ NHCO	4-CH ₃ C ₆ H ₄	2a	Me	3h	85	8'
9	4i	79	1i	Et	PhCO	4-CH ₃ C ₆ H ₄	2a	Me	3i	90	9'
10	4j	56	1j	Et	PhCO	PhCH=CH	2a	Me	3j	78	10'
11	4k	77	1k	Me	4-ClC ₆ H ₄ NHCO	4-CH ₃ C ₆ H ₄	2a	Me	3k	93	11'
12	4l	65	1l	<i>n</i> -Bu	4-ClC ₆ H ₄ NHCO	4-CH ₃ C ₆ H ₄	2a	Me	3l	86	12'
13	4m	78	1a	Et	4-ClC ₆ H ₄ NHCO	4-CH ₃ C ₆ H ₄	2b	Et	5m	95	13'
14	4n	52	1a	Et	4-ClC ₆ H ₄ NHCO	4-CH ₃ C ₆ H ₄	2c	COOEt	5n	83	14'

^a Reagents and conditions: DBU (1.5 equiv), r.t. to ~70 °C, 1.0–1.5 h, DMF. ^b Reagents and conditions: DBU (1.0 equiv), r.t., 0.5–1.0 h, DMF. ^c Isolated yields.

Scheme 2. Proposed Mechanism for the [5 + 1] Annulation

results exhibit the scope and generality of the novel benzannulation reaction with respect to a range of aliphatic and aromatic substrates. Indeed, the protocol provides a straightforward pathway to construct highly substituted phenols. Moreover, some other characteristics of this reaction are noteworthy. It describes a new route to asymmetric biaryls (e.g., in entries 1–4), which are generally prepared via metal-catalyzed crossing-coupling reactions.¹⁵ The reasonable result obtained for **4g** and **4j** illustrates the potential of this reaction for the synthesis of configuration-locked hydroxylated stilbenes, which are widely represented in nature and have become of particular interest to scientists because of their wide range of biological activity.¹⁶

In the next studies, a range of reactions with the same substrates (**1** and **2**) as described above were performed with 1 equivolar DBU at room temperature for a relatively short time (0.5–1 h). The results are summarized in Table 2 (entries 1'–14'). To our delight, the corresponding cyclohexenones **3** were obtained in high yields in most cases (entries 1'–12'). Actually, substituted cyclohexenones are also an important kind of organic molecule present in numerous natural products along with bio- and pharmacological activities. Therefore, we present a [5C + 1C] strategy for the synthesis of such useful compounds.¹⁷ Interestingly, Michael addition adducts **5m** and **5n** were obtained in cases **2b** and **2c** (entries 13' and 14'). This result provides the evidence for the mechanism of the annulation reaction.



On the basis of all of the above results, a possible mechanism for annulation of **1** and **2** is proposed as shown in Scheme 2. The anion of nitroalkanes first adds to the double bond bearing an aryl group, followed by an intramolecular addition–elimination (S_NV) reaction to afford a cyclohexenone of type **3**, which sheds HNO₂ and is then aromatized to furnish a target product of type **4**.

In summary, a novel [5 + 1] annulation strategy is developed for the synthesis of highly functionalized phenols and cyclohex-

enones. The simplicity of execution, ready availability of substrates, and broad range of potential products make this synthetic strategy most attractive for academic research and practical applications.

Acknowledgment. Financial support of this research was provided by the NNSFC (20272008) and the Key Grant Project of Chinese Ministry of Education (10412).

Supporting Information Available: Experimental details and spectral data for **1a**–**1l**, **4a**–**4n**, **3a**–**3l**, **5m**, and **5n**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002. (b) *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley-VCH: New York, 2003.
- (2) Döt, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, 28, 187.
- (3) (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, 49, 1672. (b) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, 112, 3093.
- (4) (a) Xi, Z.; Sato, K.; Gao, Y.; Lu, J.; Takahashi, T. *J. Am. Chem. Soc.* **2003**, 125, 9568. (b) Takahashi, T.; Ishikawa, M.; Huo, S. *J. Am. Chem. Soc.* **2002**, 124, 388 and reference therein.
- (5) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, 100, 2901.
- (6) (a) Langer, P.; Bose, G. *Angew. Chem., Int. Ed.* **2003**, 42, 4033. (b) Katritzky, A. R.; Li, J.; Xie, L. *Tetrahedron* **1999**, 55, 8263.
- (7) (a) Serra, S.; Fuganti, C.; Moro, A. *J. Org. Chem.* **2001**, 66, 7883. (b) Turnbull, P.; Moore, H. W. *J. Org. Chem.* **1995**, 60, 644.
- (8) (a) Smith, A. B., III; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, 122, 4984. (b) Dudley, G. B.; Takaki, K. S.; Cha, D. D.; Danheiser, R. L. *Org. Lett.* **2000**, 2, 3407.
- (9) Wulff, W. D.; Tang, P.-C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, 103, 7677.
- (10) Reviews: (a) Dieter, R. K. *Tetrahedron* **1986**, 42, 3029. (b) Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, 46, 5423.
- (11) (a) Kocienski, P. J.; Pontiroli, A.; Liu, Q. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2356. (b) Ila, H.; Junjappa, H.; Barun, O. *J. Organomet. Chem.* **2001**, 624, 34. (c) Datta, A.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1988**, 29, 497.
- (12) Barun, O.; Nandi, S.; Panda, K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2002**, 67, 5398.
- (13) Selected examples: (a) Wang, M.; Xu, X.; Liu, Q.; Xiong, L.; Yang, B.; Gao, L. *Synth. Commun.* **2002**, 32 (22), 3437. (b) Bi, X.; Liu, Q.; Sun, S.; Liu, J.; Pan, W.; Zhao, L.; Dong, D. *Synlett* **2005**, 1, 49.
- (14) Ono, N. In *The Nitro Group in Organic Synthesis*; Feuer, H., Ed.; Wiley-VCH: New York, 2001; p 182.
- (15) Anastasia, L.; Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; p 311.
- (16) (a) Belofsky, G.; French, A. N.; Wallace, D. R.; Dodson, S. L. *J. Nat. Prod.* **2004**, 67, 26. (b) Dogan, Z.; Paulini, R.; Rojas Stütz, J. A.; Narayanan, S.; Richert, C. J. *Am. Chem. Soc.* **2004**, 126, 4762.
- (17) Selected synthetic methods for cyclohexenones: (a) Lee, S. I.; Park, J. H.; Chung, Y. K.; Lee, S.-G. *J. Am. Chem. Soc.* **2004**, 126, 2714. (b) Tanaka, K.; Fu, G. C. *Org. Lett.* **2002**, 4, 933. (c) Taber, D. F.; Kanai, K.; Jiang, Q.; Bui, G. *J. Am. Chem. Soc.* **2000**, 122, 6807.

JA043023C