JOC*Note*

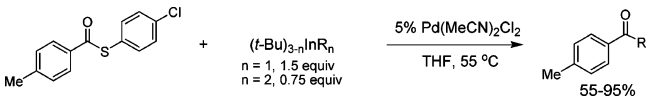
Palladium-Catalyzed Coupling of Thiol Esters with Aryl and Primary and Secondary Alkyl Organoindium Reagents

Bryan W. Fausett and Lanny S. Liebeskind*

Emory University, Department of Chemistry, 1515 Dickey Drive, Atlanta, Georgia 30322

chemLL1@emory.edu

Received January 19, 2005



Thiol esters and organoindium reagents undergo palladium-catalyzed cross-coupling under mild conditions to give ketones in moderate to excellent yields. Aryl and primary/secondary alkyl organoindium reagents can be used as coupling partners. This method has two advantages over the cross-coupling of thiol esters with boron and tin reagents: (1) no added copper reagent is required to mediate the reaction and (2) for the case of alkyl transfer, no added base is required to activate organoindium reagents for cross-coupling as is required for the coupling of alkyl boron reagents with thiol esters.

Thioorganics are excellent cross-coupling partners with boronic acids[1] and organostannanes[2] under mild and nonbasic conditions.[3] The breadth of this methodology is still being explored and has recently been extended to the cross-coupling of thiol esters with alkyl boron reagents.[4] With boronic acids in particular, the palladium-catalyzed coupling of thioorganics relies on the unique ability of a copper(I) carboxylate additive to labilize a palladium thiolate ligand toward transmetalation, while at the same time providing a stoichiometric quantity of a borophilic carboxylate counterion to pair with the $-B(OH)_2$ moiety (eq 1). This understanding suggests that the palladium-catalyzed cross-coupling of thioorganics could proceed directly with sufficiently thiophilic organometallic cross-coupling partners without the requirement of a stoichiometric Cu(I) carboxylate activator (eq 2).

$$R^1{-}SR' + R^2{-}B(OH)_2 \xrightarrow[\text{cat. Pd}]{\text{stoich Cu(I)OCOR}} R^1{-}R^2 + Cu{-}SR' + RC(O)O{-}B(OH)_2 \quad (1)$$

$$R^1{-}SR' + R^2{-}M \xrightarrow[\text{if M is thiophilic}]{\text{cat. Pd}} R^1{-}R^2 + M{-}SR \quad (2)$$

Pursuing this analysis led to consideration of the indium−sulfur bond, which is assumed to be strong on the basis of the Pearson Hard−Soft Principle,[5] and thus to an exploration of the palladium-catalyzed coupling of thiol esters with organoindium reagents.[6] The latter are versatile coupling partners in their own right.[7,8] Initially 0.4 equiv of various triorganoindium reagents[9] were treated with *S*-4-chlorophenyl 4-methylbenzothioate in the presence of 5% $Pd(CH_3CN)_2Cl_2$ as precatalyst in THF at 55 °C to probe the number of organic groups that would transfer from indium to form the product ketone (Table 1). These results demonstrated that aryl and primary alkyl triorganoindium reagents easily transferred between 2 and 3 of the organic groups, while only one secondary alkyl was readily transferred.[10] Conversion was high in all cases since unreacted thiol ester could be recovered (entry 5). The coupling with vinyl- and alkynylindium reagents performed poorly, giving only a trace of or no product.[11] Control experiments without Pd (entries 6−8) demonstrated that triphenylindium was capable of transferring the first of its three phenyl groups to the thiol ester in an uncatalyzed reaction to give 33% yield of the corresponding ketone. This uncatalyzed reactivity did not extend to either tri-*n*-butyl- or tri-*sec*-

(1) (a) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260. (b) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91. (c) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979. (d) Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 2149. (e) Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett.* **2002**, *4*, 983. (f) Liebeskind, L. S.; Srogl, J.; Savarin, C.; Polanco, C. *Pure Appl. Chem.* **2002**, *74*, 115. (g) Kusturin, C.; Liebeskind, L. S.; Rahman, H.; Sample, K.; Schweizer, B.; Srogl, J.; Neumann, W. L. *Org. Lett.* **2003**, *5*, 4349. (h) Lengar, A.; Kappe, C. O. *Org. Lett*. **2004**, *6*, 771.

(2) (a) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033. (b) Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 801. (c) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 803.

(3) Organozinc reagents are also good partners for coupling with thioorganics under mild reaction conditions: (a) Roberts, W. P.; Ghosh, I.; Jacobi, P. A. *Can. J. Chem*. **2004**, *82*, 279. (b) Ghosh, I.; Jacobi, P. A. *J. Org. Chem.* **2002**, *67*, 9304. (c) Angiolelli, M. E.; Casalnuovo, A. L.; Selby, T. P. *Synlett* **2000**, (6), 905. (d) Srogl, J.; Liu, W.; Marshall, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 9449. (e) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189.

(4) Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554.

(5) Pearson, R. G. *Chemical Hardness*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1997.

(6) Recent syntheses of ketones via cross-coupling methods: (a) Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* ASAP, Nov. 18, **2004**, 126, 15964−15965. (b) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc*. **2004**, *126*, 15666−15667. (c) Tatamidani, H.; Yokota, K.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 5615. (d) Tatamidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* **2004**, *6*, 3597. (e) Fukuyama, T.; Tokuyama, H. *Aldrichim. Acta* **2004**, *37*, 87. See also footnotes 1a, 2a, and 3e.

(7) (a) Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267. (b) Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155. (c) Lee, P. H.; Sung, S.; Lee, K. *Org. Lett.* **2001**, *3*, 3201. (d) Lee, K.; Lee, J.; Lee, P. H. *J. Org. Chem.* **2002**, *67*, 8265. (e) Lee, P. H.; Lee, S. W.; Seomoon, D. *Org. Lett.* **2003**, *5*, 4963. (f) Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997.

(8) Organoindium reagents have been used to make ketones via carbonylative cross-coupling procedures: (a) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *Synthesis* **2003**, *5*, 780. (b) Lee, P. H.; Lee, S. W.; Lee, K. *Org. Lett.* **2003**, *5*, 1103. (c) Lee, S. W.; Lee, K.; Seomoon, D.; Kim, S.; Kim, H.; Kim, H.; Shim, E.; Lee, M.; Lee, S.; Kim, M.; Lee, P. H. *J. Org. Chem.* **2004**, *69*, 4852.

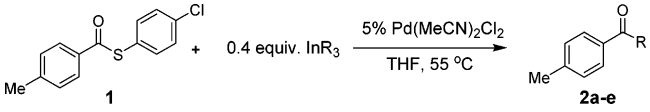
(9) Organoindium reagents were prepared from $InCl_3$ and 3 equiv of a Grignard reagent in THF at room temperature for 30 min.

(10) InR_3 are more reactive than InR_2X reagents. Wilkinson, G.; Stone, F. G. A.; Abel, E. W. *Comprehensive Organometallic Chemistry*; Pergamon Press: New York, 1982; Vol. I, p 711.

(11) Of related interest is a nickel-catalyzed coupling of aryl and alkyl but not alkenyl or alkynyl Grignard reagents: Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222.

10.1021/jo050110u CCC: $30.25
Published on Web 05/13/2005

TABLE 1. Coupling of Triorganoindium Reagents with *S*-4-Chlorophenyl 4-Methylbenzothioate



entry	R	product	% isolated yield
1	phenyl	**2a**	89
2	*p*-methoxyphenyl	**2b**	60
3	*p*-fluorophenyl	**2c**	69
4	*n*-butyl	**2d**	70
5	*sec*-butyl	**2e**	53 (47[a])
6	phenyl[b,c]	**2a**	35
7	*n*-butyl[c]	**2d**	<5
8	*sec*-butyl[c]	**2e**	<5

[a] Recovered starting material. [b] 0.33 equiv of $InPh_3$. [c] Control: no Pd catalyst.

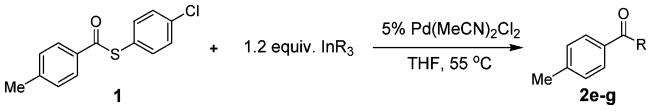
butylindium, perhaps reflecting the greater Lewis acidity of the triphenyl- versus the trialkylindium reagents.

In the cross-coupling of thiol esters to form ketones the organoindium reagents possess two specific attributes that differentiate them from boronic acids and organostannanes. First, indium is thiophilic and, therefore, like zinc,[12] the reaction does not require an added Cu(I) carboxylate to facilitate the coupling. Second, the use of indium allows a facile coupling with primary and secondary alkyl groups. Alkyl cross-couplings are now known for Grignard,[13] 9-BBN,[14] trifluoroorganoborate,[15] and organozinc reagents.[16] More recently conditions for the transfer of alkyl groups from boronic acids have been developed.[17]

The ability to couple secondary alkyl groups by using organoindium reagents prompted further exploration of the reaction. Since only slightly more than one of the three alkyl groups of tri(*sec*-butyl)indium was transferred efficiently (entry 5, Table 1), the yield of ketone was maximized by employing 1.2 equiv of the tri(*sec*-alkyl)-indium reagent (Table 2). This produced very good yields of ketone, but at the expense of requiring 3.6 equiv of a secondary alkyl group.

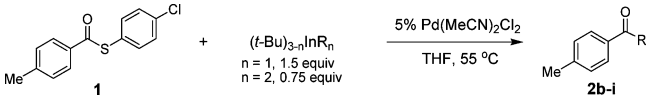
To mitigate the need for an excess of the secondary alkyl group and achieve high yields of ketone, a nontransferring *tert*-butyl "dummy ligand" on indium was employed. Two types of mixed organoindium reagents were prepared: those bearing two nontransferring *tert*-butyl groups and those bearing only one nontransferring *tert*-butyl group. These reagents were generated in situ by treating $InCl_3$ with $(3 - n)$ equiv of *t*-BuMgCl followed by n equivalents of a secondary alkyl Grignard reagent ($n = 1$ and 2). The resulting mixed organoindium reagents $t\text{-Bu}_{3-n}\text{InR}_n$ were exposed to *S*-4-chlorophenyl

TABLE 2. Coupling of *S*-4-Chlorophenyl 4-Methylbenzothioate with Secondary Alkyl Organoindium Reagents



entry	R	product	% isolated yield
1	*sec*-butyl	**2e**	83
2	cyclopentyl	**2f**	80
3	cyclohexyl	**2g**	95

TABLE 3. Coupling *S*-4-Chlorophenyl 4-Methylbenzothioate with $t\text{-Bu}_{3-n}\text{InR}_n$ ($n = 1$ or 2)



entry	reagent	product	% isolated yield
1	$(t\text{-Bu})_2$In(*sec*-butyl)	**2e**	73
2	$(t\text{-Bu})_2$In(cyclopentyl)	**2f**	69
3	$(t\text{-Bu})_2$In(cyclohexyl)	**2g**	65
4	$(t\text{-Bu})$In(*sec*-butyl)$_2$	**2e**	64
5	$(t\text{-Bu})$In(cyclopentyl)$_2$	**2f**	83
6	$(t\text{-Bu})$In(cyclohexyl)$_2$	**2g**	77
7	$(t\text{-Bu})$In(*p*-methoxyphenyl)$_2$[a]	**2b**	72
8	$(t\text{-Bu})$In(*p*-fluorophenyl)$_2$[a]	**2c**	85
9	$(t\text{-Bu})$In(*n*-butyl)$_2$[a]	**2d**	83
10	$(t\text{-Bu})$In(*o*-tolyl)$_2$[a]	**2h**	55
11	$(t\text{-Bu})$In(*o*-methoxyphenyl)$_2$[a]	**2i**	60

[a] Using 0.6 equiv of $(t\text{-Bu})\text{InR}_2$.

4-methylbenzothioate in the presence of 5% $Pd(MeCN)_2Cl_2$ in THF and produced the corresponding aryl *sec*-alkyl ketones in good yields (Table 3). No evidence of *tert*-butyl transfer was noted. Significantly, efficient production of ketone could be achieved by using only 1.5 equiv of the transferring secondary alkyl group with either of the new reagent systems. Of the two reagents, that with only one nontransferring *tert*-butyl group requires only 0.75 equiv of indium and gives slightly better yields of ketone in some cases. Applying this same technique to the aryl- and *n*-butylorganoindium reagents shown earlier in Table 1 gave increased yields and required only 0.6 equiv of indium. Using these same conditions ortho-substituted arylindium reagents (entries 10 and 11) were less reactive, which resulted in decreased yields.

Two additional observations are of synthetic interest. Depicted in Scheme 1 is the selective coupling of an indium reagent at a thiol ester in the presence of a reactive aryl bromide and a demonstration of the use of an aliphatic thiol ester in the coupling chemistry.

In conclusion, a new palladium-catalyzed coupling of thiol esters with organoindium reagents has been developed. This protocol does not require a thiophilic additive and is effective with arylindium and primary and secondary alkylindium reagents.

Experimental Section

General Procedures. All cross-coupling reactions were performed under an atmosphere of dry N_2 or Ar. THF was dried over 4 Å molecular sieves and titrated for water level with a

(12) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189.

(13) (a) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222. (b) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (c) Furstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609.

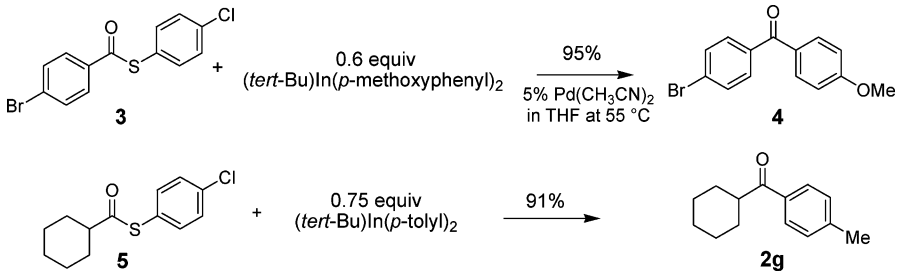
(14) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(15) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393.

(16) Devasagayaraj, A.; Stuedemann, T.; Knochel, P. *Angew. Chem., Int. Ed.* **1995**, *34*, 2723.

(17) (a) Zhou, J.; Fu, G. *J. Am. Chem. Soc.* **2003**, *125*, 14726. (b) Zhou, J.; Fu, G. *J. Am. Chem. Soc.* **2004**, *126*, 1340. (c) Powell, D. A.; Fu, G. *J. Am. Chem. Soc.* **2004**, *126*, 7788.

SCHEME 1. Selectivity and Generality of Thiol Ester/Organoindium Cross-Coupling



Fisher Coulomatic K-F titrater and purged with dry N_2 or Ar before use. Et_3N was dried over KOH pellets. ^1H NMR and ^{13}C NMR spectra were taken at room temperature in $CDCl_3$ and internally referenced to $CDCl_3$ (7.26, 77.23 ppm).

Starting Materials: 4-Methylthiobenzoic Acid *S*-(4-Chlorophenyl) Ester, 1.[18] *p*-Chlorothiophenol (50 mmol, 7.23 g) and *p*-toluoyl chloride (50 mmol, 7.73 g) were added to 115 mL of THF and cooled in an ice bath. To this solution triethylamine (100 mmol, 10.12 g) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. Diethyl ether (100 mL) was added and the precipitated salts that resulted were filtered off. The solvent was then evaporated and the product was recrystallized from acetone to give a white solid (9.48 g, 72% yield). Mp 119−120 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 8.4 Hz, 2 H), 7.43 (m, 4 H), 7.29 (d, J = 9.0 Hz, 2 H), 2.44 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.4, 145.1, 136.6, 136.1, 134.0, 129.7, 127.8, 126.2, 22.0. IR (neat) 1671 (s) cm^{-1}. Anal. Calcd for $C_{14}H_{11}S$: C, 64.00; H, 4.22; S, 12.20. Found: C, 64.04; H, 4.42; S, 12.15.

4-Bromothiobenzoic Acid *S*-(4-Chlorophenyl) Ester, 3.[19] *p*-Chlorothiophenol (10 mmol, 1.45 g) and 4-bromobenzoyl chloride (10 mmol, 2.19 g) were added to 30 mL of THF and cooled in an ice bath. To this solution triethylamine (20 mmol, 2.02 g) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. Diethyl ether (20 mL) was added and the precipitated salts that resulted were filtered off. The solvent was then evaporated and the product recrystallized from acetone giving a white solid (2.36 g, 72% yield). Mp 145−146 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2 H), 7.65 (d, J = 8.4 Hz, 2 H), 7.44 (s, 4 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.0, 136.5, 136.4, 135.4, 132.4, 129.8, 129.23, 129.16, 125.6. IR (neat) 1675 (s) cm^{-1}. Anal. Calcd for $C_{13}H_8S$: C, 47.66; H, 2.46; S, 9.79. Found: C, 47.42; H, 2.55; S, 9.80.

Cyclohexanecarbothioic Acid *S*-(4-Chlorophenyl) Ester, 5. *p*-Chlorothiophenol (10 mmol, 1.45 g) and cyclohexanecarbonyl chloride (10 mmol, 1.47 g) were added to 30 mL of THF and cooled in an ice bath. To this solution triethylamine (20 mmol, 2.02 g) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. Diethyl ether (20 mL) was added and the precipitated salts that resulted were filtered off. The solvent was then evaporated and the product recrystallized from acetone giving a white solid (2.33 g, 91% yield). Mp 34−35 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 4 H), 2.60 (m, 1 H), 2.01−1.27 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 136.0, 135.7, 129.5, 126.6, 52.7, 29.6, 25.7, 25.6. IR (neat) 1702 (s) cm^{-1}. Anal. Calcd for $C_{13}H_{15}S$: C, 61.28; H, 5.93; S, 12.59. Found: C, 61.02; H, 5.98; S, 12.40.

Representative Procedures for Preparing Triorganoindium Reagents: Triphenylindium. Indium(III) chloride (0.2 mmol, 44 mg) was placed in a flask with a vacuum attachment and stirring bar. This was heated with a heat gun while stirring under vacuum for several minutes to ensure dryness. After heating the flask was filled with Ar and then reevacuated; this was repeated 3 times before filling the flask a final time with Ar. Next, THF (1.5 mL) was added via syringe. Once the indium(III) chloride was dissolved, PhMgCl (0.6 mmol) was added dropwise and allowed to stir for 0.5 h. This reagent was used directly in the coupling reaction.

***tert*-Butyl(cyclopentyl)$_2$indium.** Indium(III) chloride (0.375 mmol, 83 mg) was placed in a flask with a vacuum attachment and stirring bar. This was heated with a heat gun while stirring under vacuum for several minutes to ensure dryness. After heating, the flask was filled with Ar and then reevacuated; this was repeated 3 times before filling the flask a final time with Ar. Next, THF (1.5 mL dry/degassed) was added via syringe. Once the indium(III) chloride was dissolved *t*-BuMgCl (0.375 mmol, 1.9 M in diethyl ether, 0.20 mL) was added dropwise and allowed to stir for 0.5 h giving a slightly milky reaction mixture. To this was added cyclopentylMgCl (0.75 mol, 1.96 M in diethyl ether, 0.39 mL) dropwise and the resulting solution was stirred another 0.5 h to give a solution of *tert*-butyl(cyclopentyl)$_2$indium. This reagent used directly in the coupling reaction.

Representative Procedure for Cross-Coupling: 4-Methylbenzophenone. 4-Methylthiobenzoic acid *S*-(4-chlorophenyl) ester (0.50 mmol, 131 mg) was added with $Pd(MeCN)_2Cl_2$ (5 mol %, 6.5 mg) to a flask that was subsequently flushed with Ar. THF (0.5 mL) was added to the flask followed immediately by a solution of triphenylindium (0.2 mmol) as prepared above. Finally, the reaction mixture was heated in an oil bath at 55 °C and stirred for 16 h. The reaction mixture was diluted with 5 mL of 1:1 diethyl ether/hexanes and 3 mL of water was added. The organics were removed and the resultant aqueous slurry was washed with three 5 mL portions of 1:1 diethyl ether/hexanes. The organics were combined and filtered through a plug of silica gel and the solvent was evaporated. After preparative plate chromatography (1:1 CH_2Cl_2/hexanes) 4-methylbenzophenone was obtained (87 mg, 89%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, J = 7.2 Hz, 2 H), 7.71 (d, J = 7.8 Hz, 2 H), 7.56 (m, 1 H), 7.46 (m, 2 H), 7.27 (d, J = 8.4 Hz, 2 H), 2.42 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.7, 143.4, 138.1, 135.0, 132.3, 130.5, 130.1, 129.1, 128.4, 21.8. IR (neat) 1656 (s) cm^{-1}.

Full characterization details of the cross-coupling products **2a**−**i** and **4** are provided in the Supporting Information.

Acknowledgment. The National Institutes of General Medical Sciences, DHHS supported this investigation through Grant No. GM066153.

Supporting Information Available: A complete description of the synthesis and characterization data of all compounds prepared in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050110U

(18) Kingsbury, C. A.; Ebert, G. *Phosphorus, Sulfur Silicon Relat. Elem.* **1980**, *9*, 315.

(19) Komives, T.; Marton, A. F.; Dutka, F. *J. Prakt. Chem.* **1976**, *318*, 248.