A Convenient and Practical Approach to α-Diketones via Reactions of Internal Aryl Alkynes with *N*-Iodosuccinimide/Water

Mingyu Niu,[a] Hua Fu,*[a] Yuyang Jiang,[a,b] Yufen Zhao[a]

[a] Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. of China

[b] Key Laboratory of Chemical Biology, Guangdong Province, College of Shenzhen, Tsinghua University, Shenzhen 518057, P. R. of China
Fax +86(10)62781695; E-mail: fuhua@mail.tsinghua.edu.cn

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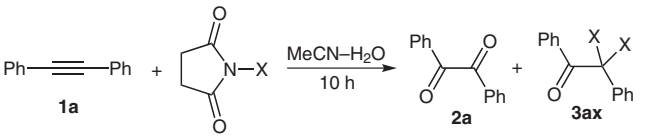
Abstract: A convenient and practical approach to α-diketones via reactions of alkynes with *N*-iodosuccinimides/water at 70 °C has been developed.

Key words: α-diketones, alkynes, *N*-iodosuccinimide, convenient and practical, water

A convenient and efficient approach to α-diketones is highly desirable because such compounds are versatile building blocks for a variety of chemical transformations[1] such as the preparation of biologically active heterocyclic compounds,[2] photoinitiators[3] and chiral alcohols.[4] Although several methods have been reported for synthesis of α-diketones,[5] the oxidation of properly substituted internal alkynes is the most straightforward process. Previous oxidation methods include the use of potassium permanganate,[6] DMSO[7] or ozonolysis, or are peroxidant-based,[8] transition-metal-catalyzed[9] or acid-promoted.[10] Practical applications of these methods is limited, however, since many are neither environmentally benign nor operatively efficient and involve hazardous transition-metals, high temperatures or cryogenic reaction conditions. Herein, we report a more convenient, practical and environmentally friendly one-pot method for the synthesis of α-diketones via reaction of internal alkynes with *N*-iodosuccinimide (NIS) and water.

Initially, we chose diphenylacetylene and *N*-halosuccinimides (NCS, NBS, NIS) or I_2 as model substrates with which to optimize the reaction conditions in an acetonitrile–water mixture (10:1 v/v). Room temperature reactions with NCS and NBS for 10 hours provided dichloroketone (**3aCl**) and dibromoketone (**3aBr**) in 18% and 17% yields, respectively, but no α-diketone product (benzil) was found (Table 1, entries 1 and 2). NIS gave only α-diketone product under the same conditions (entry 3). When the reaction temperature was increased to 70 °C, yields of dihaloketones (**3aCl** and **3aBr**) significantly increased, and benzil was observed (see entries 4 and 5). We reasoned that the use of NBS provided more benzil than NCS because the α-diketone was formed through hydrolysis of the dihaloketones due to the better leaving power of bromine over chlorine. Extending this logic, we believed that NIS could thus be a better halogenation reagent than either NCS or NBS, so we attempted the reaction of diphenylacetylene with NIS in a acetonitrile–water mixture at 70 °C for 10 hours. Surprisingly, a 62% yield of benzil was obtained, with all the diiodoketone transformed into the α-diketone (entry 6). When iodine was used, the benzil was only obtained in 19% yield under the same conditions (entry 7). After optimizing the conditions, the oxidation of the internal alkynes to α-diketones was found to proceed best with NIS/water as the oxidant and acetonitrile as the solvent at 70 °C.

Table 1 Reactions of Diphenylacetylene and Water with *N*-Halosuccinimides or Iodine: Optimization of Conditions[a]



Entry	NXS	Solvent	Temp (°C)	Yield of **2a** (%)[b]	Yield of **3ax** (%)[b]
1	NCS	MeCN–H_2O	r.t.	trace	18
2	NBS	MeCN–H_2O	r.t.	trace	17
3	NIS	MeCN–H_2O	r.t.	20	0
4	NCS	MeCN–H_2O	70	11	51
5	NBS	MeCN–H_2O	70	29	23
6	**NIS**	**MeCN–H_2O**	**70**	**62**	**0**
7	I_2	MeCN–H_2O	70	19	0

[a] Reaction conditions: diphenylacetylene (0.25 mmol), *N*-halosuccinimide or I_2 (0.5 mmol), MeCN (2 mL), H_2O (0.2 mL).
[b] Isolated yield.

As shown in Table 2, when the reaction was performed on a range of substrates, the corresponding α-diketones were obtained in various yields. Diarylacetylenes showed higher reaction activity than monoarylacetylenes, and the internal alkynes containing electron-donating groups provided higher yields than those containing electron-withdrawing groups. For example, the yields of the corresponding α-diketones gradually decreased using substrates bearing increasingly electron-withdrawing groups

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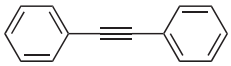
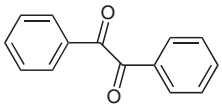
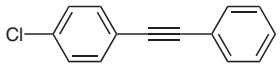
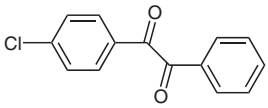
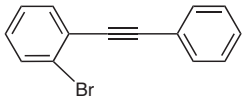
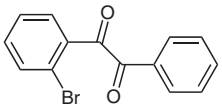
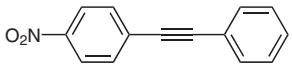
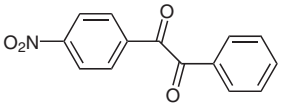
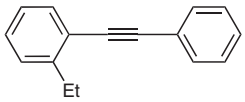
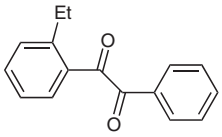
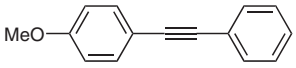
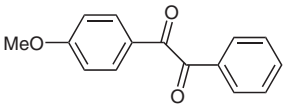
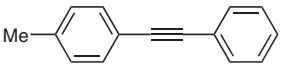
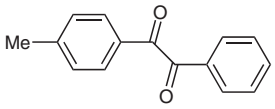
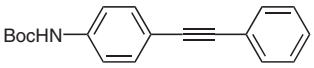
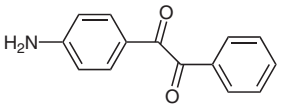
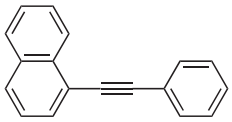
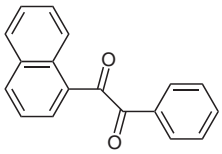
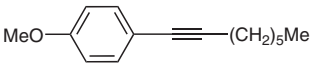
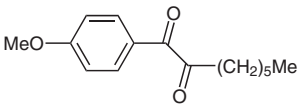
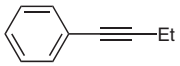
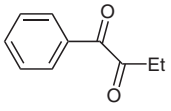
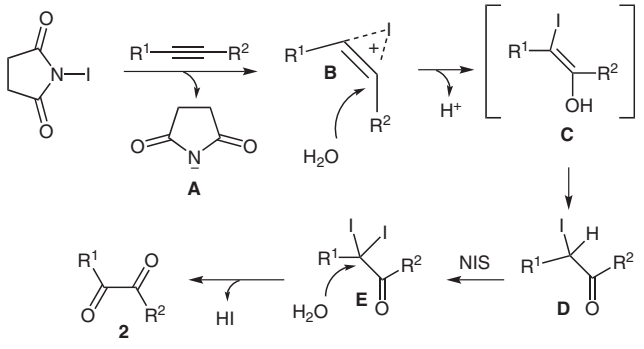
Table 2 Oxidation of Internal Alkynes with NIS/H_2O to α-Diketones[a]

Entry	1	2	Yield (%)[b]
1	 **1a**	 **2a**	62
2	 **1b**	 **2b**	60
3	 **1c**	 **2c**	56
4	 **1d**	 **2d**	29
5	 **1e**	 **2e**	66
6	 **1f**	 **2f**	65
7	 **1g**	 **2g**	63
8	 **1h**	 **2h**	54
9	 **1i**	 **2i**	53
10	 **1j**	 **2j**	52
11	 **1k**	 **2k**	37

[a] Reaction conditions: internal alkyne (0.25 mmol), NIS (0.5 mmol), MeCN (2 mL), H_2O (0.2 mL), 70 °C, 10 h.
[b] Isolated yield.



Scheme 1 Possible mechanism of α-diketone formation via reaction of alkynes with NIS/H_2O.

on the aryl ring (entries 1–4), while introduction of electron-donating groups on aryl ring could improve the yields of the α-diketones (see entries 5–7). Compound **1h**, containing a Boc-protected amine, yielded the free amino α-diketone; presumably the Boc group was cleaved by HI generated during the reaction of the internal alkynes with NIS and water.

According to our experimental results and the reported literature,[11] a possible reaction mechanism for the conversion of internal alkynes into α-diketones under the action of NIS and water, is shown in Scheme 1. Reaction of NIS with internal alkyne first provides **B**, leaving a succinimide anion **A**. Nucleophilic attack of water on **B** leads to an *ortho*-iodohydroxyl alkene intermediate **C**, whose isomerization gives the α -iodoketone **D**. Iodination of **D** produces the dibromoketone **E** (in fact, dichloroketone (**3aCl**) and diiodoketone (**3aBr**) were obtained as shown in Table 1), whose hydrolysis provides the target product **2**.

In summary, we have developed a convenient, practical and environmentally friendly method for the synthesis of α-diketones. The protocol uses NIS and water as the oxidant, acetonitrile as the solvent, and oxidation of the internal alkynes was performed at 70 °C. The direct functionalization of α-diketones by this inexpensive system (NIS/H_2O) is of practical importance.

All reactions were performed under air. Unless otherwise noted, all reagents were purchased from commercial sources and used without further purification. Substituted alkynes are prepared via Sonogashira coupling.[12] *N*-Iodosuccinimide was prepared according to the reported procedure.[13] NMR measurments were recorded with TMS or solvent resonance as the internal standard (^{1}H NMR: TMS at δ = 0.00 ppm, $CDCl_3$ at δ = 7.26 ppm; ^{13}C NMR: $CDCl_3$ at δ = 77.0 ppm).

Synthesis of α-Diketones; General Procedure

Solid NIS (0.5 mmol, 113 mg) was added to a flask charged with internal alkyne (0.25 mmol) in MeCN (2 mL) and H_2O (0.2 mL). The solution was stirred at 70 °C for 10 h then the resulting solution was cooled to r.t. and $CHCl_3$ (10 mL) and aq $Na_2S_2O_3$ (1 M, 10 mL) were added. The separated organic phase was dried over anhydrous Na_2SO_4 and concentrated under rotary evaporation, and the residue was purified by column chromatography on silica gel (petroleum ether) (for compound **2h**, a small amount of EtOAc was used to adjust polarity of solvent) to provide the pure α-diketone.

1,2-Diphenylethane-1,2-dione (2a)[9c]

Light-yellow solid; mp 93–94 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96–7.99 (m, 4 H), 7.63–7.69 (m, 2 H), 7.48–7.54 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.5, 134.8, 133.0, 129.9, 129.0.

MS (EI): *m*/*z* [M^+] = 210.3.

1-(4-Chlorophenyl)-2-phenylethane-1,2-dione (2b)[9c]

Light-yellow solid; mp 75–76 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91–7.98 (m, 4 H), 7.65–7.70 (m, 1 H), 7.48–7.55 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.9, 193.0, 141.6, 135.1, 132.7, 131.3, 131.2, 129.9, 129.4, 129.1.

MS (EI): *m*/*z* [M^+] = 244.2.

1-(2-Bromophenyl)-2-phenylethane-1,2-dione (2c)[14]

Light-yellow solid; mp 40–41 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06–8.08 (m, 2 H), 7.80–7.83 (m, 1 H), 7.44–7.69 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.1, 191.4, 136.0, 134.5, 134.3, 133.7, 132.7, 132.5, 130.3, 128.9, 127.8, 121.8.

MS (EI): *m*/*z* [M^+] = 288.2, 290.3.

1-(4-Nitrophenyl)-2-phenylethane-1,2-dione (2d)[9c]

Light-yellow solid; mp 139–140 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 8.9 Hz, 2 H), 8.17 (d, *J* = 8.9 Hz, 2 H), 7.98–8.01 (m, 2 H), 7.69–7.74 (m, 1 H), 7.55 (t, *J* = 7.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.8, 192.1, 151.2, 137.3, 135.4, 132.4, 130.9, 130.0, 129.2, 124.1.

MS (EI): *m*/*z* [M^+] = 255.4.

1-(2-Ethylphenyl)-2-phenylethane-1,2-dione (2e)[15]

Light-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.99 (m, 9 H), 3.10 (q, *J* = 7.6 Hz, 2 H), 1.30 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7, 194.7, 147.5, 134.6, 133.9, 133.2, 131.5, 131.0, 130.0, 129.0, 125.9, 27.4, 15.4.

MS (EI): *m*/*z* [M^+] = 238.1.

1-(4-Methoxyphenyl)-2-phenylethane-1,2-dione (2f)[9c]

Light-yellow solid; mp 60–61 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93–7.98 (m, 4 H), 7.61–7.67 (m, 1 H), 7.49 (t, *J* = 7.5 Hz, 2 H), 6.97 (m, 2 H), 3.88 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.8, 193.1, 164.9, 134.7, 133.2, 132.3, 129.8, 128.9, 126.1, 114.3, 55.6.

MS (EI): *m*/*z* [M^+] = 240.2.

1-Phenyl-2-(*p*-tolyl)ethane-1,2-dione (2g)[9c]

Light-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.2 Hz, 2 H), 7.86 (d, *J* = 7.9 Hz, 2 H), 7.61–7.67 (m, 1 H), 7.49 (t, *J* = 7.2 Hz, 2 H), 7.29 (d, *J* = 7.9 Hz, 2 H), 2.43 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.7, 194.3, 146.2, 134.7, 133.1, 130.6, 129.9, 129.8, 129.7, 128.9, 21.9.

MS (EI): *m*/*z* [M^+] = 224.3.

1-(4-Aminophenyl)-2-phenylethane-1,2-dione (2h)[16]
Yellow solid; mp 125–126 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.98 (m, 7 H), 6.64 (d, *J* = 8.6 Hz, 2 H), 4.25 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.5, 192.7, 152.9, 134.5, 133.4, 132.6, 129.9, 128.8, 123.1, 113.9.

MS (EI): *m*/*z* [M$^+$] = 225.4.

1-Naphthyl-2-phenylethane-1,2-dione (2i)[17]
Light-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.30 (d, *J* = 8.6 Hz, 1 H), 7.89–8.13 (m, 5 H), 7.45–7.77 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.1, 194.6, 135.9, 135.1, 134.7, 134.1, 133.3, 130.9, 129.9, 129.4, 129.0, 128.8, 128.6, 127.1, 125.9, 124.4.

MS (EI): *m*/*z* [M$^+$] = 260.1.

1-(4-Methoxyphenyl)octane-1,2-dione (2j)
Light-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.9 Hz, 2 H), 6.95 (d, *J* = 8.9 Hz, 2 H), 3.88 (s, 3 H), 2.85 (t, *J* = 7.5 Hz, 2 H), 1.63–1.73 (m, 2 H), 1.26–1.41 (m, 6 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.0, 191.2, 164.7, 132.6, 124.9, 114.2, 55.5, 38.8, 31.5, 28.8, 22.9, 22.4, 13.9.

MS (EI): *m*/*z* [M$^+$] = 248.3.

1-Phenylbutane-1,2-dione (2k)[18]
Light-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.2 Hz, 2 H), 7.64 (t, *J* = 7.2 Hz, 1 H), 7.49 (t, *J* = 7.9 Hz, 2 H), 2.91 (q, *J* = 7.2 Hz, 2 H), 1.20 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 192.5, 134.5, 132.0, 130.1, 128.8, 32.1, 6.8.

MS (EI): *m*/*z* [M$^+$] = 162.4.

2,2-Dibromo-2-phenylacetophenone (3aBr)[19]
Light-yellow solid; mp 108–109 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.75 (m, 2 H), 7.63–7.67 (m, 2 H), 7.24–7.46 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.2, 140.9, 133.1, 131.4, 130.8, 129.7, 128.9, 128.0, 126.7, 69.5.

2,2-Dichloro-2-phenylacetophenone (3aCl)[20]
Light-yellow solid; mp 65–66 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77–7.80 (m, 2 H), 7.64–7.69 (m, 2 H), 7.27–7.49 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.7, 139.5, 133.2, 131.8, 131.1, 129.8, 128.9, 128.1, 126.0, 89.9.

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References

(1) (a) Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron Lett.* **1995**, *40*, 7305; and references therein. (b) De Kimpe, N.; Stanoeva, E.; Boeykens, M. *Synthesis* **1994**, 427; and references therein.
(2) (a) Barta, T. E.; Stealey, M. A.; Collins, P. W.; Weier, R. M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3443. (b) Zhao, Z. J.; Wisnoski, D. D.; Wolkenberg, S. E.; Leister, W. H.; Wang, Y.; Lindsley, C. W. *Tetrahedron Lett.* **2004**, *45*, 4873. (c) Held, I.; Xu, S. J.; Zipse, H. *Synthesis* **2007**, 1185. (d) Rong, F.; Chow, S.; Yan, S. Q.; Larson, G.; Hong, Z.; Wu, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1663.
(3) (a) Bibaut-Renauld, C.; Burget, D.; Fouassier, J. P.; Varelas, C. G.; Thomatos, J.; Tsagaropoulos, G.; Ryrfors, L. O.; Karlsson, O. J. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 3171. (b) Ams, M. R.; Wilcox, C. S. *J. Am. Chem. Soc.* **2007**, *129*, 3966.
(4) (a) Casey, C. P.; Guan, H. *J. Am. Chem. Soc.* **2007**, *129*, 5816. (b) Procuranti, B.; Connon, S. J. *Chem. Commun.* **2007**, *14*, 1421.
(5) (a) Naoki, K.; Nasuo, U. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 755. (b) Katritzky, A. R.; Zhang, D. Z.; Kirichenko, K. *J. Org. Chem.* **2005**, *70*, 3271; and references therein.
(6) (a) Srinvasan, N. S.; Lee, D. G. *J. Org. Chem.* **1979**, *44*, 1574. (b) Lee, D. G.; Chang, V. S. *Synthesis* **1978**, *6*, 462.
(7) (a) Wolfe, S.; Pilgrim, W. R.; Garrad, T. F.; Chamberlain, P. *Can. J. Chem.* **1971**, *49*, 1099. (b) Yusybov, M. S.; Filimonov, V. D. *Synthesis* **1991**, 131. (c) Chi, K. W.; Yusubov, M. S.; Filimonov, V. D. *Synth. Commun.* **1994**, *24*, 2119. (d) Foster, E. J.; Babuin, J.; Nguyen, N.; Williams, V. E. *Chem. Commun.* **2004**, *18*, 2052.
(8) (a) McDonald, R. N.; Schwab, P. A. *J. Am. Chem. Soc.* **1964**, *86*, 4866. (b) Aronovitch, C.; Tal, D.; Mazur, Y. *Tetrahedron Lett.* **1982**, *23*, 3623.
(9) (a) Sheats, W. B.; Olli, L. K.; Stout, R.; Lundeen, J. T.; Justus, R.; Nigh, W. G. *J. Org. Chem.* **1979**, *44*, 4075. (b) Che, C. M.; Yu, W. Y.; Chan, P. M.; Cheng, W. C.; Peng, S. M.; Lau, K. C.; Li, W. K. *J. Am. Chem. Soc.* **2000**, *122*, 11380. (c) Giraud, A.; Provot, O.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron* **2006**, *62*, 7667. (d) Tummatorn, J.; Khorphueng, P.; Petsom, A.; Muangsin, N.; Chaichitc, N.; Roengsumran, S. *Tetrahedron* **2007**, *63*, 11878.
(10) (a) Dayan, S.; Ben-David, I.; Rozen, S. *J. Org. Chem.* **2000**, *65*, 8816. (b) Wan, Z. H.; Jones, C. D.; Mitchell, D.; Pu, J. Y.; Zhang, T. Y. *J. Org. Chem.* **2006**, *71*, 826.
(11) (a) Reed, S. F. Jr. *J. Org. Chem.* **1965**, *30*, 2195. (b) Heasley, V. L.; Shellhamer, D. F.; Chappell, A. E.; Cox, J. M.; Hill, D. J.; McGovern, S. L.; Eden, C. C. *J. Org. Chem.* **1998**, *63*, 4433.
(12) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.
(13) Chaikovskii, V. K.; Skorokhodov, V. I.; Filimonov, V. D. *Russ. J. Org. Chem.* **2001**, *37*, 1572.
(14) Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Bartoli, D. *J. Org. Chem.* **1991**, *56*, 4529.
(15) Noh, T.; Choi, K.; Kwon, H.; Chang, D. J.; Park, B. S. *Bull. Korean Chem. Soc.* **1999**, *20*, 539.
(16) Yi, X. B.; Wu, G. S.; Lu, F. C. *Chin. J. Polym. Sci.* **2002**, *20*, 219.
(17) Yamamori, T.; Adachi, I. *Tetrahedron Lett.* **1980**, *21*, 1747.
(18) Chang, C. L.; Kumar, M. P.; Liu, R. S. *J. Org. Chem.* **2004**, *69*, 2793.
(19) Correia, J. *J. Org. Chem.* **1992**, *57*, 4555.
(20) Nobrega, J. A.; Goncalves, S. M. C.; Peppe, C. *Synth. Commun.* **2002**, *32*, 3711.