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Facile Synthesis of Polysubstituted Oxazoles via A Copper-Catalyzed Tandem Oxidative Cyclization

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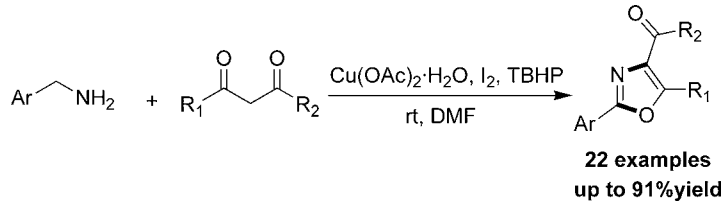
ABSTRACT



A highly efficient synthesis of polysubstituted oxazoles was developed via a copper-catalyzed tandem oxidative cyclization. The desired products can be obtained from readily available starting materials under mild conditions. This is an attractive alternative method for the synthesis of oxazole derivatives.

The ubiquitous oxazoles have attracted more and more attention in both industrial and academic fields for decades.[1] This interest arises from the fact that a variety of natural and synthetic compounds which contain the oxazole substructure exhibit significant biological activities such as anticancer, antifungal, antitumor, anti-inflammatory, and antiviral properties.[2] For instance, Leucamide A and its analogues, which are very important anticancer reagents,[3] are mainly composed of several oxazole moieties. Moreover, oxazole derivatives can also be employed as organic materials, such as a corrosion inhibitor.[4] Owing to their important applications, various synthetic methodologies of oxazole derivatives have been developed.[5] Classical procedures for the synthesis of oxazoles include a cyclodehydration of acyclic precursors,[6,7] the coupling of the prefunctionalized oxazoles with organometallic reagents,[8] and the oxidation of oxazolines.[9] However, these methods always suffered from the limitation of harsh conditions and tedious synthetic procedures. As far as we know, the reports for the direct

(1) (a) Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 382. (b) Nicolaou, K. C.; Bella, M.; Chen, D. Y. K.; Huang, X.-H.; Ling, T.-T.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3495. (c) Pattenden, G.; Ashweek, N. J.; Baker-Glenn, C. A. G.; Walker, G. M.; Yee, J. G. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4359.

(2) (a) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597. (b) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464. (c) Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961. (d) Wipf, P. *Çhem. Rev.* **1995**, *95*, 2115. (e) Riego, E.; Hernandez, D.; Albericio, F.; Álvarez, M. *Synthesis* **2005**, 1907. (f) Kende, A. S.; Kawamura, K.; DeVita, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4070. (g) Vedejs, E.; Barda, D. A. *Org. Lett.* **2000**, *2*, 1033.

(3) Wang, W.; Yao, D.; Gu, M.; Fan, M.; Li, J.; Xing, Y.; Nan, F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5284.

(4) (a) Palmer, D. C.; Venkatraman, S. *Oxazoles: Synthesis, Reactions and Spectroscopy, Part A*; J. Wiley & Sons: Hoboken, NJ, 2004. (b) Iddon, B. *Heterocycles* **1994**, *37*, 1321.

(5) (a) Japp, F. R.; Murry, T. S. *J. Chem. Soc.* **1893**, 469. (b) Bonne, D.; Dekhane, M.; Zhu, J.-P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2485. (c) Clapham, B.; Spanka, C.; Janda, K. D. *Org. Lett.* **2001**, *3*, 2173. (d) Santos, A.; Kaim, L. E.; Grimaud, L.; Ronsseray, C. *Chem. Commun.* **2009**, 3907. (e) Williams, D. R.; Fu, L.-F. *Org. Lett.* **2010**, *12*, 808. (f) Tarzia, G.; Schiatti, P.; Selva, D.; Favara, D.; Ceriani, S. *Eur. J. Med. Chem.* **1976**, *11*, 263. (g) Davies, J. R.; Kane, P. D.; Moody, C. J. *Tetrahedron* **2004**, *60*, 3967.

(6) (a) Ferrini, P. G.; Marxer, A. *Angew. Chem., Int. Ed.* **1963**, *2*, 99. (b) Merkul, E.; Muller, T. J. J. *Chem. Commun.* **2006**, 4817. (c) Pan, Y.-M.; Zheng, F.-J.; Lin, H.-X.; Zhan, Z.-P. *J. Org. Chem.* **2009**, *74*, 3148. (d) Verrier, C.; Martin, T.; Hoarau, C.; Marsais, F. *J. Org. Chem.* **2008**, *73*, 7383. (e) Young, G. L.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 3797.

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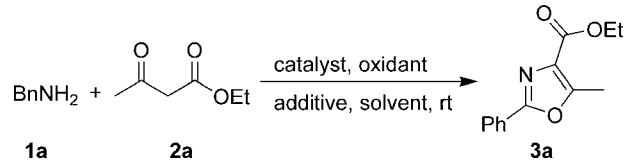
approach to the highly functionalized oxazoles are rare.[10] Therefore, developing a milder and more general procedure to access polysubstituted oxazole derivatives is still highly desirable.

Copper, among transition metals, is particularly attractive in organic synthesis because of its low price, slight toxicity, and environmentally benign feature.[11] Collectively, there are many reports on copper-catalyzed oxidative C−H bond activation.[12] For example, the Li group has reported a cross dehydrogenative coupling (CDC) reaction in the presence of copper and the corresponding oxidant.[13] Herein, we developed a novel and efficient copper-catalyzed oxidative tandem cyclization from easily available benzylamines and 1,3-dicarbonyl derivatives, providing the polysubstituted oxazole derivatives with moderate to good yields.

To initiate our study, the reaction of ethyl acetoacetate with benzylamine was chosen as a model reaction in the presence of a copper source and *t*-BuOOH (TBHP) solution in *n*-hexane at room temperature.[14] It was found that the reaction led to the desired product ethyl 5-methyl-2-phenyl-oxazole-4-carboxylate with a yield of 9% (Table 1, entry 1). Then we optimized the reaction conditions further to increase the reaction yield. However, changing the reaction temperature or modulating the reaction time had no positive influence on this reaction. The addition of benzylamine in two portions can increase the yield (Table 1, entry 2) and avoid the oxidation of benzylamine. After a series of tries, we introduced different additives to the reaction system to improve the reaction efficiency. It was noted that the addition of 1.2 equiv of NBS or iodine could enhance the reaction yield up to 35% and 56% respectively (Table 1, entries 3 and 4). Following these results, the other oxidants, such as *t*-BuOO*t*-Bu, TBHP, and air, were tested for this reaction in the presence of molecular iodine. Among them, TBHP solution in *n*-hexane gave the best result (Table 1, entries 4−6). Aqueous TBHP disfavored this reaction, nevertheless, resulting in a poor yield of 29% (Table 1, entry 7). Subsequently, different copper salts were examined in the reaction. Without copper catalysts, the reaction was carried out inefficiently, and the desired product was obtained with a poor yield of 32% (Table 1, entry 8). Normally, all of these copper salts can catalyze this reaction and improve the reaction yields. Among these different copper salts, $Cu(OAc)_2{\cdot}H_2O$ was the best catalyst for this reaction, and the corresponding yield was enhanced up to 61% (Table 1, entries 9−11). Afterward, various solvents were screened for this reaction. When the reaction solvent was changed from acetonitrile to toluene or dioxane, no product was observed. When THF or ethanol was employed as the reaction solvent, the desired oxazole was obtained in a lower yield of 43% and 39%, respectively (Table 1, entries 12−16). Finally, it was found that DMF was the most suitable solvent for this reaction, with which the highest yield of 93% was obtained (Table 1, entry 15). The reaction temperature also had great influence on the reaction. Raising the reaction temperature incurred a lower yield, while reducing the reaction temperature led to a slower reaction rate (Table 1, entry 17). In compromise, room temperature should be the optimized reaction temperature.

Finally, the optimal reaction condition was obtained, that is, 2 equiv of benzylamine (**1a**) and 1 equiv of ethyl acetoacetate (**2a**) as substrates, 0.01 equiv of copper acetate as catalyst, 2 equiv of TBHP as oxidant, and 1.2 equiv of

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a**

entry	catalyst	oxidant	additive	solvent	yield (%)[b]
1[c]	CuI	TBHP	–	CH_3CN	9
2	CuI	TBHP	–	CH3CN	15
3	CuI	TBHP	NBS	CH_3CN	35
4	CuI	TBHP	I_2	CH_3CN	56
5	CuI	Air	I_2	CH_3CN	17
6	CuI	*t*-BuOO*t*-Bu	I_2	CH_3CN	34
7[d]	CuI	TBHP	I_2	CH_3CN	29
8	–	TBHP	I_2	CH_3CN	32
9	CuCl	TBHP	I_2	CH_3CN	53
10	$Cu(OAc)_2{\cdot}H_2O$	TBHP	I_2	CH_3CN	61
11	CuBr	TBHP	I_2	CH_3CN	57
12	$Cu(OAc)_2{\cdot}H_2O$	TBHP	I_2	toluene	0
13	$Cu(OAc)_2{\cdot}H_2O$	TBHP	I_2	THF	39
14	$Cu(OAc)_2{\cdot}H_2O$	TBHP	I_2	EtOH	43
15	$Cu(OAc)_2{\cdot}H_2O$	TBHP	I_2	DMF	93
16	$Cu(OAc)_2{\cdot}H_2O$	TBHP	I_2	dioxane	0
17[e]	$Cu(OAc)_2{\cdot}H_2O$	TBHP	I_2	DMF	73

[a] Reaction conditions: benzylamine (2 equiv, addition in two portions), ethyl acetoacetate (1 equiv, 0.5 mmol), catalyst (0.05 mmol, 10 mmol %), oxidant (2 equiv), additive (1.2 equiv), solvent (3 mL). The reaction was performed for 6 h. [b] Determined by GC-MS with internal standard. [c] Addition of benzylamine in one portion. [d] Aqueous TBHP (70%) was used as oxidant. [e] The reaction was carried out at 60 °C.

(7) (a) Lister, J.; Robinson, R. *J. Chem. Soc.* **1912**, 1297. (b) Keni, M.; Tepe, J. J. *J. Org. Chem.* **2005**, *70*, 4211. (bb) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604. (c) Kumar, M. P.; Liu, R.-S. *J. Org. Chem.* **2006**, *71*, 4951. (d) Kison, C.; Opatz, T. *Chem.—Eur. J.* **2009**, *15*, 843. (e) Shi, B.; Blake, A. J.; Lewis, W.; Campbell, I. B.; Judkins, B. D.; Moody, C. J. *J. Org. Chem.* **2005**, *75*, 152.

(8) (a) Derridj, F.; Djebbar, S.; Benali-Baitich, O.; Doucet, H. *J. Organomet. Chem.* **2008**, *693*, 135. (b) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2006**, *8*, 2495. (c) Lee, K.; Counceller, C. M.; Stambuli, J. P. *Org. Lett.* **2009**, *11*, 1457.

(9) (a) Williams, D. R.; Lowder, D. P.; Gu, G.-Y.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331. (b) Meyers, A. I.; Tavares, F. X. *J. Org. Chem.* **1996**, *61*, 8207. (c) Uto, A. J. Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.

(10) (a) Coqueron, P. Y.; Didier, C.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1411. (b) Lechel, T.; Lentz, D.; Reissig, H. U. *Chem.—Eur. J.* **2009**, *15*, 5432.

(11) (a) Sherman, E. S.; Chemler, S. R.; Tan, T.-B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573. (b) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250. (c) Adrio, L. A.; Hill, K. K. *Chem. Commun.* **2008**, 2325. (d) Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2008**, 835.

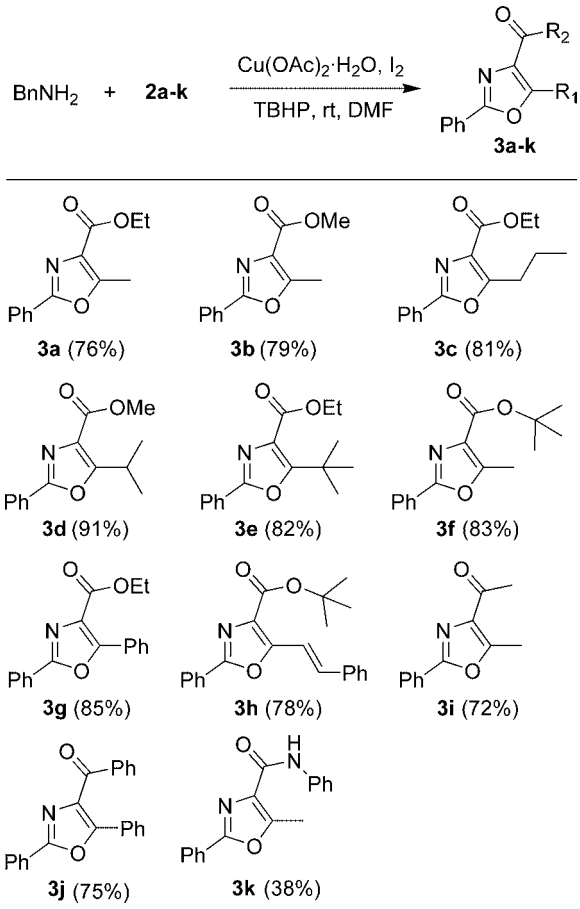
(12) (a) Borduas, N.; Powell, D. A. *J. Org. Chem.* **2008**, *73*, 7822. (b) Boldron, C.; Gamez, P.; Tooke, D. M.; Spek, A. L.; Reedijk, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3585. (c) Niu, M.-Y.; Yin, Z.-M.; Fu, H.; Jiang, Y.-Y.; Zhao, Y.-F. *J. Org. Chem.* **2008**, *73*, 3961.

(13) (a) Li, Z.-P.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (b) Li, Z.-P.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (c) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (d) Baslé, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047. (e) Baslé, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661.

(14) Hill, J. G.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3607.

iodine as additive; DMF was the reaction solvent at room temperature. With the optimized conditions in hand, the scope of the reaction substrates was investigated. First, we examined the reaction with a series of 1,3-dicarbonyl compounds, and the results are listed in Scheme 1. From

Scheme 1. Copper-Catalyzed Oxidative Cyclization with Different 1,3-Dicarbonyl Compounds[a]

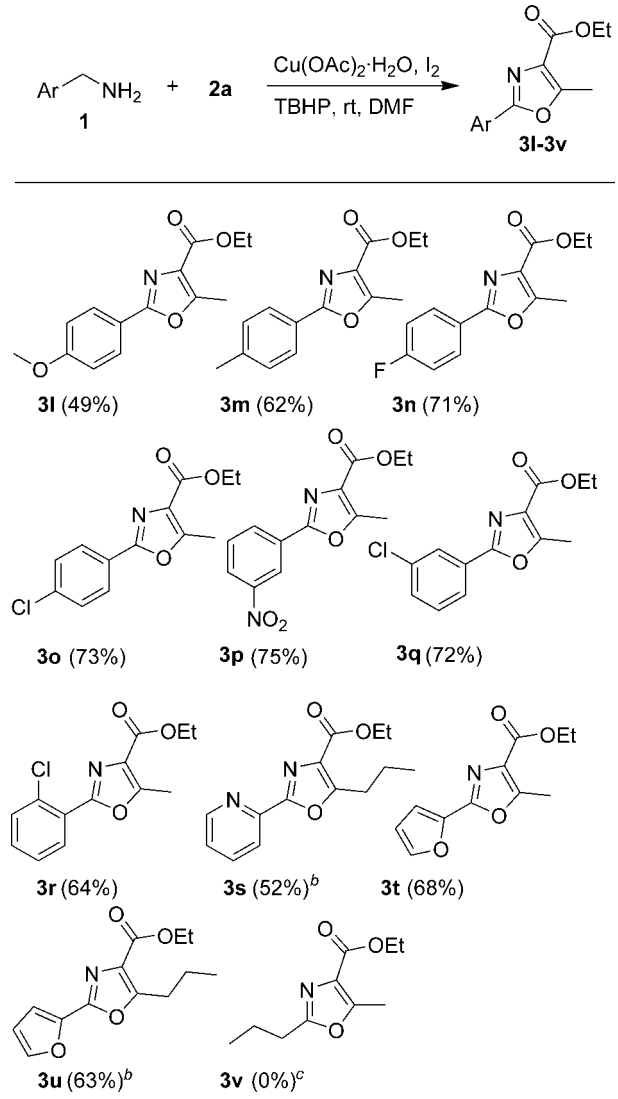


[a] Reaction conditions: benzylamine (2 equiv), 1,3-dicarbonyl compounds (1 equiv, 1 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol, 10 mmol %), TBHP (2 euqiv), I_2 (1.2 equiv), DMF (3 mL). Isolated yield was given.

Scheme 1 it was found that various substrates were converted into the corresponding products with moderate to good yields under the conditions. For example, β-keto esters with different alkyl substituents could provide the corresponding products with high yields regardless of the difference of the substituent (Scheme 1, **3a**−**3g**). This meant that steric effect and electronic effect had little influence on the reaction. The reaction condition was so mild that the unsaturated functional group can survive the reaction. For example, **3h** was obtained smoothly in a yield of 78% (Scheme 1, **3h**) without any change of styrene group, whose structure was also confirmed by X-ray crystallography.[15] When the reaction substrates were switched from β-keto esters to β-diketones, the reactions can be carried out smoothly to give the corresponding products with good yields (Scheme 1, **3i**−**3j**). When β-keto ester was replaced with β-keto amide (3-oxo-*N*-phenylbutanamide), the reaction gave the product with a lower yield of 38% (Scheme 1, **3k**).

Next, different benzylamine derivatives were investigated as the reaction substrates (Scheme 2).

Scheme 2. Copper-Catalyzed Oxidative Cyclization with Different Benzylamine Derivatives[a,b,c]



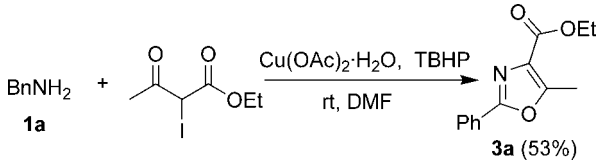
[a] Reaction conditions: benzylamine derivatives (2 equiv), ethyl acetoacetate (1 equiv, 1 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol, 10 mmol %), TBHP (2 euqiv), I_2 (1.2 equiv), DMF (3 mL). Isolated yield was given. [b] Ethyl 3-oxohexanoate as substrate. [c] Butylamine as substrate.

Electron-withdrawing substituents on the aromatic ring were more beneficial for this transformation, while the electron-donating group decreased the reaction yields (Scheme 2, **3l**−**3q**). Steric effect also had a slightly adverse influence on the reaction. For instance, (2-chlorophenyl)methanamine gave a lower reaction yield (Scheme 2, **3r**). Then several heterocyclic amines were employed as the reaction substrates and the corresponding reactions afforded the oxazoles with moderate to good yields (Scheme 2, **3s**−**3u**). However, butylamine failed to yield the desired product (Scheme 2,

3v). This perhaps implied that it was necessary for a weak C−H bond to be adjacent to the amino group for this reaction.

To explore the reaction process, the reaction of ethyl 2-iodo-3-oxobutanoate with benzylamine was performed in the presence of copper acetate and TBHP. It was found that the reaction can give the oxazole product with a yield of 53%, as shown in Scheme 3. On the basis of the experimental

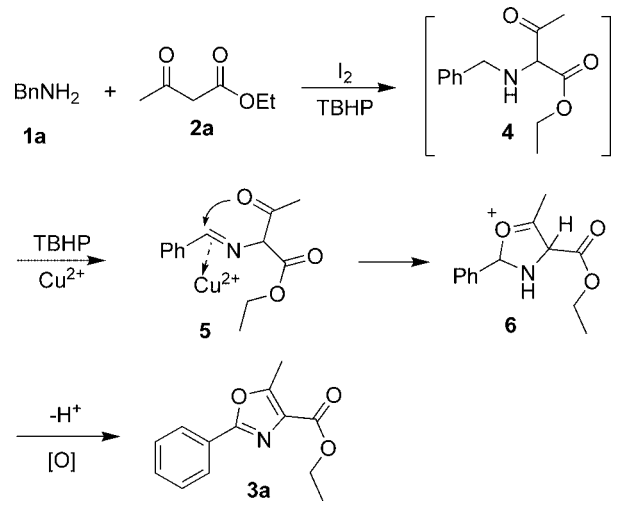
Scheme 3. Reaction of Benzylamine with Ethyl 2-Iodo-3-oxobutanoate



results and the previous reports,[13,16] we proposed a tentative mechanism, as shown in Scheme 4. First, **4** is formed from **1a** and **2a** in the presence of iodine. The oxidation of **4** and coordination of copper ions provides **5**, which undergoes an intramolecular cyclization via an oxygen atom attacking to double bonds and gives the intermediate **6** in a tandem process. Further oxidation of **6** affords the product **3a**.

In summary, we developed a facile and efficient oxidative synthesis of polysubstituted oxazoles from readily available starting materials. This transformation from benzylamine and

Scheme 4. Possible Mechanism for the Copper-Catalyzed Formation of Oxazoles



β-diketone derivatives into oxazoles was achieved involving a tandem oxidative cyclization. In contrast to the traditional synthetic methods for oxazoles, the reaction condition was much milder, and the reaction substrates were extended. Therefore, this method is an attractive alternative to synthesize oxazoles. The investigation of the reaction mechanism is in process in our laboratory.

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Supporting Information Available: Typical procedure for the reaction and characterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Crystallographic data of compound **3h**: $C_{22}H_{21}NO_3$, MW = 347.40, monoclinic, space group $P2_1/n$; a = 6.715, b = 17.086, c = 16.786 Å, α = 90.000°, β = 95.5°, μ = 90.000°, V = 1917.1 Å^3, Z = 4, D_c = 1.204 g/cm^3, F(000) = 736, μ = 0.080 mm^{-1}, crystal dimensions 0.30 × 0.24 × 0.20 mm was used for measurement on a CrysAlis RED, Oxford Diffraction Ltd. diffractometer with a graphite monochromater. $I > 2\sigma(I)$. Final indices: R1 = 0.0384, wR2 = 0.0595. The crystal structure of compound **3h** was solved by direct method SHLXS-97 (Sheldrick, 1990) and expanded using difference Fourier technique, refined by the program SHLXL-97 (Sheldrick, 1997) and the full-matrix least-squares calculations. CCDC 756060.

(16) Kumler, W. D. *J. Am. Chem. Soc.* **1938**, *60*, 855.