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Multiple Regioselective Functionalizations of Quinolines via Magnesiations

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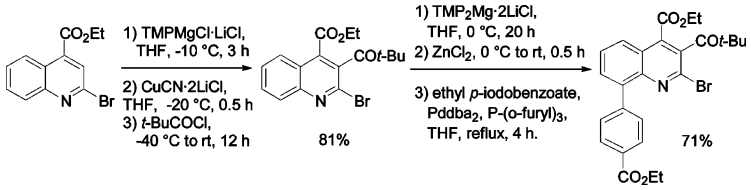
ABSTRACT



A wide range of polyfunctionalized quinolines was prepared via chemo- and regioselective magnesiation reactions using appropriate Mg reagents, such as *i*-PrMgCl·LiCl, MesMgBr·LiCl, Mes_2Mg·2LiBr, TMPMgCl·LiCl, and TMP_2Mg·2LiCl. An application to the total synthesis of the biologically active compound talnetant was performed (six steps, 28%).

The preparation of polyfunctionalized quinolines is of great interest since this structural unit (Figure 1) is found in various drugs such as mefloquine (**1**), an antimalarial,[1] talnetant (**2**),[2] a potential NK3 receptor antagonist developed by GSK, or irinotecan (**3**),[3] an anticancer drug, marketed by Pfizer. The lithiation of quinolines via Br/Li exchange reactions or by using a lithium base has been reported.[4] Mongin and Quéguiner described also Br/Mg exchange[5] on monobrominated quinolines using Bu_3MgLi.[6] These approaches are often complicated by a lack of regioselectivity and the propensity of lithium or magnesium reagents to undergo nucleophilic substitution at the C2 position. Recently, we have found that Br/Mg exchange reactions[7] or the use of TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidyl)[8] allows an efficient

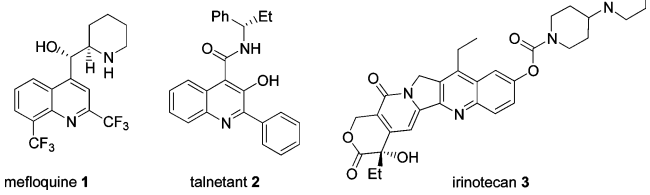


Figure 1. Drugs containing the quinoline skeleton.

(1) Wiesner, J.; Ortmann, R.; Jomaa, H.; Schlitzer, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5274.

(2) Elliott, J. M.; Carling, R. W.; Chambers, M.; Chicchi, G. G.; Hutson, P. H.; Jones, A. B.; MacLeod, A.; Marwood, R.; Meneses-Lorente, G.; Mezzogori, E.; Murray, F.; Rigby, M.; Royo, I.; Russell, M. G. N.; Sohal, B.; Tsao, K. L.; Williams, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5748.

(3) Duffour, J.; Gourgou, S.; Desseigne, F.; Debrigode, C.; Mineur, L.; Pinguet, F.; Poujol, S.; Chalbos, P.; Bressole, F.; Ychou, M. *Cancer Chemother. Pharmacol.* **2007**, *60*, 283.

(4) (a) Comins, D. L.; Nolan, J. M. I.; Bori, D. *Tetrahedron Lett.* **2005**, *46*, 6697. (b) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059. (c) Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120. (d) Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron* **1999**, *55*, 12149. (e) Marull, M.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, 1569. (f) Marull, M.; Schlosser, M. *Eur. J. Org. Chem.* **2004**, 1008. (g) For review, see: Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376.

(5) Dumouchel, S.; Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron Lett.* **2003**, *44*, 2033.

(6) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481.

(7) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) Boudet, N.; Knochel, P. *Org. Lett.* **2006**, *8*, 3737.

(8) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958.

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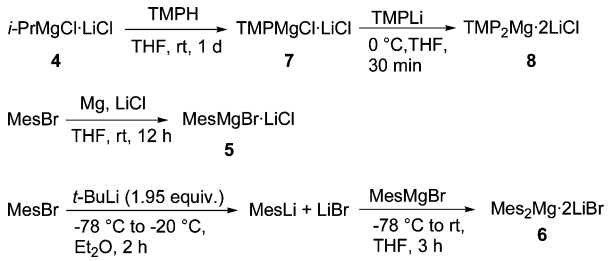
direct magnesiation of various heterocycles. Herein, we wish to report chemo- and regioselective magnesiation of quinolines using Mg reagents (Scheme 1) such as *i*-PrMgCl·LiCl

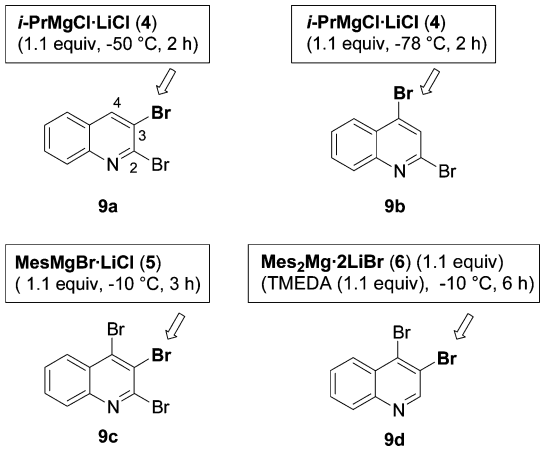
Scheme 1. Synthesis of the Magnesiation Reagents **5**, **6**, **7**, and **8**



(**4**),[9] MesMgBr·LiCl (**5**, Mes = mesityl), Mes_2Mg·2LiBr (**6**), TMPMgCl·LiCl (**7**),[8] and TMP_2Mg·2LiCl (**8**),[10] starting from readily available polybrominated quinolines. The new Grignard reagents MesMgBr·LiCl and Mes_2Mg·2LiBr were readily prepared as indicated in Scheme 1. They proved to be highly selective for challenging Br/Mg exchanges.

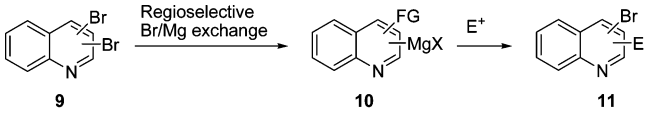
Thus, the reaction of 2,3-dibromoquinoline (**9a**) with *i*-PrMgCl·LiCl (**4**, 1.1 equiv, −50 °C, 2 h, Scheme 2)

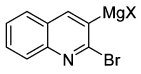
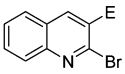
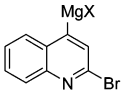
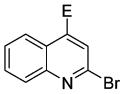
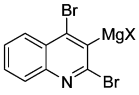
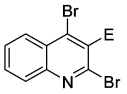
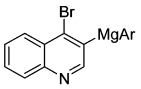
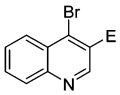
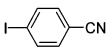
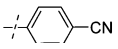
Scheme 2. Regioselective Br/Mg Exchange Reactions on Polybrominated Quinolines of Type **9**



provided quantitatively[11] and regioselectively[12] the corresponding 3-magnesiated 2-bromoquinoline (**10a**, Table 1). Similarly, starting from 2,4-dibromoquinoline (**9b**),[13] the

Table 1. Regioselective Magnesiation via Br/Mg Exchange of Polybromoquinolines of Type **9** and Trapping with Electrophiles



entry	magnesium species of type **10**[a]	electrophile	product of type **11**	yield (%)[b]
	 **10a**			
1	**10a**	TosCN	**11a** : E=CN	84
2	**10a**	C_2H_5CHO	**11b**: E=CH(OH)-C_2H_5	76
	 **10b**			
3	**10b**	$PhSO_2SPh$	**11c**: E=SPh	91
4	**10b**	TosCN	**11d**: E=CN	85
5	**10b**	LiHMDS ; chloranil	**11e**:E=NH_2	75[c]
	 **10c**			
6	**10c**	TosCN	**11f**: E=CN	88
7	**10c**	NC-CO_2Et	**11g**: E=CO_2Et	90
	 **10d**[d]			
8	**10d**[d]	$PhSO_2SMe$	**11h**: E= SMe	79
9	**10d**[d]		**11i**:E= 	71[e,f]

[a] X = Cl·LiCl or Br·LiCl. [b] Isolated yield of analytically pure product. [c] Reaction performed after transmetalation with CuCl·2LiCl (1.2 equiv). [d] Ar = Mes·LiBr. [e] Reaction performed after transmetalation with $ZnCl_2$. [f] 2 mol % of $Pddba_2$ and 4 mol % of P-(*o*-furyl)$_3$ were added.

addition of **4** (1.1 equiv, −78 °C, 2 h) gave the corresponding 4-magnesiated 2-bromoquinoline (**10b**). In contrast, the reactions of 2,3,4-tribromoquinoline (**9c**) or 3,4-dibromoquinoline (**9d**)[14] with *i*PrMgCl·LiCl (**4**) were not selective and provided regioisomeric mixture of Grignard reagents. Related selectivity problems have been observed with dibromopyridines.[15,16] However, using the sterically more demanding MesMgBr·LiCl (**5**, 1.1 equiv, −10 °C, 3 h), a complete regioselective magnesiation at the C3 position was observed for the 2,3,4-tribromoquinoline (**9c**), providing the corresponding intermediate **10c** (Table 1). The Grignard

(9) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) The reagent **4** was directly used from commercial sources such as Chemetall GmbH.

(10) Clososki, G. C.; Rohbogner, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681.

(11) The completion of the Br/Mg exchange reaction was checked by GC analysis of a reaction of aliquots quenched with saturated NH_4Cl (aqueous).

(12) The regioselectivity of the Br/Mg exchange reaction was checked by ^1H NMR of the crude product quenched with saturated NH_4Cl (aqueous).

(13) Osborne, A. G.; Buley, J. M.; Clarke, H.; Dakin, R. C. H.; Price, P. I. *J. Chem. Soc., Perkin Trans. 1* **1993**, *22*, 2747.

(14) Steck, E. A.; Hallock, L. L.; Holland, A. J. *J. Am. Chem. Soc.* **1946**, *68*, 1241.

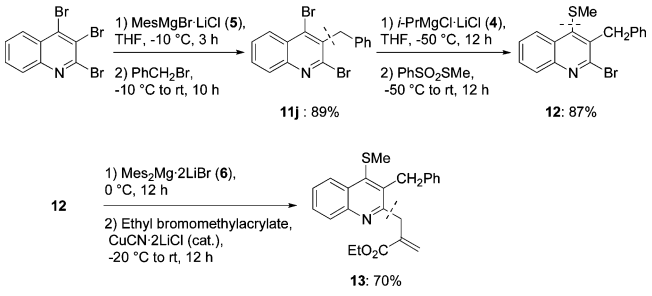
(15) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 1349.

(16) Mallet, M.; Quéguiner, G. *Tetrahedron* **1986**, *42*, 2253.

reagent **5** was not reactive enough to perform an exchange in the case of the 3,4-dibromoquinoline (**9d**). However, by using the corresponding dimesitylmagnesium·2LiBr (1.1 equiv of **6**, 1.1 equiv of TMEDA,[17] −10 °C, 6 h), a smooth regioselective magnesiation furnished the diaryl magnesium reagent **10d** (Table 1).

The Grignard compounds **10a**−**d** were trapped with various electrophiles as shown in Table 1. Thus, the C3-magnesiated 2-bromoquinoline **10a** was quenched with tosyl cyanide or propionaldehyde and gave 3-cyano-2-bromoquinoline (**11a**, 84%) or the corresponding alcohol (**11b**, 76%) (entries 1 and 2). Similarly, the Grignard intermediate **10b** afforded after quenching with $PhSO_2SPh$[18] or tosyl cyanide the corresponding phenylsulfanyl quinoline (**11c**, 91%) or 4-cyano-2-bromoquinoline (**11d**, 85%) (entries 3 and 4). Interestingly, the transmetalation of the C4-magnesiated 2-bromoquinoline **10b** using CuCl·2LiCl (1.2 equiv, −50 °C, 1 h) followed by the addition of LiHMDS (2 equiv, −60 °C, 1 h) provided the corresponding amidocuprate[19] which was oxidized using chloranil (1.2 equiv, −78 °C, 12 h) and then deprotected with TBAF (2.0 equiv, 25 °C, 15 min) leading to the 4-amino-2-bromoquinoline (**11e**, entry 5) in 75% yield. The reaction with C4-magnesiated 2,3-dibromoquinoline (**10c**) and tosyl cyanide afforded the corresponding quinoline **11f** (88%, entry 6). The Grignard intermediate **10c** was also quenched with ethyl cyanoformate giving the quinoline ester **11g** (90%, entry 7). The C3-magnesiated 4-bromoquinoline (**10d**) provided after trapping with $PhSO_2SMe$[20] the thioether **11h** (entry 8, 79% yield). Interestingly, the diarylmagnesium reagent **10d** underwent, after transmetalation with $ZnCl_2$, a Pd-catalyzed Negishi cross-coupling with 4-iodobenzonitrile and furnished the coupling product (**11i**) in 71% yield (entry 9). Remarkably, multiple selective exchanges can also be performed starting with the tribromoquinoline **9c**. Thus, the reaction of MesMgBr·LiCl (**5**, 1.1 equiv, −10 °C, 3 h) with **9c** provided, after quenching with benzyl bromide, the corresponding benzylated quinoline **11j** in 89% yield (Scheme 3). This product **11j** underwent a second Br/Mg exchange reaction using **4** (1.1 equiv, −50 °C, 12 h) and led after quenching with $PhSO_2SMe$ to the 3,4-functionalized 2-bromoquinoline **12** in 87% yield.

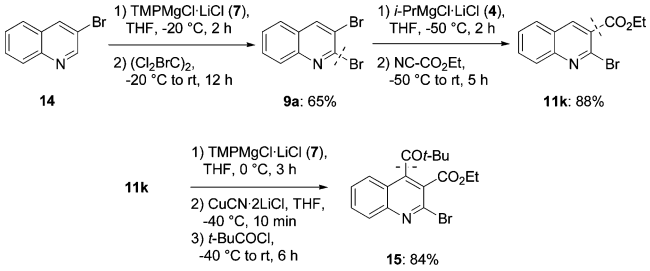
Scheme 3. Successive Regioselective Br/Mg Exchange Reactions at the C3, C4, and C2 Positions



A third Br/Mg exchange was performed on **12** using Mes_2Mg·2LiBr (**6**, 1.2 equiv, 0 °C, 12 h), and a copper-catalyzed allylation with ethyl (2-bromomethyl)acrylate[21] afforded the highly functionalized quinoline **13** in 70% yield. This last exchange reaction completed the sequence of successive functionalization at C4, C3, and C2 positions.

The direct magnesiation of quinolines using TMPMgCl·LiCl (**7**) and TMP_2Mg·2LiCl (**8**) further enhanced both the flexibility for regioselective magnesiations as well as the tolerance toward sensitive functional groups such as ketones or esters. Thus, successive magnesiations in positions C2, C3, and C4 could be achieved. Commercially available 3-bromoquinoline (**14**, Scheme 4) underwent a C2-deprotonation using TMPMgCl·LiCl (**7**, 1.1 equiv, −20 °C, 2 h)[8] and was quenched with 1,2-dibromo-1,1,2,2-tetrachloroethane, giving the 2,3-dibromoquinoline **9a** in 65% yield. The treatment of **9a** with *i*PrMgCl·LiCl (**4**) provided, after reaction with ethyl cyanoformate, the 2-bromoquinoline-3-carboxylic acid ethyl ester **11k** in 88% yield. Addition of TMPMgCl·LiCl (**7**) to **11k** gave regioselectively the C4-magnesiated intermediate under mild conditions (0 °C, 3 h). Then, a smooth carboxylation in the presence of CuCN·2LiCl led to the quinoline **15** in 84% yield. Thus, the sequence of functionalization C2 > C3 > C4 was accomplished. The pertinent combination of Br/Mg exchanges and direct metalations allowed a regioselective functionalization of up to three new positions of the 2,4-dibromoquinoline (**9b**). Performing a Br/Mg exchange on **9b** using *i*-PrMgCl·LiCl (**4**, −78 °C, 2 h, Scheme 5) led, after reaction with ethyl cyanoformate, to the quinoline **11l** in 92% yield. Then, the regioselective deprotonation of **11l** at the C3 position using **7** (−10 °C, 3 h) followed by a copper-mediated acylation using pivaloyl chloride gave the quinoline derivative **16** in 81% yield. Remarkably, a second regioselective deprotona-

Scheme 4. Successive Regioselective Magnesiations at the C2, C3, and C4 Positions



(17) (a) Without the addition of TMEDA, the C3/C4 regioselectivity was found to be 19:1, whereas using TMEDA (1.1 equiv), it was 99:1. (b) For the use of TMEDA, see also: Wang, X. J.; Xu, Y.; Zhang, L.; Krishnamurthy, D.; Senanayake, D. H. *Org. Lett.* **2006**, *8*, 3141.

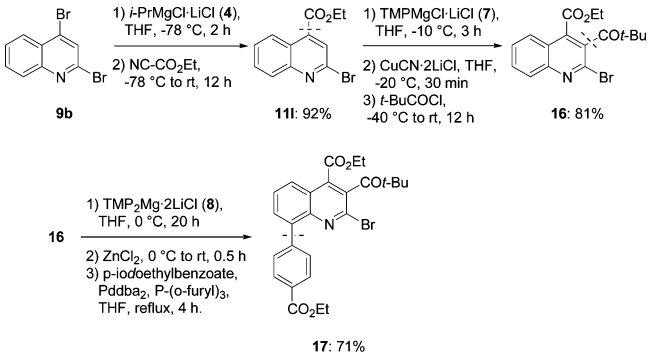
(18) Fujiki, K.; Tanifuji, N.; Sasaki, Y.; Yokoyama, T. *Synthesis* **2002**, 343.

(19) del Amo, V.; Dubbaka, S. R.; Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7838.

(20) Stoll, A. H.; Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 606.

(21) Villieras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220.

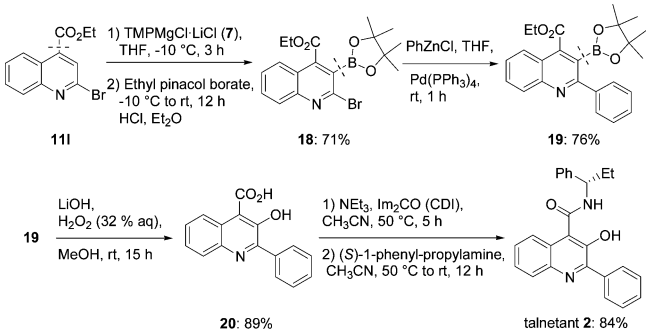
Scheme 5. Successive Regioselective Magnesiations at the C4, C3, and C8 Positions



tion on the quinoline **16** was performed at the C8 position (N-coordination), using the magnesium bisamide $TMP_2Mg\cdot 2LiCl$ (**8**, Scheme 1)[22] under mild conditions (0 °C, 20 h). After transmetalation with $ZnCl_2$, the corresponding diorganomagnesium species underwent a Pd-catalyzed Negishi cross-coupling using ethyl 4-iodobenzoate, furnishing the highly functionalized quinoline **17** in 71% yield.

As an application to our methodology, the total synthesis of talnetant **2** was performed (Scheme 6). The treatment of

Scheme 6. Successive Regioselective Functionalizations at the C4, C3, and C2 Positions



the 4-carbethoxy-2-bromoquinoline **11l** with TMPMgCl·LiCl (**7**, −10 °C, 3 h) followed by quenching with ethyl pinacol borate[23] (1.5 equiv, −10 °C to rt, 12 h) and acidic workup (1.2 equiv of HCl[24] in Et_2O) furnished the corresponding pinacol boronic ester **18** in 71% yield. The Pd(0)-catalyzed cross-coupling of PhZnCl with **18** gave the corresponding functionalized boronic ester **19** in 76% yield. A basic oxidation using LiOH (6 equiv) and aq H_2O_2 (3 equiv) in MeOH (rt, 15 h) afforded the quinoline salicylic acid **20** in 89% yield. Treatment[25] of **20** with NEt_3 in acetonitrile (rt, 30 min) using CDI (1.1 equiv, 50 °C, 5 h) and (*S*)-1-phenylpropylamine (1.1 equiv, 50 °C to rt, 12 h) gave talnetant (**2**) in 84% yield.

By this method, we obtained a new sequence of functionalization, C4 > C3 > C2, and have found an alternative method to the Pfitzinger synthesis.[26]

In summary, we have described various versatile regioselective functionalizations of quinolines using a combination of Br/Mg exchange reaction[27] and direct magnesiations. Several sensitive functionalities are tolerated such as an ester and a ketone. This approach opens a new route for the direct preparation of highly functionalized quinolines. Further extensions of this work are currently underway in our laboratories.

Acknowledgment. We thank the Fonds der Chemischen Industrie, the DFG, Merck Research Laboratories (MSD), Chemetall GmbH (Frankfurt), and BASF AG (Ludwigshafen) for financial support and generous gift of chemicals. We thank also Sanofi-Aventis (Frankfurt) for a fellowship to N.B.

Supporting Information Available: Experimental procedures and full characterization of all compounds. This material is available free of charge via Internet at http://pubs.acs.org

OL702494K

(22) TMPMgCl·LiCl (**7**) was found to be ineffective for this metalation.

(23) Ethyl pinacol borate was preferentially used instead of commercially available isopropyl pinacol borate because of a transesterification side reaction.

(24) Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631.

(25) Labaw, C. S.; Liu, P. PCT Int. Appl. WO 2007016609, 2007.

(26) Kaila, N.; Janz, K.; Huang, A.; Moretto, A.; DeBernardo, S.; Bedard, P. W.; Tam, S.; Clerin, V.; Keith, J. C., Jr.; Tsao, D. H. H.; Sushkova, N.; Shaw, G. D.; Camphausen, R. T.; Schaub, R. G.; Wang, Q. *J. Med. Chem.* **2007**, *50*, 21.

(27) **Typical procedure. Synthesis of 2-bromo-3-cyanoquinoline (11a).** A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 2,3-dibromoquinoline (**9a**) (1.23 g, 4.3 mmol) in dry THF (4 mL). *i*-PrMgCl·LiCl (**4**, 1.05 M in THF, 4.7 mmol, 1.1 equiv) was added slowly at −50 °C, and the resulting mixture was stirred for 2 h to complete the bromine−magnesium exchange (checked by GC−MS analysis of reaction aliquots). Tosyl cyanide (1.02 g, 1.3 equiv) was then added dropwise at −50 °C. The reaction mixture was warmed to rt for 12 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic fractions were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (*n*-pentane/diethyl ether = 7:3) yielded 837 mg (84% yield) of **11a** as a colorless solid (mp 176.6−177.4 °C).