Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient Selective Formation of C-C Single Bonds and C=C Double Bonds by NBS-Promoted Oxidative Coupling of β-Keto Esters

Zhiguo Wang [a], Guodong Yin [a], Aihua Chen [a], Shengli Hu [a] & Anxin Wu [a]
[a] Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan, China
Version of record first published: 14 Dec 2007.

To cite this article: Zhiguo Wang , Guodong Yin , Aihua Chen , Shengli Hu & Anxin Wu (2007): Efficient Selective Formation of C-C Single Bonds and C=C Double Bonds by NBS-Promoted Oxidative Coupling of β-Keto Esters, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:24, 4399-4405

To link to this article: http://dx.doi.org/10.1080/00397910701578123

Synthetic Communications®, 37: 4399–4405, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701578123

Efficient Selective Formation of C-C Single Bonds and C═C Double Bonds by NBS-Promoted Oxidative Coupling of β-Keto Esters

Zhiguo Wang, Guodong Yin, Aihua Chen, Shengli Hu, and Anxin Wu

Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan, China

Abstract: A new application of NBS, which results in the oxidative coupling of β-keto esters to selectively form C-C single and C═C double bonds, can be controlled by the amount of NBS and *t*-BuOK employed. This methodology adds a new entry to C-C single and C═C double-bond formation between active methylene groups under mild conditions with high selectivity.

Keywords: active methylene groups, β-keto esters, NBS, oxidative coupling

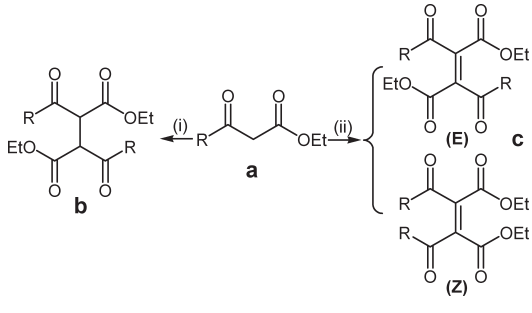
Saturated and unsaturated 1,4-diketones are important precursors for synthesis of some natural and synthetic products containing furan, pyrrole, thiophene, and pyridazine derivative systems. To date, a variety of synthetic methods for the preparation of 1,4-diketones via homocoupling procedures have been developed.[1–8] In addition, in terms of availability and ease of handling, N-bromosuccinimide (NBS) is a superior brominating reagent, and lots of 1,3-dicarbonyl compounds, such as β-keto esters, β-diketones, and

Received January 26, 2007
Address correspondence to Zhiguo Wang, Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, China. E-mail: chwangzg@yahoo.com.cn

β-sulfonyl ketones, may be reacted with NBS to afford the corresponding α-brominated products in good yields.[9,10]

In this article, we report a novel application of NBS, namely the oxidative coupling of β-keto esters to selectively synthesize saturated or unsaturated 1,4-diketones, which is efficiently controlled by the amount of NBS and *t*-BuOK employed. For example, 2.1 molar equivalents of NBS and an equimolar amount *t*-BuOK delivered only saturated 1,4-diketones (Scheme 1, left). When the amounts of NBS and *t*-BuOK were in the range of 2.1–4.0 molar, a mixture of saturated and unsaturated 1,4-diketones was obtained. When the amount was continually increased to 5.0 molar, experimental results indicated that only unsaturated 1,4-diketones were produced (Scheme 1, right). To the best of our knowledge, this is a previously unknown method for the formation of C-C single and C=C double bonds.

To begin our study, several base systems (K_2CO_3, $CsCO_3$, Na-EtOH, NaH, and *t*-BuOK) were tested, and *t*-BuOK was proven to be more effective for the reaction. The typical procedure for synthesis of compound **5b** is as follows: To a stirred solution of ethyl benzoylacetate **5a** (236 mg, 1 mmol) in anhydrous THF (10 mL) under a nitrogen atmosphere, *t*-BuOK (235 mg, 2.1 mmol) was added. To this mixture, a solution of NBS (372 mg, 2.1 mmol) in anhydrous THF (15 mL) was added dropwise, and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure; the residue was quenched with water (40 mL), followed by extraction with dichloromethane (3 × 10 mL). Then the solvent was evaporated, and the residue was purified by column chromatography with hexane–EtOAc (5:1), which delivered the saturated product **5b** (223 mg) in 95% yield. To establish the generality of the procedure, under these optimized reaction conditions, other substrates, as shown in Table 1, were examined. The corresponding saturated 1,4-diketones were obtained in excellent yields (90–96%, Table 1, product **b**) except for ethyl 4-nitrobenzoylacetate **7a** as substrate (entry 7). Probably, the α-brominated β-keto esters intermediate was readily converted to other



Scheme 1.

Table 1. Selective preparation of C-C single and C═C double bonds

Entry	Substrates **a**	Products **b**[a]	Products **c**[a]
1	R = C_6H_5	**1b** (95)	**1c** (80, *E:Z* = 3:2)
2	R = 4-$MeOC_6H_4$	**2b** (96)	**2c** (80, *E*-isomer)[b]
3	R = 3,4-$(MeO)_2C_6H_3$	**3b** (92)	**3c** (68, *E*-isomer)[b]
4	R =3,4,5,-$(MeO)_3C_6H_2$	**4b** (90)	**4c** (65, *E*-isomer)[b]
5	R = 3,4-$(OCH_2O)C_6H_3$	**5b** (95)	**5c** (90, *E*-isomer)[b]
6	R = 3-MeO-4-$PhCH_2O$-C_6H_3	**6b** (90)	**6c** (82, *E:Z* = 4:1)
7	R = 4-$NO_2C_6H_4$	—	**7c** (55, *E*-isomer)[b]
8	Ethyl acetoacetate	**8b** (95)	—
9	Acetylacetone	**9b** (94)	—
10	Diethyl malonate	**10b** (92)	**10b** (82)

[a]Isolated yields in parentheses.
[b]*E*-isomers were the exclusive isolated products.

products in the presence of the strong electron-withdrawing (NO_2) on the aromatic ring.

Interestingly, when 5.0 molar equivalents of NBS and an equivmolar amount *t*-BuOK were employed, the only unsaturated olefinic product (*E*)-**5c** was obtained in 90% yield (entry 5). In contrast to the ^{1}H NMR spectrum recorded for **5b**, the spectrum for (*E*)-**5c** did not show the CH methine resonance at $\delta = 5.43$ ppm. To further confirm the presence of a C═C double bond and to determine precise structural features of (*E*)-**5c**, an X-ray structure determination (Fig. 1) was performed.[11] Specifically, the bond length between C9–C9a was found to be 1.334 Å, confirming the presence of a double bond. *E*-Isomer was the exclusive isolated product, and only a trace amount of the *Z*-isomer was detected by ^{1}H NMR analysis of the crude reaction mixture. Similar reactions with substrates **2a**–**4a**

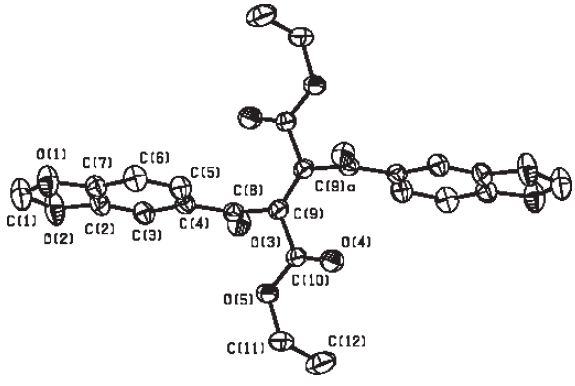


Figure 1. X-ray structure of compound (*E*) **5c**.

yielded the corresponding major olefinic products, *E*-isomers of **2c**–**4c** in moderate to good yields (65–80%), respectively (entries 2–4). When ethyl benzoylacetate **1a** (entry 1) was reacted under the same conditions, an inseparable mixture of regioisomeric products, (*E*)- and (*Z*)-**1c**, in an approximate ratio of 3:2 (estimated from ^{1}H NMR analysis of crude product mixtures) was produced. Similarly, employing substrate **6a** afforded (*E*)-and (*Z*)-**6c** in a ratio of 4:1 (entry 6). It was notable that **7a** gave (*E*)-**7c** in moderate yield (55%) even though the corresponding saturated product was not obtained in that case.

To extend the scope of this novel reaction, we further investigated the use of aliphatic 1,3-dicarbonyl compounds, ethyl acetoacetate **8a**, acetylacetone **9a**, and diethyl malonate **10a** under identical reaction conditions. Most notably, when the acetyl group was present in the substrates (entries 8 and 9), oxidation to the C=C double-bond level was not observed even when the reaction time was prolonged to three days or the reaction temperature was elevated to 50°C. We hypothesize that the presumed keto-enol tautomerization precludes further oxidation.[12] X-ray crystal structure confirms the structure of **9b** as the double enol tautomer.[13] In addition, the ^{1}H NMR spectrum recorded for **9b** displays a resonance at $\delta = 16.8$ ppm, which corresponds to the H-atom involved in the intramolecular hydrogen-bonding interaction.

In summary, we have described the novel use of NBS/*t*-BuOK mixtures to selectively form C-C single bonds or C=C double bonds during the oxidative coupling of β-keto esters. This research represents a new approach to C-C single and C=C double-bond formation, which should be broadly applicable to active methylene compounds. The reaction possesses several advantageous features including good yields and easily accessible starting materials, which suggest that this synthetic approach should be widely applicable in organic synthesis of natural and synthetic products.

EXPERIMENTAL

NBS was recrystallized from AcOH and dried in vacuo before use. THF was absolutely dried before use. Column chromatography was performed using 200- to 300-mesh silica gel. The melting point was determined with an XT4A micromelting-point apparatus and was uncorrected. Infrared spectra were recorded on a Perkin-Elmer PE-983 spectrometer as KBr film with absorption in centimeters^{-1}. NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 400 spectrometer, and resonances are given in parts per million (δ) relative to TMS. Mass spectra were measured on a Finnigan Trace MS spectrometer. Elemental analyses were performed on a Vario EL III elementary analysis instrument. The general experimental procedure for synthesis of compounds **b** and **c** are analogous as given in the text. Selected new compounds are characterized and listed.

(*E*)-**2c**: White crystals, mp 137–138°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.97$ (d, 4H, $J = 8.8$ Hz), 6.99 (d, 4H, $J = 8.8$ Hz), 4.03 (q, 4H, $J = 7.2$ Hz), 3.89 (s, 6H), 0.97 (t, 6H, $J = 7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 189.6$, 164.1, 162.7, 141.8, 131.2, 128.9, 114.1, 62.5, 55.5, 13.4. IR (KBr): 1721 (s), 1665 (s) cm^{-1}. EI-MS: m/z (%) = 441 (14) $[M + 1]^+$, 135 (100). Anal. calcd. for $C_{24}H_{24}O_8$: C, 65.45; H, 5.49. Found: C, 65.34; H, 5.56.

(*E*)-**3c**: White crystals, mp 142–143°C. ^{1}H NMR (400 MHz, $CDCl_3$):δ= 7.57–7.53 (m, 4H), 6.90 (d, 2H, $J = 8.4$ Hz), 4.21 (q, 4H, $J = 7.2$ Hz), 3.96 (s, 6H), 3.94 (s, 6H), 1.27 (t, 6H, $J = 7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.0$, 167.5, 153.6, 148.9, 129.0, 123.3, 110.0, 109.8, 61.1, 55.8, 55.7, 13.8 (only 12 of the 13 expected resonances were observed). IR (KBr): 1738 (s), 1675 (s) cm^{-1}. EI-MS: m/z (%) = 501 (7) $[M + 1]^+$, 165 (100). Anal. calcd. for $C_{26}H_{28}O_{10}$: C, 62.39; H, 5.64. Found: C, 62.48; H, 5.58.

(*E*)-**4c**: White crystals, mp 151–152°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$ (s, 4H), 4.38 (t, 4H, $J = 7.2$ Hz), 3.92–3.90 (m, 18H), 1.40 (t, 6H, $J = 7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.2$, 152.9, 142.1, 125.5, 107.2, 106.7, 61.1, 60.9, 56.2, 14.4 (only 10 of the 11 expected resonances were observed). IR (KBr): 1718 (s), 1638 (s) cm^{-1}. EI-MS: m/z (%) = 561 (9) $[M + 1]^+$, 195 (100). Anal. calcd. for $C_{28}H_{32}O_{12}$: C, 59.99; H, 5.75. Found: C, 60.08; H, 5.71.

(*E*)-**5c**: Green crystals, mp 145–146°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.54–7.51 (m, 4H), 6.89 (d, 2H, $J = 8.0$ Hz), 6.09 (s, 4H), 4.07 (q, 4 H, $J = 7.2$ Hz), 1.01 (t, 6H, $J = 7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 189.0$, 162.5, 152.6, 148.4, 141.7, 130.6, 126.0, 108.2, 107.7, 102.0, 62.6, 13.4. IR (KBr): 1721 (s), 1668 (s) cm^{-1}. EI-MS: m/z (%) = 469 (39) $[M + 1]^+$, 148 (100). Anal. calcd. for $C_{24}H_{20}O_{10}$: C, 61.54; H, 4.30. Found: C, 61.50; H, 4.37.

(*E*)-**7c**: White crystals, mp 147–148°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.28$ (d, 4H, $J = 2.4$ Hz), 8.22 (d, 4H, $J = 2.4$ Hz), 4.44 (q, 4H, J =7.2 Hz), 1.43 (t, 6H, $J = 7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.7$, 150.5, 135.8, 130.6, 123.5, 61.9, 14.2 (only 7 of the 9 expected resonances were observed). IR (KBr): 1733 (s), 1674 (s). EI-MS: m/z (%) = 471 (14) $[M + 1]^+$, 150 (100). Anal. calcd. for $C_{22}H_{18}N_2O_{10}$: C, 56.17; H, 3.86; N, 5.96. Found: C, 56.21; H, 3.80; N, 6.02.

ACKNOWLEDGMENT

This work was supported by Central China Normal University, the Scientific Research Foundation for the Returned Overseas Chinese Scholars, and State Education Ministry (No. [2005] 383).

REFERENCES

1. Linker, T.; Linker, U. Simple synthesis of tetra-Acceptor-substituted alkenes by the formal dehydrodimerization of malonates. *Angew. Chem. Int. Ed.* **2000**, *39*, 902.
2. Quast, H.; Seefelder, M.; Ivanova, S.; Heubes, M.; Peters, E. M.; Peters, K. Tetraacylethenes as dienophiles and hetero dienes in two-step Diels-Alder reactions. *Eur. J. Org. Chem.* **1999**, 3343.
3. Wu, A.; Zhao, Y.; Chen, N.; Pan, X. A Modification of the knorr oxidative coupling method for preparation of 1,4-diketones. *Synth. Commun.* **1997**, *27*, 331.
4. Skarzewski, J.; Zon, J. Tetramethyl ethene-1,1,2,2-tetracarboxylate: oxidative homocoupling of dimethyl malonate in the presence of magnesium oxide. *Synth. Commun.* **1995**, *25*, 2953.
5. Liu, Y.-C.; Romero, J. R. Chemical and electrochemical oxidative dimerization of carbonyl compounds by cerium(IV) salts. a comparative Study. *Tetrahedron Lett.* **1995**, *36*, 8757.
6. Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C. Reactions of arylazosulfones with the conjugate bases of active-methylene compounds. *Tetrahedron* **1995**, *51*, 3905.
7. Villemin, D.; Alloum, A. B. Potassium fluoride on alumina: oxidative coupling of acidic carbon compounds with diiodine. *Synth. Commun.* **1992**, *22*, 3169.
8. Aidhen, I. S.; Narasimhan, N. S. Intramolecular arylation of soft carbon centre or enolate using Mn(III) acetate: studies towards spirostructure of fredericamycin A. *Tetrahedron Lett.* **1989**, *30*, 5323.
9. (a) Yang, D.; Yan, Y.-L.; Lui, B. Mild α-halogenation reactions of 1,3-dicarbonyl compounds catalyzed by lewis acids. *J. Org. Chem.* **2002**, *67*, 7429; (b) Misra, A. P.; Raj, K.; Bhaduri, A. P. In Search of Imidazo [1,2-a] pyridine derivatives exhibiting resistance for catalytic hydrogenation. *Synth. Commun.* **1999**, *29*, 3227; (c) Coats, S. J.; Wasserman, H. H. The conversion of α-bromo-β-dicarbonyls to vicinal tricarbonyls using dimethyldioxirane and base. *Tetrahedron Lett.* **1995**, *36*, 7735; (d) Endo, M.; Droghini, R. 1-β-Methylcarbapenem intermediates Stereoselective synthesis of (3*S*,4*R*)-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-4-[(1*R*)-3-methoxycarbonyl-1-methyl-2-oxopropyl]azetidin-2-one and its related chemistry. *Can. J. Chem.* **1988**, *66*, 1400; (e) Hlavka, J.; Bitha, P.; Lin, Y.; Strohmeyer, T. Reactions of 2,3-diamino-4(3*H*)-pyrimidinones. II. *J. Heterocycl. Chem.* **1985**, *22*, 1317; (f) Yoshida, J.; Yano, S.; Ozawa, T.; Kawabata, N. Regioselective synthesis of dihydrofurans from 2,2-dibromo-1,3-diketone and olefin using copper. *Tetrahedron Lett.* **1984**, *25*, 2817; (g) Kaye, P. T.; Meakins, G. D.; Smith, A. K.; Tirel, M. D. *N*,*N*-disubstituted 2-aminothiazole-5-carboxylates: preparation and rotation of functional groups. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1677.
10. (a) Boyd, R. E.; Rasmussen, C. R.; Press, J. B. Regiospecific synthesis of unsymmetrical α-bromoketones. *Synth. Commun.* **1995**, *25*, 1045; (b) Karimi, S.; Grohmann, K. G. Intramolecular ring-opening of cyclopropanones by enolate anions. *J. Org. Chem.* **1995**, *60*, 554; (c) Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. Rate constants for halogen atom transfer from representative α-halo carbonyl compounds to primary alkyl radicals. *J. Org. Chem.* **1989**, *54*, 1826; (d) Curran, D. P.; Chang, C. T. Atom transfer cyclization reactions of α-iodo esters, ketones, and malonates: examples of selective 5-exo, 6-endo, 6-exo, and 7-endo ring closures. *J. Org. Chem.* **1989**, *54*, 3140.
11. Wang, Z.; Chen, A.; Yin, G.; Wu, A. Diethyl 2,3-bis(benzo[1,3]dioxole-5-carbonyl)-but-2-enedioate. *Acta Cryst.* **2005**, *E61*, o2320.

12. Burdett, J. L.; Rogers, M. T. Keto-Enol tautomerism in β-dicarbonyls studied by nuclear magnetic resonance spectroscopy.[1] I. Proton chemical shifts and equilibrium constants of pure compounds. *J. Am. Chem. Soc.* **1964**, *86*, 2105.
13. (a) Schaefer, J. P.; Wheatley, P. J. The crystal and molecular structure of tetra-acetylethane. *J. Chem. Soc. A* **1966**, 528; (b) Power, L. F.; Turner, K. E.; Moore, F. H. J. Refinement of the crystal and molecular structure of tetraacetylethane by neutron diffraction. *Cryst. Mol. Struct.* **1975**, *5*, 59; (c) Lyssenko, K. A.; Lyubetsky, D. V.; Antipin, M. Y. Intramolecular H-bonds in the crystal of tetraacetylethane: 3c-4e interaction or a dynamic disorder?. *Mendeleev Commun.* **2003**, *13*, 60.