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Regioselective Synthesis of Tetrahydrothiochromen-5-ones via a One-Pot Three-Component Solvent-Free Domino Protocol

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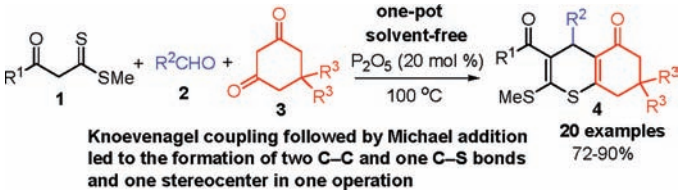
ABSTRACT



A highly efficient one-pot three-component regioselective synthesis of 4-aryl-3-aroyl-2-methylsulfanyl-4,6,7,8-tetrahydrothiochromen-5-ones has been developed by annulation of β-oxodithioesters with aldehydes and cyclic 1,3-diketones under solvent-free conditions promoted by P_2O_5. No cocatalyst or activator is needed in this protocol. The merit of this process is highlighted by its high efficiency of producing three new bonds and a stereocenter in one operation.

In the past decade, interest in green chemistry[1] has expanded, and it now encompasses wide areas of the chemical enterprise and is an alternative way to reduce drastic requirements for reactions. Their is a need for facile, efficient, and nonpolluting synthetic procedures that reduce the use of organic solvents and toxic reagents. For the reasons of economy and pollution prevention, multicomponent reactions[2] (MCRs) have considerable ecological interest as they address the fundamental principles of synthetic efficiency and reaction design, arising from minimization of waste, time, energy, and cost. Multicomponent reactions involving a domino process[3] with at least three different substrates particularly performed under solvent-free conditions[4] have emerged as a powerful strategy for the synthesis of chemically and biologically important organic frameworks. This protocol allows molecular complexity and diversity in a one-pot transformation and quite closely approaches the concept of an ideal synthesis.

Molecules with a thiochromene framework not only are important starting materials for numerous biologically active compounds but also are widely present as key

(1) (a) Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301. (b) Anastas, P. T.; Warner, J. C. In *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998, p. 30. (c) Ramachary, D. B.; Kishor, M. *J. Org. Chem.* **2007**, *72*, 5056. (d) Leitner, W. *Green Chem.* **2009**, *11*, 603.

(2) (a) Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2005. (b) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (c) Sunderhaus, J. D.; Martin, S. F. *Chem.—Eur. J.* **2009**, *15*, 1300. (d) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463. (e) Padwa, A. *Chem. Soc. Rev.* **2009**, *38*, 3072. (f) Domling, A. *Chem. Rev.* **2006**, *106*, 17. (g) Polshettiwar, V.; Varma, R. S. *Chem. Soc. Rev.* **2008**, *37*, 1546. (h) Shore, G.; Yoo, W. J.; Li, C. J.; Organ, M. *Chem.—Eur. J.* **2010**, *16*, 126. (i) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (j) Balamurugan, K.; Perumal, S.; Menendez, J. C. *Tetrahedron* **2011**, *67*, 3201. (k) Muschelknautz, C.; Frank, W.; Müller, T. J. J. *Org. Lett.* **2011**, *13*, 2556.

(3) (a) D'Souza, D. M.; Kiel, A.; Herten, D. P.; Müller, T. J. J. *Chem.—Eur. J.* **2008**, *14*, 529. (b) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 153.

(4) (a) Tanaka, K.; Toda, F. *Solvent-free Organic Synthesis*; Wiley-VCH: Weinheim, 2003. (b) Hernández, J. G.; Juaristi, E. *J. Org. Chem.* **2010**, *75*, 7107. (c) Li, S.; Wang, J. –X.; Wen, X.; Ma, X. *Tetrahedron* **2011**, *67*, 849. (d) Nelson, W. M. *Green Solvents for Chemistry—Perspectives and Practice*; Oxford University Press: Oxford, NY, 2003. (e) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267. (f) Corma, A.; Garcia, H. *Chem. Rev.* **2003**, *103*, 4307.

(5) (a) Hisio, M.; Ito, T.; Eliada, Y.; Nagaoka, K.; Nomiya, Y. Japanese Patent No. 24984, 1970; *Zh. Khim.* 23N432P, 1966. (b) Kulikova, L. K.; Klimenko, S. K.; Stolbova, T. V.; Kharchenko, V. G. *Khim.—Farm. Zh.* **1976**, 73.

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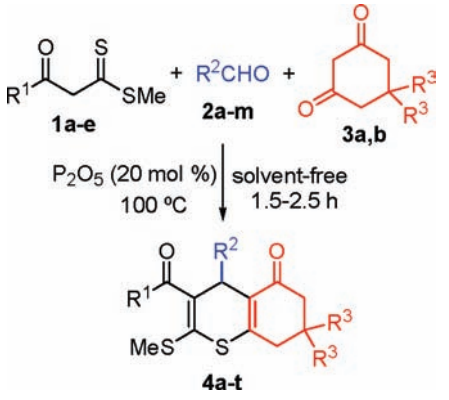
structural motifs in many natural products and are structurally related to plant pigments like flavonoids and anthocyanins. The thiochromene derivatives exhibit tumorigenic, antibacterial,[5] and antifungal[6] activities together with applications in dyes for chemical fibers.[7] Furthermore, chromene and thiochromene analogs of the HIV-1 protease inhibitor Ritonavir have been prepared and are under clinical trials.[8] According to reports of some of the patents they also act as modulators of the estrogen receptors.[9] In addition, 4*H*-thiochromenoapomorphines have been found to possess a high dopamine receptor binding affinity.[10]

A thorough literature survey revealed that the reports for the synthesis of thiochromones are limited[11] and are mainly prepared from substituted thiophenols.[12,13] 2-Trifluoromethyl thiochromones were synthesized by treating 2-mercaptophenyl ketones with trifluoroacetic anhydride in THF in the presence of triethylamine.[14] Further, thiochromone derivatives have been achieved by an organocatalytic domino thia-Michael/aldol reaction.[15] However, the above methods suffer from drawbacks such as toxic organic solvents, costly reagents, cumbersome experimental procedures, and lacking generality. Therefore, more general, efficient, and viable routes with operational simplicity for the synthesis of thiochromone derivatives are very much desirable and would be of great relevance to both synthetic and medicinal chemists.

It is pertinent to note that P_2O_5 is a mild, cheap, biodegradable, and readily available reagent, which has recently emerged as a powerful catalyst for various organic transformations.[16] Furthermore, we devised a straightforward, versatile, and one-pot synthesis of heterocycles utilizing P_2O_5 as a catalyst.[17] P_2O_5 is not only a versatile stable acidic enolizing agent but also a dehydrating reagent uniquely suited for a one-pot transformation. To the best of our knowledge, no report on the use of P_2O_5 as a catalyst for the synthesis of thiochromones utilizing β-oxodithioesters is known. As part of our ongoing research program on the development of new protocols for the synthesis of heterocycles *via* a one-pot multicomponent reaction,[18] herein we report, for the first time, a one-pot three-component synthesis of thiochromone frameworks by the coupling of β-oxodithioesters, aldehydes, and cyclic 1,3-diketones catalyzed by P_2O_5 under solvent-free conditions.

Recently, β-oxodithioesters have received much attention as a key intermediate in the synthesis of various important bioactive frameworks such as dihydropyrimidinone,[19] pyridopyrimidinone,[19] pyrazole,[20] benzo[*a*]quinolizine-4-thione,[21] and 2*H*-chromene-2-thione.[22] Therefore, we became intrigued in scouting the use of β-oxodithioesters to develop a more generalized synthetic strategy for the synthesis of functionalized thiochromones. β-Oxodithioesters are synthesized by reported methods[23] in good yields (70−80%). Thus, when β-oxodithioesters **1** were treated with aldehydes **2** and cyclic 1,3-diketones **3** under solvent-free conditions in the presence of P_2O_5 at 100 °C, the corresponding 4-aryl-3-aroyl-2-methylsulfanyl-4,6,7,8-tetrahydrothiochromen-5-ones **4a**−**t** were obtained in high yields (Scheme 1).

Scheme 1. Synthesis of Thiochromen-5-ones **4**



Initially, a mixture of 3-oxo-3-phenyldithiopropionic acid methyl ester **1a** (1.0 mmol), 4-nitrobenzaldehyde **2c**

(6) Wang, G.; Yang, G.; Ma, Z.; Tian, W.; Fang, B.; Linbo Li, L. *Int. J. Chem.* **2010**, *2*, 19.
(7) (a) Tilak, B. D.; Vaidya, V. M. *Tetrahedron Lett.* **1963**, *9*, 487. (b) Tilak, B. D.; Jain, S. K. *Indian J. Chem.* **1969**, *7*, 17.
(8) (a) Kaye, P. T.; Musa, M. A.; Nchinda, A. T.; Nocanda, X. W. *Synth. Commun.* **2004**, *34*, 2575. (b) Kaye, P. T. *S. Afr. J. Chem.* **2004**, *57*, 545.
(9) (a) Kaltenbach, R. F.; Robinson, S. P.; Trainor, G. L. U.S. Patent 2005/0267183 A1, December 1, 2005. (b) Zhang, X.; Sui, Z. U.S. Patent 2006/0020018 A1, January 26, 2006.
(10) Attila Sipos, A.; Toth, M.; Mueller, F. K. U.; Lehmann, J.; Berenyi, S. *Monatsh. Chem.* **2009**, *140*, 473.
(11) (a) Katoaka, T.; Tomoto, A.; Shimizu, H.; Hori, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2913. (b) Banzatti, C.; Mellini, P.; Salvadori, P. *Gazz. Chim. Ital.* **1987**, *117*, 259. (c) Kaye, P. T. *S. Afr. J. Sci.* **2004**, *100*, 545.
(12) (a) Rasolofonjatovo, E.; Tréguier, B.; Provot, O.; Hamze, A.; Morvan, E.; Brion, J. -D.; Alami, M. *Tetrahedron Lett.* **2011**, *52*, 1036. (b) Kenny, R. S.; Mashelkar, U. C.; Rane, D. M.; Bezawada, D. K. *Tetrahedron* **2006**, *62*, 9280.
(13) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354.
(14) (a) Usachev, B. I.; Shafeev, M. A.; Sosnovskikh, V. Y. *Russ. Chem. Bull. Int. Ed.* **2006**, *55*, 504. (b) Usachev, B. I.; Sosnovskikh, V. Y.; Shafeev, M, A.; Röschenthaler, G. -V. *Phosphorus, Sulfur, Silicon* **2005**, *180*, 1315.
(15) Rios, R.; Sunden, H.; Ibrahem, I.; Zhao, G. -L.; Eriksson, L.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 8547.
(16) (a) Massah, A. R.; Dabagh, M.; Shahidi, S.; Naghash, H. J.; Momeni, A. R.; Aliyan, H. *J. Iran. Chem. Soc.* **2009**, *6*, 405. (b) Hajipour, A. R.; Zarei, A.; Ruoho, A. E. *Tetrahedron Lett.* **2007**, *48*, 2881. (c) Eshghi, H.; Rahimizadeh, M.; Saberi, S. *Chin. Chem. Lett.* **2008**, *19*, 1063. (d) Zarei, A.; Hajipour, A. R.; Khazdooz, L.; Mirjalili, B. F.; Zahmatkesh, S. *J. Mol. Catal. A: Chem.* **2009**, *301*, 39.
(17) (a) Nandi, G. C.; Samai, S.; Kumar, R.; Singh, M. S. *Tetrahedron* **2009**, *65*, 7129. (b) Nandi, G. C.; Samai, S.; Kumar, R.; Singh, M. S. *Tetrahedron Lett.* **2009**, *50*, 7220. (c) Kumar, R.; Raghuvanshi, K.; Verma, R. K.; Singh, M. S. *Tetrahedron Lett.* **2010**, *51*, 5933. (d) Verma, G. K.; Raghuvanshi, K.; Verma, R. K.; Dwivedi, P.; Singh, M. S. *Tetrahedron* **2011**, *67*, 3698.
(18) (a) Samai, S.; Nandi, G. C.; Kumar, R.; Singh, M. S. *Tetrahedron Lett.* **2009**, *50*, 7096. (b) Samai, S.; Nandi, G. C.; Singh, P.; Singh, M. S. *Tetrahedron* **2009**, *65*, 10155. (c) Nandi, G. C.; Samai, S.; Singh, M. S. *Synlett* **2010**, 1133. (d) Samai, S.; Nandi, G. C.; Singh, M. S. *Tetrahedron Lett.* **2010**, *51*, 5555.
(19) Nandi, G. C.; Samai, S.; Singh, M. S. *J. Org. Chem.* **2010**, *75*, 7785.
(20) Peruncheralathan, S.; Khan, T. A.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2005**, *70*, 10030.
(21) Roy, A.; Nandi, S.; Ila, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 229.
(22) Verma, R. K.; Verma, G. K.; Raghuvanshi, K.; Singh, M. S. *Tetrahedron* **2011**, *67*, 584.
(23) Samuel, R.; Asokan, C. V.; Suma, S.; Chandran, P.; Retnamma, S.; Anabha, E. R. *Tetrahedron Lett.* **2007**, *48*, 8376.

(1.0 mmol), and dimedone **3a** (1.0 mmol) was heated at 100 °C under solvent-free conditions in the presence of different catalysts such as *p*-TSA, $InCl_3$, KF-Alumina, piperidine, SiO_2, and P_2O_5 (20 mol % each) separately. *p*-TSA, $InCl_3$, KF-Alumina, piperidine, and SiO_2 did catalyze the reaction to furnish the desired product **4c** albeit in low yields (Table 1, entries 1−5). To our delight, P_2O_5 gave the desired thiochromone **4c** in 90% yield (Table 1, entry 6). Encouraged by this result, we then focused on optimizing the reaction conditions.

Table 1. Optimization of Reaction Conditions for the Synthesis of **4**[a]

entry	catalyst (mol %)	temp (°C)	time (h)	yield[b] (%)
1	*p*-TSA (20)	100	4	45
2	$InCl_3$ (20)	100	6	30
3	KF-Alumina (20)	100	5	20
4	Piperidine (20)	100	2.5	35
5	SiO_2 (20)	100	4	40
6	P_2O_5 (20)	100	1.5	90
7	P_2O_5 (10)	100	3	60
8	P_2O_5 (15)	100	2.5	76
9	P_2O_5 (25)	100	1.5	88
10	P_2O_5 (20)	80	4	35
11	P_2O_5 (20)	90	3	45
12	P_2O_5 (20)	120	1.5	87
13	H_3PO_4 (40)	80	4	25

[a] Reaction of 3-oxo-3-phenyldithiopropionic acid methyl ester **1a** (1.0 mmol), 4-nitrobenzaldehyde **2c** (1.0 mmol), and dimedone **3a** (1.0 mmol) under solvent-free conditions. [b] Isolated pure yields.

The P_2O_5 loading was subsequently examined (entries 6−9), and it was found that 20 mol % of P_2O_5 provided the maximum yield in minimum time (Table 1, entry 6). We immediately undertook a study to examine the effects of temperature on this transformation. The results demonstrated that 100 °C appeared to be the optimum temperature for this transformation (Table 1, entries 6 and 10−12). During the course of the reaction, water probably reacts with P_2O_5 to form H_3PO_4, which may catalyze the reaction. Thus, to check the efficacy of H_3PO_4, the above model reaction was further investigated in the presence of H_3PO_4 (10 mol %, 20 mol %, and 40 mol %) separately. Phosphoric acid did catalyze the reaction to form the desired thiochromone albeit in low yield (Table 1, entry 13), while the major product formed was characterized as a xanthene derivative. Thus, the best yield, cleanest reaction, and most facile workup were achieved employing 20 mol % of P_2O_5 at 100 °C under solvent-free conditions. The starting materials were completely consumed to afford the desired compound that was highly visible on TLC under UV light. Control experiments verified that the reaction does not proceed in the absence of P_2O_5.

To generate a small library of functionalized thiochromen-5-ones **4**, we next utilized a variety of substrates to explore the synthetic scope and generality of this accelerated one-pot Knoevenagel condensation/Michael addition/cyclization cascade reaction under the optimal conditions. Representative results are shown in Table 2.

Table 2. Exploration of the Substrate Scope for the Synthesis of **4**

entry	R^1	R^2	R^3	time (h)	yield[a] (%)
4a	C_6H_5	C_6H_5	Me	1.75	82
4b	C_6H_5	4-FC_6H_4	H	1.5	86
4c	C_6H_5	4-$NO_2C_6H_4$	Me	1.5	90
4d	C_6H_5	2,4-$Cl_2C_6H_3$	Me	1.5	87
4e	C_6H_5	3-$NO_2C_6H_4$	Me	1.5	83
4f	C_6H_5	4-BrC_6H_4	Me	2.0	84
4g	4-$OMeC_6H_4$	4-ClC_6H_4	Me	1.75	82
4h	4-$OMeC_6H_4$	2-$OMeC_6H_4$	Me	2.5	75
4i	4-$OMeC_6H_4$	3-$NO_2C_6H_4$	H	1.5	82
4j	2-thienyl	4-BrC_6H_4	Me	1.75	83
4k	2-thienyl	2-ClC_6H_4	Me	2.0	74
4l	2-thienyl	3-$NO_2C_6H_4$	H	1.75	80
4m	2-thienyl	4-Cl-3-FC_6H_3	Me	1.5	82
4n	3-pyridyl	3-$NO_2C_6H_4$	Me	2.0	72
4o	3-pyridyl	2,4-$Cl_2C_6H_3$	H	2.0	74
4p	2-furyl	4-BrC_6H_4	H	1.75	78
4q	2-furyl	4-$NO_2C_6H_4$	Me	1.75	80
4r	2-furyl	4-MeC_6H_4	Me	2.0	74
4s	2-furyl	4-$CF_3C_6H_4$	Me	1.75	82
4t	2-furyl	3-OHC_6H_4	Me	2.5	76

[a] Isolated pure yields.

Notably, a wide range of *β*-oxodithioesters **1a**−**e**, aromatic aldehydes **2a**−**m**, and cyclic 1,3-diketones **3a,b** were well tolerated and proceeded smoothly under the optimized reaction conditions. However, unfortunately, when some aliphatic aldehydes (acetaldehyde, propionaldehyde, and isobutyraldehyde) and cyclic 1,3-diketones

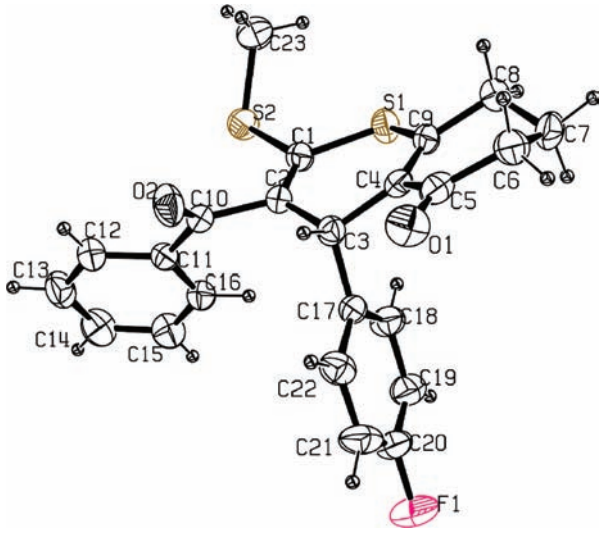
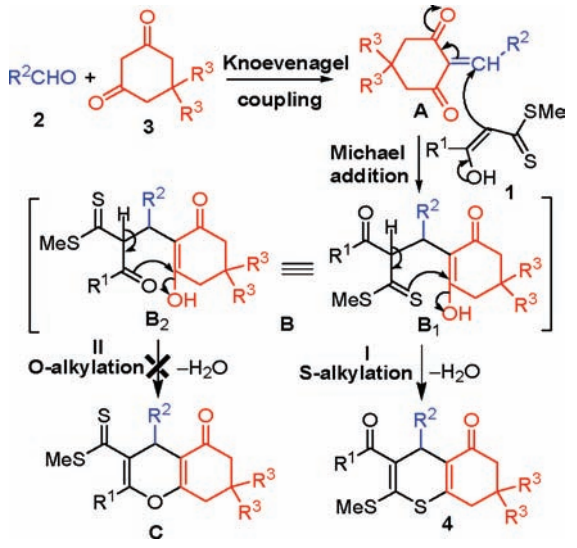


Figure 1. ORTEP diagram of compound **4b**.

Scheme 2. Plausible Mechanism for the Formation of Thiochromen-5-one **4**



(Indane-1,3-dione and meldrum acid) were utilized under the optimized reaction conditions, it led to mixture of several very close spots on the TLC plate, which could not be isolated, thus, limiting the scope of this reaction to some extent.

The structures of all the newly synthesized compounds were deduced from their satisfactory elemental and spectral (IR, ^{1}H, ^{13}C NMR, and MS) studies. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. Finally, the structure of one representative compound 3-benzoyl-4-(4-fluorophenyl)-2-methylsulfanyl-4,6,7,8-tetrahydrothio-chromen-5-one **4b** was confirmed unambiguously by the X-ray single crystal diffraction analysis (see the Supporting Information) (Figure 1).[24]

Although we have not established the mechanism of the reaction experimentally, a plausible reaction scenario for the domino cyclocondensation is outlined in Scheme 2. The first step is believed to be the Knoevenagel condensation between the aldehyde **2** and cyclic 1,3-diketone **3** to generate adduct **A**, which acts as a Michael acceptor. The enol form of β-oxodithioester **1** attacks Knoevenagel adduct **A** in a Michael-type addition to produce an open chain intermediate **B**. Intermediate **B** may undergo intramolecular cyclization *via* its two possible rotamers $\mathbf{B_1}$ and $\mathbf{B_2}$ through pathways **I** and **II** to furnish thiochromone **4** and chromone **C**, respectively. $\mathbf{B_1}$ undergoes regiospecific S-alkylation *via* route **I** followed by dehydration to give the desired thiochromone **4**. The alternative O-alkylation of $\mathbf{B_2}$ could lead to chromone **C** *via* route **II**. During our investigation, we did not observe a trace of **C**, and **4** was obtained exclusively. It should be emphasized that S-alkylation is more favorable than O-alkylation making the protocol highly regioselective.

In summary, we have developed a mild, efficient, and versatile annulation protocol for densely functionalized thiochromone derivatives involving β-oxodithioesters, aldehydes, and cyclic 1,3-diketones under solvent-free conditions *via* a one-pot multicomponent domino reaction in high yields. To the best of our knowledge, this is the first report of thiochromone synthesis *via* ring annulation of β-oxodithioesters utilizing P_2O_5, which acts as a catalyst as well as a dehydrating agent in the same transformation. It is worth mentioning that in the course of our reactions three new bonds (two C–C and one C–S) and one stereocenter are formed in one operation. Importantly, this method is suitable to library generation, diversity-oriented synthesis, and drug discovery, which makes the methodology more attractive for organic synthesis. Furthermore, it can be considered as environmentally friendly, since it requires the use of neither solvent nor metal-containing catalysts.

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Supporting Information Available. Full experimental details; analytical and spectroscopic data (copies of ^{1}H and ^{13}C NMR for compounds **4a**–**t**); X-ray data and structure for compound **4b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(24) Crystallographic data for compound **4b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 819852. These data can be obtained free of charge at www.ccdc.cam.ac.uk.