Pergamon

Tetrahedron 55 (1999) 13735–13740

TETRAHEDRON

Cycloaddition of Homophthalic Anhydrides with Aldehydes and Ketones: a Route to 3,4-dihydroisocoumarin-4-carboxylic Acid Derivatives

Niefang Yu[a], Rébecca Poulain[b], André Tartar[a] and Jean-Claude Gesquiere[a]*

[a] Faculté de Pharmacie, Institut Pasteur and UMR CNRS, 3 rue du Pr. Laguesse, 59006 Lille, France

[b] CEREP, 1 rue Calmette 59021 Lille, France

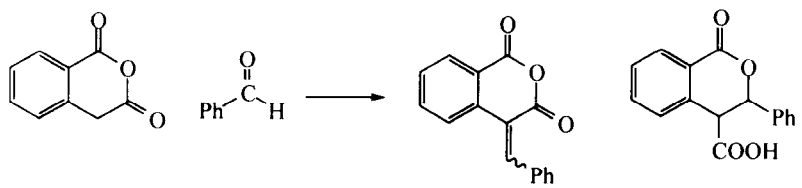
Received 26 November 1998; accepted 24 September 1999

Abstract: Homophthalic anhydride reacts with benzaldehyde, in the presence of boron trifluoride - diethyl ether complex to give the cycloadduct 3-phenyl-3,4-dihydroisocoumarin-4-carboxylic acid in good to excellent yield. Under these conditions, we did not observe the formation of Perkin-type products. The reaction can be extended to a wide variety of aldehydes and to some ketones in synthetically useful yields. Amides can be obtained in good yields after activation of the carboxylic function with DCC at O°C.
© 1999 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Cycloaddition of homophthalic anhydride with methylene double bonds has been recognised as an important tool for the preparation of heterocycles with various biological activities.[1-7] Moreover, these reactions give rise to compounds having a carboxylic function, which can be used to anchor additional building blocks, increasing the chemical diversity.

Among these, the reaction with carbon-nitrogen double bonds has been thoroughly explored and much work has also been dedicated to cycloaddition of carbon-carbon double bonds.[6-7] By contrary, the cycloaddition of homophthalic anhydride with carbon-oxygen double bonds from aldehydes and ketones has been less documented.[8-10] The previously described reactions had been performed in basic media, where carboxylic anhydrides are expected to react with carbonyl compounds according to the Perkin reaction, leading to α, β unsaturated carboxylic acids. A survey of the literature revealed that the reaction of homophthalic anhydride **1** with aldehydes in the presence of pyridine or sodium carbonate,[9] was reported to give the C-4 methylene condensed products **2**, as well as the desired cycloaddition products **3** (Scheme 1).



1 **2** **3**

A : Na_2CO_3,	r.t.	43%	35%
B : NaH,	O° C	-	83%
C : NaH,	20-50°C	82%	5%

Scheme 1

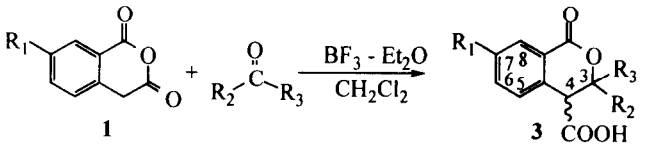
E-mail : jcgesqui@phare.univ-lille2.fr

Fax: +33 3 20 96 40 22

0040-4020/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(99)00840-6

When catalysed at low temperature by strong bases, e.g. sodium hydride (NaH) or lithium diisopropylamide (LDA),[10] this reaction yielded **3** as the main product, but when the reaction was performed at room temperature, the strong base-induced reaction gave mainly the product **2**.

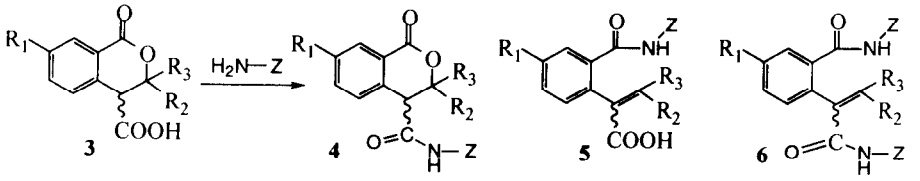
In a precedent study of the cycloaddition reaction of homophthalic anhydride with carbon-nitrogen double bonds, we have demonstrated that the $BF_3 \cdot Et_2O$ complex could induce the cycloaddition of imines, even in cases where they did not react according to other conditions.[11] As part of our investigation of the reactions of homophthalic anhydride with various double bonds, we now report that under the presence of $BF_3 \cdot Et_2O$, the cycloaddition reaction of **1** with aldehydes occurs with good to excellent yields to giving **3** under mild conditions. The reaction has been extended to some aliphatic ketones which afford products in lower yields (Scheme 2).



Scheme 2

This reaction gives access to three centers of chemical diversity around the heterocycle, which can be further increased due to the presence of the carboxylic function, leading to derivatives such as amides or esters.

However, these compounds have two reactive functional groups: the lactone, that is a part of the heterocyclic ring, and the carboxylic function that needs to be activated, so that 3 different products could be expected (Scheme 3).



Scheme 3

We have demonstrated that the reactivity of **3** towards amines depends on the reagents used to activate the carboxylic group and that dicyclohexylcarbodiimide (DCC) at 0°C allows the selective formation of the monoamides 4.

RESULTS AND DISCUSSION

Synthesis of isocoumarin-4-carboxylic acids

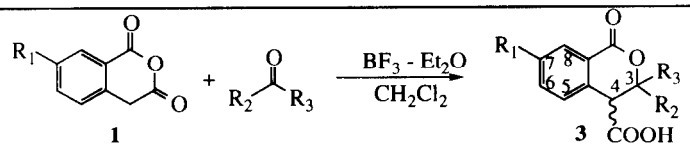
We first used cyclization conditions similar to those used for the reaction with imines ($BF_3 \cdot Et_2O$ - MeCN).[11] When the reactions were performed in acetonitrile, the expected products were obtained. However, the presence of minor by-products made their isolation difficult. Modifications of either reagents ratios or temperature from 0 °C to reflux were unsuccessful in avoiding their formation. By contrary, modifying the solvent of the reaction led to satisfactory results. According to our optimised method, the reactions of homophthalic anhydride with aldehydes were carried out by stirring the reactants in dichloromethane at 25-35°C for 5-14 hours. Under these conditions, we did not detect the formation of any Perkin product. All the isolated cycloadducts gave satisfactory spectroscopic data (IR, ^{1}H NMR and MS).

In all cases two diastereomeric cycloadducts were formed as shown by HPLC, and ^{1}H NMR analysis of the crude reaction mixtures and of the purified products. Although in few cases *cis* and *trans* products were

isolated, they were generally characterized by ^{1}H NMR analysis of the mixture. The ^{1}H-NMR spectrum of *cis*-diastereoisomers showed two doublets (J >5 Hz) closed to δ = 6.5 ppm and 5 ppm, respectively for the H_4 and H_3 hydrogens, while the *trans*-diastereoisomer gave two doublets closed to δ = 6.0 ppm and 5 ppm, with a coupling constant $J_{3,4}$<4 Hz.

This reaction has also been extended to ketones. With dialiphatic ketones, the reactions proceed smoothly leading to the correspondent cycloadducts. By contrary, in our hands, benzophenone, acetophenone and aromatic ketones did not react or gave very poor yield of complex mixtures that cannot be used for synthetic purpose. Table 1 summarises the reactions of homophthalic anhydrides with aldehydes and ketones.

Table 1: Reaction of Homophthalic Anhydride with Carbonyl Compounds



1 3

	R_1	R_2	R_3	Reaction Time	Yield* %		R_1	R_2	R_3	Reaction Time	Yield* %
a	H	C_6H_5	H	5 h	81	f	H	C_6H_5	CH_3	24 h	0
b	H	2,4-$Cl_2C_6H_3$	H	7 h	71	g	NO_2	C_6H_5	H	14 h	90
c	H	CH_3	CH_3	14 h	50	h	NO_2	3-$NO_2C_6H_4$	H	14 h	65
d	H	CH_2-CH_3	CH_3	14 h	22	i	NO_2	CH_3	CH_3	14 h	50
e	H	C_6H_5	C_6H_5	24 h	0	k	NO_2	CH_2-CH_3	CH_3	-	nd

Yields of isolated products, without optimisation

Synthesis of amides

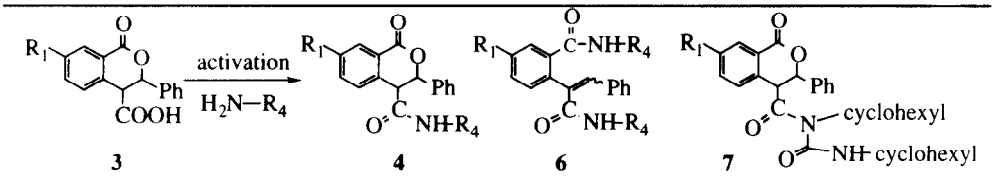
In order to increase the chemical diversity, the dihydroisocoumarine-4-carboxylic acids **3** were further reacted with N-nucleophiles.

We have observed that their reactivity depends on the nature of the activating agent (Table 2). In the absence of activating agent, the lactone ring did not react with amines, and the reaction mixture remained unchanged. Use of dicyclohexylcarbodiimide (DCC) as an activating agent, at 0°C, led to the formation of **4** in excellent yields.

Using the more reactive 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) or DCC at higher temperature led to a mixture of two products **4** and **6**. Interestingly, when **4** was treated with amines, in the presence of various activating agents including DCC, HBTU, N,N'-carbonyldiimidazole (CDI), etc., no reaction occurred even after refluxing in tetrahydrofurane. This indicates that **4** is not an intermediate in the formation of the double substituted **6**.

Reaction of the amines with the more reactive nitro compound **3g**, activated with DCC, led to an unusually fast rearrangement of the intermediate O-acylisourea to the unreactive N-acylurea which was in all cases the only product to be formed.

Table 2: Reactivity of 3,4-Dihydroisocoumarin-4-carboxylic Acids with Amines.



3 4 6 7

3	R_4	activation	solvent	4*	6*	7*
3a	Ph -CH(COOMe)-	none	DCM		no reaction	
3a	Ph -CH(COOMe)-	CDI	DCM	50%	50%	0%
3a	C_6H_5-CH_2-	none	DCM		no reaction	
3a	C_6H_5-CH_2-	HBTU:DIPEA	DMF	40%	60%	0%
3a	C_6H_5-CH_2-	DCC	DCM	> 95%	< 5%	0%
3a	Ph -CH(COOMe)-	DCC	DCM	> 95%	< 5%	0%
3g	C_6H_5-CH_2-	DCC	DCM	0%	0%	100%
3g	use of $HN(C_4H_9)_2$	DCC	DCM	0%	0%	100%

* Estimated conversion from HPLC of the new products related to **4** + **6** + **7** in the reaction mixture

CONCLUSION

We have presented a new procedure for the synthesis of isocoumarin-4-carboxylic acid derivatives by a cycloaddition reaction catalyzed by BF_3• Et_2O complex, of homophthalic anhydrides with aldehydes. Our method is easy to handle and applicable to robotic parallel synthesis. Due to its mildness and the acidic media, this procedure should be specially useful when basic catalysts must be avoided. This procedure can be extended to a wide variety of aldehydes and to some ketones. Moreover, we have shown that dihydroisocoumarin-4-carboxylic acids **3** when activated at 0°C by DCC only react with amines by their free carboxylic function, leading to carboxamides 4.

Acknowledgements. The authors thank CEREP France for their financial support and especially for the research grant of Niefang Yu, G. Montagne for NMR spectra, C. Landry for LC-MS and Guy Ricart for MALDI TOF mass analysis.

EXPERIMENTAL

Melting points were measured on a BÜCHI SMP 20 melting point apparatus, and are uncorrected. The infrared spectra were carried out on PERKIN 6 ELMER 297 in the Faculty of Pharmacy of Lille, and expressed in cm^{-1}. ^{1}H-NMR spectra were recorded in DMSO-d6 on a BRUKER 300 MHz in the Laboratoire d'Applications RMN de l'Université de Lille 2 and in the Pasteur Institute of Lille, France and chemical shifts are determined relative to solvent and converted to ppm. LC/MS were carried out in Cerep, Lille, on a HP

1100 HPLC and APCI Micromass. MALDI TOF spectra were recorded in the Laboratoire de Spectrométrie de Masse de l'Université de Lille 1 on a Finnigan Mat Vision 2000 (Bremmenn), without matrix, UV (N_2) 337 nm.

General Procedure for the preparation of 3: A round-bottom flask equipped with a magnetic stirring bar was charged with equimolar amounts of cycloanhydrides and aldehydes or ketones (25 mmoles) in dichloromethane and added with $BF_3 \cdot Et_2O$ (175 mmoles). The mixture was stirred at room temperature or 35°C for several hours and monitored by HPLC. The products were obtained either by filtration or by removing the solvent under reduced pressure and the residue purified by precipitation or crystallisation.

3-Phenyl-3,4-dihydroisocoumarin-4-carboxylic acid (3a): *cis*-diastereoisomer was obtained by filtration, purity : 100% by HPLC. Isolated yield: 43%. mp: 180.2-181.6°C. IR : 3250, 1735 (COOH) . ^{1}H-NMR: δ = 4.66 (1H, d, H_4, J = 6.6 Hz), 6.04 (1H, d, H_3, J = 6.6 Hz), 7.30-7.55 (7H, m), 7.72 (1H, dt, J = 1.2 and 7.8 Hz), 7.99 (1H, dd, J = 1.2 Hz and 7.8 Hz), 13.00 (1H, s, -COO*H*). MS (LCMS) m/z: 251 $(M\text{-}OH)^+$, 292 $(M+H+Na)^+$. *Trans*-diastereoisomer: after isolation of the *cis*-isomer, the solvent was removed under reduced pressure and the oily residue was triturated in diethyl ether until precipitation. Purity by HPLC: 100%. Yield: 38%. mp: 189-190.3°C. IR : 3250, 1735 (COOH) . ^{1}H-NMR: δ = 4.32 (1H, d, H_4, J = 3.5 Hz), 5.99 (1H, d, H_3, J = 3.5 Hz), 7.36-7.67 (7H, m), 7.72 (1H, dt, J = 1.1 and 7.2 Hz), 8.07 (1H, dd, J = 1.1 and 7.2 Hz), 12.71(1H, s, -COO*H*). MS (LCMS) m/z: 223 $(M - CO_2)^+$, 251$(M - OH)^+$, 292 $(M+H+Na)^+$. Anal. Calcd for $C_{16}H_{12}O_4$: C, 71,64; H, 4,51. Found: C, 71,32; H, 4,54.

3-(2',4'-Dichlorophenyl)-3,4-dihydroisocoumarin-4-carboxylic acid (3b): Precipitated as the *trans* isomer, in a solution of diethyl ether. Yield: 71%. IR: 3215, 1745 (COOH). ^{1}H-NMR: δ = 4.34 (1H, d, H_4, J = 3.4 Hz), 6.22 (1H, d, H_3, J = 3.4 Hz), 7.58-7.76 (5H, m), 7.78 (1H, d, J = 1.8), 8.06 (1H, dd, J = 1.2 and 8.3 Hz), 12.98 (1H, s, -COO*H*). MS (LCMS) m/z: 337$(M)^+$. Anal. Calcd for $C_{16}H_{10}Cl_2O_4$: C, 57,00; H, 2,99. Found: C, 56,46; H, 3,02.

3,3-Dimethyl-3,4-dihydroisocoumarin-4-carboxylic acid (3c): Precipitated in a solution of diethyl ether / ligroin (1 :1). Yield: 50%. IR: 3150, 1730 (COOH). ^{1}H-NMR: δ = 1.28 (3H, s, -CH_3), 1.52 (3H, s, -CH_3), 3.98 (1H, s, H_4), 7.41 (1H, dd, H_5, J = 1.3 and 7.7 Hz), 7.52 (1H, dt, H_6, J = 1.1 and 7.6 Hz), 7.67 (1H, dt, H_7, J = 1.3 and 7.6 Hz), 7.97 (1H, dd, H_8, J = 1.1 and 7.6 Hz), 12.87 (1H, s, -COO*H*). MS (LCMS) m/z: 234 $(M)^+$. Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49; O, 29.06. Found: C, 65.46; H, 5.39; O, 29.15.

3-Ethyl-3-methyl-3,4-dihydroisocoumarin-4-carboxylic acid (3d): Precipitated as a mixture of *cis*- and *trans*-diastereoisomers, which were not isolated, in methanol at -15°C for 1.5 days. Yield: 22%. ^{1}H-NMR, ROESY *trans*-diastereoisomer; δ =: 0.83 (3H, t, J = 7.4 Hz, CH_2-CH_3), 1.45 (3H, s, CH_3), 1.55 and 1,60 (2x 1H, 2 x m, CH_2- CH_3), 3.99 (1H, s, H_4). *cis*-diastereoisomer; δ = 1.04 (3H, t, J = 7.5 Hz, CH_2-CH_3), 1.20 (3H, s, CH_3), 1.80 (2H, q, CH_2- CH_3), 4.00 (1H, s, H_4). both-diastereoisomer; δ = 7.44, 7.52, 7.67 and 7.97 (4 x 1H, Ar -H), 12.80 (1H, s, -COO*H*). MS (MALDI TOF) m/z: 235 $(M+H)^+$, 257 $(M+Na)^+$, 273 $(M+K)^+$. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66,66; H, 6,02. Found: C, 66,54; H, 6,10.

7-Nitro-3-phenyl-3,4-dihydroisocoumarin-4-carboxylic acid (3g): Precipitated as the *trans*-product (Purity by HPLC: 100%). Yield: 90%. m. p.: 207-208°C. ^{1}H-NMR, δ = 4.55 (1H, d, J = 3.3 Hz, H_4), 6.05 (1H, d, J = 3.3 Hz, H_3), 7.30-7.51 (5H, m, Ar-H), 7.81 (1H, d, J = 8.5 Hz, H_5), 8.49 (1H, dd, J = 2.4 et 8.5 Hz, H_6), 8.67 (1H, d, J = 2.4 Hz, H_8), 13.00 (1H, s, -COOH). MS (MALDI TOF) m/z: 314 $(M+H)^+$, 336 $(M+Na)^+$. Anal. Calcd for $C_{16}H_{11}NO_6$: C, 61,35; H, 3,54; N, 4,47. Found: C, 61,61; H, 3,51; N, 4,58.

7-Nitro-3-(3-nitrophenyl)-3,4-dihydroisocoumarin-4-carboxylic acid (3h): Precipitated as the *trans*-product (Purity by HPLC : 100%). Yield: 65%. ^{1}H-NMR, δ = 4.74 (1H, d, J = 3.3 Hz, H_4), 6.24 (1H, d, J = 3.3 Hz, H_3), 7.76 (1H, t, J = 7.9 Hz, $O_2NC_6H_4$-), 7.84 (1H, d, J = 8.5 Hz, H_5), 7.99 - 8.39 (3H, m, $O_2NC_6H_4$-), 8.52 (1H, dd, J = 2.6 et 8.5 Hz, H_6), 8.68 (1H, d, J = 2.6 Hz, H_8), 13.19 (1H, s, -COOH). MS (MALDI TOF) m/z: 353 $(M+K-CO_2)^+$, 381 $(M+Na)^+$, 397 $(M+K)^+$. Calcd for $C_{16}H_{10}N_2O_8$: C, 53,64; H, 2,81; N, 7,82. Found: C, 53,79; H, 2,66; N, 7,79.

3,3-Dimethyl-7-nitro-3,4-dihydroisocoumarin-4-carboxylic acid (3i): Precipitated. Purity by HPLC: 100%. Yield: 50%. m. p.: 198-201°C. ^{1}H-NMR, δ = 1.26 (3H, s, CH_3), 1.51 (3H, s, CH_3), 4.21 (1H, s, H_4-), 7.70 (1H, d, J = 8.4 Hz, H_5), 8.46 (1*H*, dd, J = 2.2 and 8.4 Hz, H_6), 8.58 (1H, d, J = 2.2 Hz, H_8), 13.25 (1H, s, -COO*H*). MS (MALDI TOF) m/z: 288 $(M+Na)^+$, 304 $(M+K)^+$. Anal. Calcd for $C_{12}H_{11}NO_6$: C, 54.34; H, 4.18; N, 5.28; O, 36.19. Found: C, 54.28; H, 4.08; N, 5.47; O, 36.17.

General Procedure for the reaction with amines: To a solution of *cis*-3-phenyl-isocoumarine-4-carboxylic acid in dichloromethane was added 1,2 eq. of activating reagent, mixed for 10 min. and then 1.5 eq. of amine was added and stirred for 12 hours. After addition of water, the products were extracted with DCM.

N-Benzyl-3-phenyl-3,4-dihydroisocoumarin-4-carboxamide (4a): 3a (trans-diastereoisomer, 1eq) and DCC (1,05 eq.) were mixed at 0°C in DCM and then added benzylamine (1,5 eq.). The mixture was stirred at 0°C for 2 hours and then filtered off DCU. The filtrate was evaporated and the product was crystallized from THF - ether (1:1) as white needles. (Purity by HPLC: 100%). Yield: 37%. ^{1}H-NMR, δ = 3.88 and 4.20 (2 x 1H, 2 x dd, J = 4.4 and 15.2 Hz, N-CH_2-Ph), 4.28 (1H, d, J = 3.4 Hz, H_4), 5.98 (1H, d, J = 3.4 Hz, H_3), 6.72 - 8.06 (13H, m, Ar-*H*), 8.49 (1H, broad s, N*H*). MS (MALDI TOF) m/z: 380 $(M+Na)^+$, 396 $(M+K)^+$. Calcd for $C_{23}H_{19}NO_3$: C, 77,29; H, 5,36; N, 3,92. Found: C, 77,25; H, 5,25; N, 3,96.

REFERENCES

1. For review see: Shamma, M.: The Isoquinoline. In *Alkaloids, Chemistry and Pharmacology* ; Academic Press: New York 1972, and Moniot L.: Isoquinoline Alkaloids Research 1972-1977; Plenum Press : New York 1977.
2. Haimova, M. A.; Mollov, N. M.; Ivanova, S. C.; Dimitrova, A. I.; Ognyanov, V. I. *Tetrahedron*, **1977**, *33*, 331 - 334.
3. Cushman, M.; Chen, J. *J. Org. Chem.*, **1987**, *52*, 1517 - 1521 and references cited therein.
4. Fodor, L.; Szabo, R. ; Bernath, G.; Sohar, P.; Maclean, D. B.; Smith, R. W.; Ninommiya, I.; Naito, T. *J. Heterocyclic Chem.*, **1989**, *26*, 333-337.
5. Georgieva, A.; Stanoeva, E.; Spassov, S.; Haimova, M.; De Kimpe, N.; Boelens, M.; Keppens, M.; Kemme, A.; Mishnev, A. *Tetrahedron*, **1995**, *51*, 6099 - 6114 and references cited therein.
6. Govindachari, T. R.; Chinnasamy, P.; Rajeswari, S.; Chandrasekaran, S.; Pramila, M. S.; Natarajan, S.; Nagarajan, K.; Pai, B. R. *Heterocycles* **1984**, *22*, 585 (Review).
7. For review, see : (a) Kita, Y.; Okunaka, R.; Honda, T.; Shindo, M.; Taniguchi, M.; Kondo M.; Sasho, M. *J. Org. Chem.*, **1991**, *56*, 119-125. (b) Stanoeva, E.; Haimova, M. *Khim. Geterotsikl. Soedin.*, **1984**, 1587 (Review). (c) Tamura, Y.; Wada, A.; Sasho, M.; Fukunaga, K.; Maeda, H.; Kita, Y. *J. Org. Chem.*, **1982**, *47*, 4376-4378.
8. Jones, J. B.; Pinder, A. R.: *J. Chem. Soc.* **1958**, 2612, and Bun Hoi, *Compt. Rend.*, **1940**, *211*, 643
9. Nozawa, K.; Yamada, M.; Tsuda, Y.; Kawai K.; Nakajima, S. *Chem. Pharm. Bull.*, **1981**, 29, 3486 - 3493.
10. Okunaka, R.; Honda, T.; Kondo, M.; Tamura, Y. Kita Y. *Chem. Pharm. Bull.*, **1991**, *39*, 1298-1301.
11. Yu, N. Y.; Bourel, L.; Deprez, B.; Gesquiere J. C. *Tetrahedron Lett.*, **1998**, *39*, 829 - 832.