HETEROCYCLES, Vol. 87, No. 1, 2013, pp. 155 - 162. © 2013 The Japan Institute of Heterocyclic Chemistry
Received, 11th October, 2012, Accepted, 26th November, 2012, Published online, 28th November, 2012
DOI: 10.3987/COM-12-12605

SYNTHESIS OF INDOLES FROM *o,β*-DINITROSTYRENES VIA INDIUM/ACETIC ACID-MEDIATED REDUCTIVE HETEROCYCLIZATIONS

Geunsoo Lee, Jaehwan Choi, Byung Min Lee,[†] and Byeong Hyo Kim*

Department of Chemistry, Kwangwoon University, Seoul, 139-701, Korea
E-mail: bhkim@kw.ac.kr
[†]Korea Research Institute of Chemical Technology, Taejon 305-600, Korea

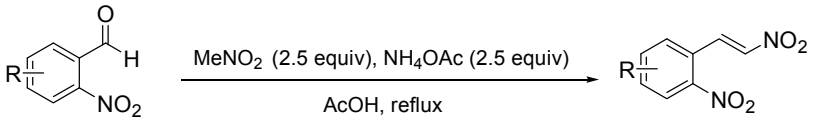
Abstract – Reductive heterocyclization reactions of various 1-nitro-2-(2-nitroaryl)ethenes to indoles were investigated. In the presence of indium/AcOH in toluene or benzene, 1-nitro-2-(2-nitroaryl)ethenes were cyclized to give corresponding indoles in good yields.

Indole rings have been continuously investigated since the early days of heterocycles given their pharmacological and biological activity and potential application.[1] Since the discovery of Fischer indole synthesis, many synthetic chemists have investigated methods for the efficient synthesis of indole compounds including various metal-catalyzed preparations.[2]

Various indium-mediated organic transformations were found in the literature in the past decades as they were found to be environmentally favorable.[3] Moreover, given that environmental issues are becoming increasingly important to society, the green chemistry characteristics of indium are noteworthy.[3b] Therefore we made continuous efforts recently for the development of new synthetic methodologies using indium-mediated reaction conditions including reductive heterocyclizations towards 2,1-benzisoxazoles,[4a,b] benzimidazoles,[4c] quinolines,[4d] indazoles,[4b] and indoles.[4e] Herein, we report the development of one-pot indole synthesis from *o,β*-dinitrostyrenes *via* indium-promoted reductive heterocyclization reactions.

We examined a one-pot reaction for the preparation of indoles from *o,β*-dinitrostyrenes since only a few examples of indole synthesis starting from *o,β*-dinitrostyrenes have been reported in the literature.[2a,5] While a range of transformation from various starting substrates is well documented in the literature, yields of the indole products by conventional conditions using reducing agents such as zinc, iron, titanium,

or tin reagent usually remain in low to middle range. Moreover, most of these reported reactions are not environmentally favorable and/or use harsh conditions.[2b,2o] Prior to study on heterocyclization reactions of *o,β*-dinitrostyrenes, the *o,β*-dinitrostyrene substrates were prepared by one-step synthesis starting from corresponding *o*-nitrobenzaldehyde derivatives (Eq. 1).[6]

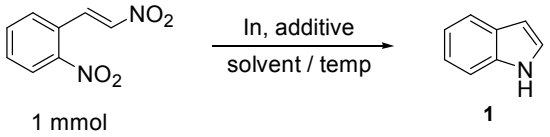


Based on our previous heterocyclization reaction conditions, the initial indium-mediated experiments were tested with synthesized *o,β*-dinitrostyrene substrate by varying solvents and additives to find an optimum reaction condition (Table 1). The reaction conditions (indium/HI in benzene)[4e] that we developed to transform 1-(2-arylethynyl)-2-nitroarenes into 2-arylindoles were not successful for heterocyclization of *o,β*-dinitrostyrene (entry 1, Table 1). The use of a strong acid such as hydrochloric acid as an additive for indium-mediated reductive cyclization was also unsuccessful. Reactions performed in protic solvents in the presence of indium/acetic acid did produce indole rings, but only in poor yield (entries 2, 3). Various reaction conditions including indium/2-bromo-2-nitropropane,[4c] indium/indium(III) chloride, and indium/iodine[4b] in diverse solvent systems failed to produce the indole as a desired major product. However, the reaction of *o,β*-dinitrostyrene in the presence of indium/acetic acid in non-polar aprotic solvent, such as benzene or toluene, produced the desired indole product with reasonably high yields (entries 4~16). Ratio of indium and acetic acid, amount of the solvent, and type of aprotic solvent were examined to obtain optimum conditions for indole formation from *o,β*-dinitrostyrenes (Table 1). The reaction condition including *o,β*-dinitrostyrenes (1 mmol)/indium (5 equiv)/acetic acid (10 equiv) in benzene (5 mL) at reflux (entry 5) or in toluene (5 mL) at 80 ^{o}C (entry 15) was the most practical reaction condition. We recommend a toluene solvent over benzene given the potential decrease in environmental and health risk.

Indium in the presence of acetic acid proved to be successful for the reductive cyclization of *o,β*-dinitrostyrenes toward indole. Given this observation, the indium/acetic acid-mediated reductive cyclization of *o,β*-dinitrostyrene to indole was extended to heterocyclizations of variously substituted indoles in order to examine for its synthetic utilizations. The heterocyclizations of substituted *o,β*-dinitrostyrenes were tested using the optimized reaction conditions of indium (5 equiv)/acetic acid (10 equiv) in benzene or toluene. Since reaction yields were not significantly different in benzene or toluene

solvent, we applied both sets of reaction conditions to various *o,β*-dinitrostyrenes. Table 2 summarizes the reactions performed. In most cases, heterocyclization of *o,β*-dinitrostyrenes was successful with reasonable yield in the range of 65 - 90%, regardless of the solvent applied. The reaction was completed in 1 - 5 hours and yield did not vary significantly depending on whether the substrate was substituted with hyperconjugative alkyl group (or with entries 7, 8) or electronegative heteroatom (entries 2 - 6). Without doubt, this methodology can be utilized to synthesize substituted indole derivatives with ease.

Table 1. Indium-mediated reductive cyclization reaction of *o,β*-dinitrostyrene to indole under various conditions



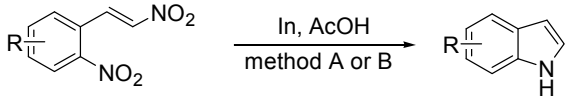
1 mmol **1**

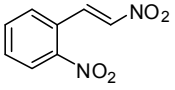
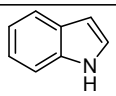
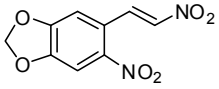
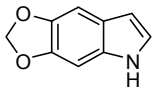
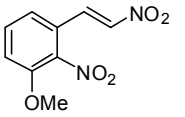
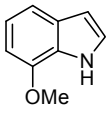
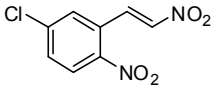
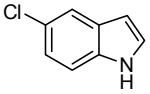
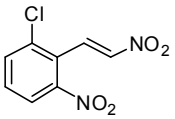
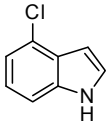
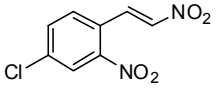
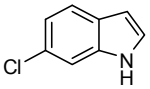
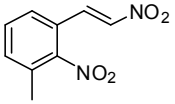
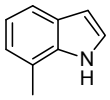
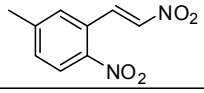
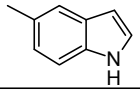
Entry	Substrate (eq)	Molar equiv.		Solvent (mL)/ Temp (^{o}C)	Time (h)	Yield[a] (%)
		In	additive (equiv)			**1**
1[b]	1	5	HI (40)	benzene (5)/reflux	2	trace[c]
2	1	4	AcOH (10)	MeOH (5)/reflux	3	26[c]
3	1	4	AcOH (10)	H_2O (5)/ reflux	2	6[d]
4	1	5	AcOH (10)	THF (5)/reflux	1	14
5	1	4	AcOH (10)	benzene (5)/reflux	2	65
6	1	5	AcOH (10)	benzene (5)/reflux	2	77
7	1	6	AcOH (10)	benzene (5)/reflux	2	73
8	1	5	AcOH (5)	benzene (5)/reflux	24	36[d]
9	1	5	AcOH (20)	benzene (5)/reflux	2	68
10	1	5	AcOH (10)	benzene (2.5)/reflux	2	59
11	1	5	AcOH (10)	benzene (10)/reflux	3	69
12	1	5	AcOH (10)	benzene (5)/50	5	30[d]
13	1	5	AcOH (10)	benzene (5)/rt	24	26[d]
14	1	5	AcOH (10)	toluene (5)/50	24	45[d]
15	1	5	AcOH (10)	toluene (5)/80	5	83 (80)[e]
16	1	5	AcOH (10)	toluene (5)/reflux	2	43[c]

[a]GC yield with an internal standard(octane). [b]Aliquat 336 (1 drop) was added.

[c]Several by-products were observed on GC analysis. [d]Unreacted initial substrate was remained. [e]Isolated yield.

Table 2. Indium-mediated reductive cyclization of *o,β*-dinitrostyrenes to indole derivatives under optimized conditions (*o,β*-dinitrostyrene (1 mmol)/indium (5 mmol)/AcOH (10 mmol)/benzene (5 mL, method A) or toluene (5 mL, method B)



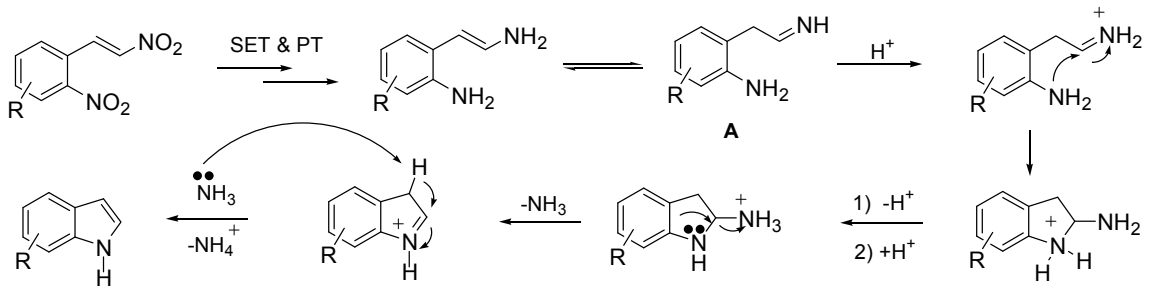
Entry	Substrate	Product	Method	Time (h)	Yield (%)[a]
1			A	2	75
			B	5	80
2			A	3	71
			B	3	65
3			A	3	84
			B	2	90
4			A	4	80
			B	3	89
5			A	1	74
			B	2	69
6			A	3	69
			B	2	69
7			A	5	76
			B	4	71
8			A	4	78
			B	4	65

[a] Isolated yield.

Based on our previous results and related literature,[5b] a plausible reaction mechanism is depicted in Scheme 1. The mechanistic picture consists of sequential processes of: 1) single electron transfer by indium metal; 2) proton transfer by acetic acid; and 3) isomerization in acidic medium to form intermediate **A** (Scheme 1). Intermediate **A** can be transformed into indole via cyclization by the nucleophilic addition of amine to protonated imine followed by proton transfer, loss of NH_3, and aromatization by acid-base chemistry.

A new, mild, environmentally friendly, and efficient one-pot synthetic protocol was developed to obtain

variously substituted indoles directly from corresponding *o,β*-dinitrostyrenes using indium/acetic acid under mild conditions. This one-pot cyclization method can be utilized to introduce the biologically active indole moiety starting with a proper dinitro compound.



Scheme 1

EXPERIMENTAL

1. General consideration

Most of the chemical reagents were purchased from Sigma-Aldrich Co. (St. Louis, Missouri, USA) and were used without further purification, in most cases. Solvents were purchased and dried using standard methods. ^{1}H and ^{13}C NMR spectra were recorded at 400 (JEOL, Tokyo, Japan) and 100 MHz, respectively. Chemical shifts were reported in parts per million relative to the residual solvent as an internal standard. GC-MS spectra were recorded on an Agilent 6890N GC connected to an Agilent 5975 mass selective detector (Hewlett-Packard Co., Palo Alto, California, USA). Infrared (IR) spectra were recorded using an MB104 FTIR (ABB Bomem, Inc., Zurich, Switzerland). Melting points were determined on an electrothermal apparatus and were uncorrected. All the major products were isolated by flash column chromatography on silica gel (230-400 mesh ATSM, purchased from Merck & Co., Inc. (Whitehouse Station, New Jersey, USA)) with eluent of mixed solvents (EtOAc/hexane).

2. General procedure for indium-mediated reductive reaction of 1-nitro-2-(2-nitroethenyl)-benzenes to indoles

A mixture of 1-nitro-2-(2-nitroethenyl)benzene derivatives (1.0 mmol), indium (0.574 g, 5.0 mmol), and acetic acid (0.601 g, 10 mmol) in benzene (5 mL) or toluene (5 mL) was stirred at 80 ^{o}C under nitrogen atmosphere. After reaction completion, the reaction mixture was diluted with DCM (30 mL), filtered through Celite, poured into 10% aqueous $NaHCO_3$ (30 mL), and extracted with DCM (30 mL x 3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was eluted with EtOAc/hexane (v/v=30/70) through a silica gel column to give the corresponding pure indoles. Indole structures were characterized by ^{1}H NMR, ^{13}C NMR, FTIR, and GC-MS.

1*H*-Indole[21]

Mp 55.5-57.8 °C; TLC (40% EtOAc/hexane) R_f 0.62; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.32-7.21 (m, 3H), 6.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.66, 127.74, 124.12, 121.91, 120.67, 119.74, 110.99, 102.49; IR (KBr) 3408, 3087, 1616, 1455 cm^{-1}; GC-MS m/z (rel. intensity) 117 (M, 100), 90 (44), 63 (12).

5*H*-[1,3]Dioxolo[4,5-f]indole[2o]

Mp 115.8-116.5 °C; TLC (50% EtOAc/hexane) R_f 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.03 (d, *J* = 18.8 Hz, 2H), 6.83 (s, 1H), 6.42 (s, 1H), 5.92 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.88, 142.99, 130.58, 122.76, 121.61, 102.77, 100.53, 99.10, 91.84; IR (KBr) 3406, 3134, 3105, 2883, 1700, 1609, 1460, 1308 cm^{-1}; GC-MS m/z (rel. intensity) 161 (M, 100), 103 (32), 76 (22), 50 (8).

7-Methoxy-1*H*-indole[7]

Oil; TLC (50% EtOAc/hexane) R_f 0.67; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.26-7.20 (m, 2H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.71 (t, *J* = 2.6 Hz, 1H), 4.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.02, 129.09, 126.27, 123.69, 120.02, 113.04, 102.62, 101.60, 55.12; IR (KBr) 3418, 3051, 2944, 1623, 1581, 1253 cm^{-1}; GC-MS m/z (rel. intensity) 147 (M, 100), 132 (67), 104 (81), 89 (11), 77 (18), 63 (6), 51 (9).

5-Chloro-1*H*-indole[2m]

Mp 75.8-78.4 °C; TLC (50% EtOAc/hexane) R_f 0.63; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.50 (d, *J* = 1.7 Hz, 1H), 7.12-7.02 (m, 3H), 6.37-6.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.99, 128.80, 125.56, 125.27, 122.15, 119.97, 111.99, 102.20; IR (KBr) 3387, 3108, 3035, 1444, 1315, 1092 cm^{-1}; GC-MS m/z (rel. intensity) 151 (M, 100), 124 (13), 116 (25), 89 (32), 75 (8), 63 (9).

4-Chloro-1*H*-indole[2o]

TLC (50% EtOAc/hexane) R_f 0.58; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.31-7.17 (m, 4H), 6.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.33, 126.59, 125.83, 124.77, 122.45, 119.43, 109.71, 101.01; IR (KBr) 3418, 3109, 1706, 1600, 1564 cm^{-1}; GC-MS m/z (rel. intensity) 151 (M, 100), 124 (14), 116 (24), 89 (38), 75 (8), 63 (13).

6-Chloro-1*H*-indole[2o]

Mp 89.4-90.7 °C; TLC (50% EtOAc/hexane) R_f 0.62; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.27 (s, 1H), 7.10-7.07 (m, 2H), 6.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.99, 127.67, 126.31, 124.87, 121.47, 120.45, 110.91, 102.59; IR (KBr) 3403, 3107, 3066, 1719, 1609, 1575 cm^{-1}; GC-MS m/z (rel. intensity) 151 (M, 100), 124 (15), 116 (21), 89 (34), 75 (8), 63 (10).

7-Methyl-1*H*-indole[8]

Mp 62.0-63.8 °C; TLC (50% EtOAc/hexane) R_f 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.53 (s, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.13-7.08 (m, 2H), 6.54 (s, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 133.95, 128.86, 127.97, 124.26, 123.47, 120.22, 110.66, 101.80, 21.36; IR (KBr) 3396, 3104, 3049, 2934, 2859, 1722, 1588 cm^{-1}; GC-MS m/z (rel. intensity) 130 (M-1, 100), 103 (12), 77 (13), 65 (5), 51 (5).

5-Methyl-1*H*-indole[2m]

Mp 87.2-89.0 °C; TLC (50% EtOAc/hexane) R_f 0.57; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.24 (s, 1H), 7.14-7.06 (m, 2H), 6.63 (s, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.39, 127.34, 123.82, 122.47, 120.19, 119.99, 118.44, 103.07, 16.69; IR (KBr) 3396, 3061, 2973, 2941, 1588, 1423, 1345, 1106 cm^{-1}; GC-MS m/z (rel. intensity) 130 (M-1, 100), 103 (12), 77 (15), 65 (6), 51 (6).

ACKNOWLEDGEMENTS

This work was supported by Kwangwoon University in 2012.

REFERENCES

1. (a) R. S. Roy, A. M. Gehring, J. C. Milne, P. J. Belshaw, and C. T. Walsh, *Nat. Prod. Rep.,* 1999, **16**, 249; (b) M. J. McKay, A. R. Carroll, R. J. Quinn, and N. A. Hooper, *J. Nat. Prod.,* 2002, **65**, 595; (c) M. Somei, F. Yamada, T. Kurauchi, Y. Nagahama, M. Hasegawa, K. Yamada, S. Teranishi, H. Sato, and C. Kaneko, *Chem. Pharm. Bull.,* 2001, **49**, 87; (d) G. Revial, I. Jabin, S. Lim, and M. Pfau, *J. Org. Chem.,* 2002, **67**, 2252.
2. (a) For detailed discussions of the classical known methods of indole synthesis, see R. K. Brown, 'Indoles', Part I, ed. by W. J. Houlihan, Wiley-Interscience, New York, N.Y., 1972; R. J. Sundburg, 'Comprehensive Heterocyclic Chemistry II', ed. by A. R. Katrizky, C. W. Rees, and E. F. V. Scriven, Pergamon Press, Oxford, UK, 1996, **2**, pp. 119-206; (b) S. Wagaw, B. H. Yang, and S. L. Buchwald, *J. Am. Chem. Soc.,* 1998, **120**, 6621; (c) R. C. Larock, E. K. Yum, and M. D. Refvic, *J. Org. Chem.,* 1998, **63**, 7652; (d) A. Yasuhara, Y. Kaneko, M. anamori, A. Numata, Y. Kondo, and T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1,* 1999, 529; (e) A. L. Rodriguez, C. Koradin, W. Dohle, and P. Knochel, *Angew. Chem. Int. Ed.,* 2000, **39**, 2488; (f) A. Dobbs, *J. Org. Chem.,* 2001, **66**, 638; (g) J. L. Rutherford, M. P. Rainka, and S. L. Buchwald, *J. Am. Chem. Soc.,* 2002, **124**, 15168; (h) W.-M. Dai, L.-P. Sun, and D.-S. Guo, *Tetrahedron Lett.,* 2002, **43**, 7699; (i) C. Koradin, W. Dohle, A. L. Rodriguez, B. Schmid, and P. Knochel, *Tetrahedron,* 2003, **59**, 1571; (j) J. Barluenga, M. Trincado, E. Rubio, and J. M. Gonzalez, *Angew. Chem. Int. Ed.,* 2003, **42**, 2406; (k) L. P. Sun, X. H. Huang, and W. M. Dai, *Tetrahedron,* 2004, **60**, 10983; (l) A. Dhakshinamoorthy and K. Pitchumani, *Appl. Catal. A,* 2005, **292**, 305; (m) B. M. Trost and A. McClory, *Angew. Chem, Int. Ed.,* 2007, **46**, 2074; (n) G. Bratulescu, *Tetrahedron Lett.,* 2008, **49**, 984; (o) I. V. Taydakov, T. Y. Dutova, E. N.

Sidorenko, and S. S. Krasnoselsky, *Chem. Heterocycl. Cpds.,* 2011, **47**, 425; (p) S. R. Banini, M. R. Turner, M. M. Cummings, and B. C. G. Söderberg, *Tetrahedron,* 2011, **67**, 3603.

3. (a) H. Yamamoto and K. Oshima, 'Main Group Metals in Organic Synthesis', Wiley-VCH, Weinheim, 2004, **1**, Ch. 8, pp. 323-386; (b) C. J. Li and T. H. Chan, 'Organic Reactions in Aqueous Media', Wiley-Interscience, New York, 1997; (c) C. J. Li, *Tetrahedron,* 1996, **52**, 5643; (d) J. Podlech and T. C. Maier, *Synthesis,* 2003, 633; (e) V. Nair, S. Ros, C. N. Jayan, and B. S. Pillai, *Tetrahedron,* 2004, **60**, 1959; (f) S. Kumar, K. Pervinder, and K. Vijay, *Curr. Org. Chem.,* 2005, **9**, 1205.
4. (a) B. H. Kim, Y. Jin, Y. M. Jun, R. Han, W. Baik, and B. M. Lee, *Tetrahedron Lett.,* 2000, **41**, 2137 and *ibid.,* 4244; (b) R. Han, K. I. Son, G. H. Ahn, Y. M. Jun, B. M. Lee, Y. Park, and B. H. Kim, *Tetrahedron Lett.,* 2006, **47**, 7295; (c) B. H. Kim, R. Han, J. S. Kim, Y. M. Jun, W. Baik, and B. M. Lee, *Heterocycles,* 2004, **62**, 41; (d) R. Han, S. Chen, S. J. Lee, F. Qi, X. Wu, and B. H. Kim, *Heterocycles,* 2006, **68**, 1675; (e) J. S. Kim, J. H. Han, J. H. Lee, Y. M. Jun, B. M. Lee, and B. H. Kim, *Tetrahedron Lett.,* 2008, **49**, 3733.
5. (a) S. Rajeswari, K. J. Drost, and M. P. Cava, *Heterocycles,* 1989, **29**, 415; (b) A. Sera, S. Fukumoto, M. Tamura, K. Takabatake, H. Qamada, and K. Itoh, *Bull. Chem. Soc. Jpn.,* 1991, **64**, 1787; (c) B.-C. Chen, J. H. Jr., C. R. Randit, R. Zhao, A. P. Skoumbourdis, H. Wu, J. E. Sundeen, and K. Leftheris, *Heterocycles,* 2001, **55**, 951.
6. J. T. Liu and C. F. Yao, *Tetrahedron Lett.,* 2001, **42**, 6147.
7. C. G. Hartung, A. Fecher, B. Chapell, and V. Snieckus, *Org. Lett.,* 2003, **5**, 1899.
8. D. Coowar, J. Bouissac, M. Hanbali, M. Paschaki, E. Mohier, and B. Luu, *J. Med. Chem.,* 2004, **47**, 6270.