

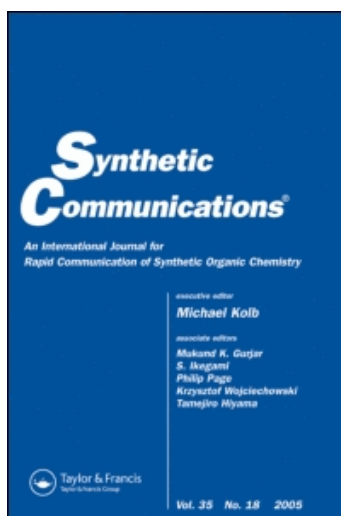
This article was downloaded by: [Aston University]

On: 21 February 2009

Access details: Access Details: [subscription number 908669322]

Publisher Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title-content=t713597304>

Mild and Efficient Synthesis of Carboxylic Acid Anhydrides from Carboxylic Acids and Triazine Coupling Reagents

Zbigniew J. Kamiński^a; Beata Kolesińska^a; Marcinkowska Magorzata^a

^a Institute of Organic Chemistry, Technical University of Łódź, Łódź, Poland

Online Publication Date: 02 January 2005

To cite this Article Kamiński, Zbigniew J., Kolesińska, Beata and Magorzata, Marcinkowska(2005)'Mild and Efficient Synthesis of Carboxylic Acid Anhydrides from Carboxylic Acids and Triazine Coupling Reagents', Synthetic Communications, 34:18, 3349 — 3358

To link to this Article: DOI: 10.1081/SCC-200030581

URL: <http://dx.doi.org/10.1081/SCC-200030581>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Mild and Efficient Synthesis of Carboxylic Acid Anhydrides from Carboxylic Acids and Triazine Coupling Reagents

Zbigniew J. Kamiński,* Beata Kolesińska,
and Marcinkowska Małgorzata

Institute of Organic Chemistry, Technical University of Łódź,
Łódź, Poland

ABSTRACT

Anhydrides of carboxylic acids were obtained in 53%–95% yield by treatment of appropriate carboxylic acids with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) or 2,4-dichloro-6-methoxy-1,3,5-triazine (DCMT) in the presence of *N*-methylmorpholine. It has been proved that synthesis proceeds via triazine active esters **3a,b**, which are able to acylate carboxylate anion but not less nucleophilic carboxylic acid.

Key Words: Carboxylic acids; Carboxylic acid anhydrides; Condensation; Naproxene; 2-Chloro-4,6-dimethoxy-1,3,5-triazine; Triazine “superactive ester.”

*Correspondence: Zbigniew J. Kamiński, Institute of Organic Chemistry, Technical University of Łódź, (Lodz), Żeromskiego 116, 90-924, Łódź, Poland; E-mail: kaminsz@mail.p.lodz.pl.

INTRODUCTION

Although anhydrides of carboxylic acids are less proficient (productive) acylating species than other derivatives of carboxylic acids, such as acyl halides or active esters, the unique properties of the former have been found superior in the syntheses of heterocycles,^[1] in reactions catalyzed by transition metals,^[2] as substrates for chemical or chemoenzymatic dissimetrization,^[3] and others.^[4] High and diversified reactivity of anhydrides is an important factor obstructing their stability but constraining the search for the new expedient method of their synthesis.

Herein we present a new synthetic approach, which is based on application of inexpensive triazine coupling reagents for dehydration of carboxylic acids **2a–j** directly to appropriate anhydrides **4a–j** under very mild reaction conditions.

RESULTS AND DISCUSSIONS

Carboxylic acid anhydrides **4a–j** were obtained in the one-pot procedure involving two steps (Fig. 1). In the first one, carboxylic acid **2a–j** was activated by treatment with triazine coupling reagent **1a,b** in the presence of *N*-methylmorpholine affording appropriate acyloxy-1,3,5-triazines **3a,b**, which, in the second stage, acylated the excess carboxylic acid to appropriate anhydride. The participation of 2-acyloxy-1,3,5-triazines as reactive intermediates formed in the preliminary stage has been proved by the isolation of **3a,b** from the reacting mixture and comparison to the isolated material, with authentic samples obtained in accord with previously described procedures.^[5] Moreover, ester **3a** treated with appropriate carboxylate anion afforded anhydride **4a** with an efficiency comparable to those obtained in the standard procedure.

It was found that the acylation of carboxylic acid has not proceeded in acidic media (Fig. 1, route a) but obligatory required formation of appropriate carboxylate salt (Fig. 1, route b). Routine procedure included the application of additional equivalent of tertiary amine used in the first stage of reaction or any other tertiary amine.

Benzoic acids, substituted analogues of benzoic acid, and aliphatic long-chain carboxylic acids have been dehydrated by means of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1a**) and/or 2,4-dichloro-6-methoxy-1,3,5-triazine (**1b**). Both reagents **1a,b** have been useful in the process; however, the later, bifunctional reagent **1b**, was found more productive due to somewhat faster activation and faster acylation as well as commercial advantages caused by the presence of two reactive centers in the triazine molecule.

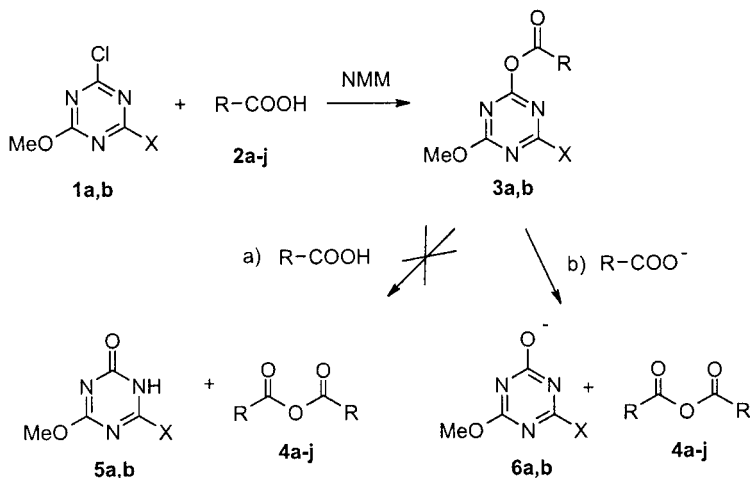


Figure 1. Synthesis of anhydrides via carboxylate anion (route b) and carboxylic acid (route a).

The broad range of solvents was found useful in the synthesis. The best yields were obtained under mild condition in experiments conducted at room temperature or below. However, the loss of yield under more vigorous conditions has been found to not be substantial, which allowed essential modification of the procedure in the case of less reactive or less soluble carboxylic acids.

Hydroxy-1,3,5-triazines **6a,b**, formed as the side product of the reaction, have been found sparingly soluble in most organic solvents but readily soluble in water. Such a feature allowed two different procedures of isolation of anhydrides **4a-j**. According to the general procedure, **6a,b** have been easily removed after completion of the synthesis by washing the crude preparation with aqueous solution of diluted acids and bases. In the case of highly reactive anhydrides, including those formed from benzoic acid substituted with EWG (Cl, Br, NO_2) groups furnished by aqueous work-up, there was, substantial loss of anhydrides **4a-j** due to hydrolytic degradation accompanying wash-out procedure. Therefore, use of ice-cold reagents and a rapid washing process are essential for obtaining reasonable yield of products. An interesting alternative procedure was found very useful in the synthesis of anhydrides readily soluble in hydrocarbon solvents. Due to very poor solubility of hydroxy-1,3,5-triazines **6a,b** in cyclohexane, it was possible to separate almost quantitatively (95% yield) the anhydride **4i** from side products by the simple extraction of the dry residue obtained after evaporation of reacting mixture.

CONCLUSIONS

The advantage of the present approach over other methods of synthesis of carboxylic acid anhydrides originates from direct use of readily accessible substrates and the two-stage procedure operating under very mild reaction conditions. The significant consequence of the presented studies is the potential of preparation of mixed anhydrides from two different carboxylic acids. Moreover, the unambiguously documented observation that triazine esters **3a,b** are uncreative when treated with carboxylic acids **2** is of crucial importance for understanding the mechanism of enantiomer differentiating activation proceeding in the presence of chiral triazine coupling reagents.^[14] Thus, according to the findings, an enantiomer of carboxylic acid activated by chiral triazine reagent forming triazine ester **3** remained unchanged during enantiodifferentiating process in the presence of excess discriminating enantiomer of carboxylic acid. Consequently, the procedure could be applied for the preparation of unsymmetrical anhydrides as well as *meso* anhydrides directly from racemic carboxylic acids.^[15]

EXPERIMENTAL

General Synthetic Procedure Involving CDMT

The vigorously stirred solution of carboxylic acid **2a–j** (20 mmol), CDMT (**1a**) (1.78 g; 10 mmol) in appropriate solvent (20 mL), was cooled to 0°C–5°C and then *N*-methylmorpholine (NMM) (1.10 mL, 10 mmol) was added in two portions. The stirring was continued for 30 min, an additional amount of NMM (1.10 mL, 10 mmole) was added, and the mixture allowed to warm up slowly to reach room temperature. The solvent was evaporated. The residue was dissolved in dichloromethane (50 mL), cooled to 0°C, and washed successively with an ice-cold solution of 0.5 *M* aq. NaHCO₃, water, 1 *M* aq. NaHSO₄; water, dried with MgSO₄; filtered; and the filtrate evaporated to dryness. The residue was dried in a vacuum dessiccator to constant weight affording appropriate anhydrides **4a–j**.

General Synthetic Procedure Involving DCMT

The vigorously stirred solution of carboxylic acid **2a–j** (20 mmol), DCMT (**1b**) (0.90 g; 5 mmol) in appropriate solvent (15 mL), was cooled to 0°C–5°C and then NMM (1.10 mL, 10 mmol) was added in two portions. The stirring was continued for 30 min, an additional amount of NMM (1.10 mL, 10 mmol) was

added, and the mixture allowed to warm up slowly to reach room temperature. The solvent was evaporated. The residue was dissolved in dichloromethane (50 mL), cooled to 0°C, and washed successively with ice cold solution of 0.5 M aq. NaHCO₃, water, 1 M aq. NaHSO₄, water; dried with MgSO₄; filtered; and the filtrate evaporated to dryness. The residue was dried in a vacuum dessicator to constant weight affording appropriate anhydrides **4a–j**.

Synthesis of Benzoic Acid Anhydride (**4a**)

A) Synthesis of 2-Benzoiloxy-4,6-Dimethoxy-1,3,5-Triazine (**3a**)

The vigorously stirred solution of benzoic acid (**2i**) (3.52 g, 20 mmol), CDMT (**1a**) (1.78 g, 10 mmol) in dichloromethane (15 mL), was cooled to 0°C–5°C and then NMM (1.10 mL, 10 mmol) was added drop-wise to maintain temperature below 5°C. The stirring was continued for 12 hr, the mixture was diluted with dichloromethane (15 mL), and washed successively with ice-cold water, 1 M aq. NaHSO₄, 0.5 M aq. NaHCO₃, water; dried with MgSO₄; filtered; and the filtrate evaporated to dryness. The residue was dried in a vacuum dessicator to constant weight. After crystallization from hexane, 2-benzoiloxy-4,6-dimethoxy-1,3,5-triazine (**3a**) (3.67 g) was obtained in 70% yield 1 mp 80°C–84°C, lit mp 83°C–85°C.^[5a]

¹H-NMR (CDCl₃) δ = 4.06 (s, 6H, O-CH₃); 7.27–7.76 (m, 3H, H_{ar}); 8.15–8.19 (m, 2H, H_{ar}). Analysis for C₁₂H₁₁N₃O₄ (261.08); calc: %C 55.17 %H 4.24 %N 16.08; found: %C 54.96 %H 4.19 %N 16.25.

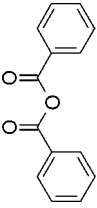
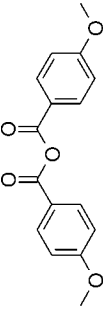
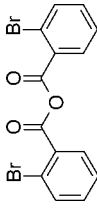
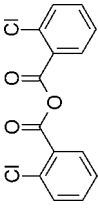
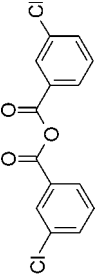
B) Synthesis of Benzoic Anhydride (**3a**)

The solution of 2-benzoiloxy-4,6-dimethoxy-1,3,5-triazine (2.61 g, 10 mmol) in dichloromethane (20 mL) was cooled to 0°C and the benzoic acid (1.22 g, 10 mmol) and triethylamine (1.39 mL, 10 mmol) were added. The mixture was allowed to warm-up and then stirred overnight at room temperature. The anhydride **3a** was isolated according to general procedure. The yield was 1.93 g (85%). Spectroscopic data, identical as products, are described in the Table 1.

Synthesis of Docosanoic Acid (Behenic Acid) Anhydride (**4i**)

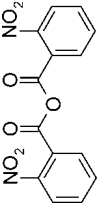


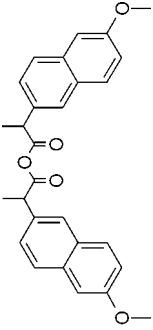
The vigorously stirred suspension of docosanoic acid **2i** (6.80 g, 20 mmol), CDMT (**1a**) (1.78 g, 10 mmol) in dichloromethane (40 mL), was cooled to 0°C–5°C and then NMM (1.10 mL, 10 mmol) was added in two

Table 1. Anhydrides **4a–j** prepared from carboxylic acid **2a–j**: reaction conditions, yield, and spectroscopic data.

| Carboxylic acid anhydride (4a–j) | Reagent 1a, b | Reaction time (hr) | Solvent | Yield (%) | mp (lit. mp) (°C) | IR (cm ^{−1}) | ¹ H-NMR (CDCl ₃), δ (ppm) |
|--|----------------------|--------------------|---------------------------------|-----------|--------------------------------|----------------------------------|--|
| 4a  | DCMT | 14 | CHCl ₃ | 84 | Oil (40–44) ^[6] | 3064 w, 1788 vs, 1212 vs, 700 vs | 7.26–7.68 (m, 6H); |
| | CDMT | 64 | THF | 81 | 39–41 | | 8.14–8.18 (m, 4H) |
| 4b  | DCMT | 24 | CH ₂ Cl ₂ | 83 | 97–99 (98–99) ^[7] | 3100 w, 2850 w; 1794 vs | 3.91 (s, 6H); |
| | CDMT | 24 | THF | 86 | 97–98 | | 6.98 (AB system, 4H, J = 8.5 Hz); 8.10 (AB system, 4H, J = 9 Hz) |
| 4c  | DCMT | 24 | CH ₂ Cl ₂ | 58 | 85–89 (76–77.5) ^[8] | 3000 w, 1788 vs, 1604 m, 1448 m | 7.99–8.03 (m, 4H); 7.73–7.77 (m, 4H) |
| | | | | | | | |
| 4d  | CDMT | 24 | CH ₂ Cl ₂ | 84 | 63–68 (78–79) ^[8] | 1798 vs, 1104 s | 1.09 (d, 4H, J = 2.25 Hz); 7.52 (d, 4H, J = 2.25 Hz) |
| | | | | | | | |
| 4f  | CDMT | 24 | CH ₂ Cl ₂ | 73 | 85–88 (93–94) ^[9] | 1798 vs, 1144 s | 8.00–8.20 (m, 4H) |
| | | | | | | | |

Synthesis of Carboxylic Acid Anhydrides

3355

| | | | | | | | | |
|-----------|---|------|----|---------------------------------|----|--------------------------------------|---------------------------------------|--|
| 4g |  | DCMT | 24 | CHCl ₃ | 53 | 129–132 (136–137) ^[10] | 3104 w, 1804 vs, 1092 s | 8.10 (dd, 4H, <i>J</i> = 9 Hz); 7.80–7.67 (m, 4H) |
| 4h |  | DCMT | 24 | CH ₂ Cl ₂ | 53 | 70–72 (70–72) ^[11] | 2912 s, 2880 s, 1804 vs, 1468 s | 0.95 (t, 6H, <i>J</i> = 12 Hz); 1.26 (s, 56H); 1.46 (m, 4H), 2.40 (t, 4H, <i>J</i> = 7.5 Hz) |
| | | CDMT | 24 | THF | 53 | 70–73 (70–72) | | |
| 4i |  | DCMT | 20 | CH ₂ Cl ₂ | 88 | 85–88 (77–77.7) ^[12] | 2920 s, 2872 s, 1804 vs, 1468 m | 0.88 (t, 6H, <i>J</i> = 7.5 Hz); 1.25 (s, 72H); 1.65 (m, 4H); 2.44 (t, 4H, <i>J</i> = 7.5 Hz) |
| | | CDMT | 24 | CH ₂ Cl ₂ | 95 | 82–84 | | |
| 4j |  | CDMT | | | 85 | 115–117 (103–105) ^[13] | 1794 | 1.49 (d, 6H, <i>J</i> = 7.5 Hz); 3.81 (q, 2H, <i>J</i> = 3.8 Hz); 3.91 (s, 6H); 7.01–7.48 (m, 12H) |

portions. The stirring was continued for 0.5 hr, then an additional amount of NMM (1.10 mL, 10 mmol) was added and the mixture allowed to warm up slowly to reach room temperature overnight. The solvent was evaporated. The residue was extracted with boiling cyclohexane (2×40 mL) and collected extracts were evaporated. After crystallized being from cyclohexane gave docosanoic acid (behenic acid) anhydride (**4i**) (6.28 g). Yield 95%; mp 80°C – 82°C ; lit mp 77.5° – 77.7°C .^[12]

ACKNOWLEDGMENT

This work was supported by the State Committee for Scientific Research (KBN) Grant 4-T09A 189 25.

REFERENCES

1. (a) Natekar, R.S.; Samant, S.D. Studies in the Friedel-Crafts reaction: part VI. Synthesis and intra- and intermolecular Friedel-Crafts reaction of 2-methyl-4-phenylpentanedioic anhydride. *Indian J. Chem. Sect. B.* **2002**, *41B*, 187–190; (b) Brzozowski, Z.; Saczewski, F. A new type of mixed anhydride and its applications to the synthesis of 7-substituted 8-chloro-5,5-dioximidazo[1,2-b][1,4,2]benzodithiazines with in vitro antitumor activity. *J. Med. Chem.* **2002**, *45*, 430–437; (c) Onal, Z.; Saripinar, E.; Ilhan, I.O. Reactions of 1-amino-5-benzoyl-4-phenyl-1H-pyrimidine-2-one with carboxylic anhydrides: experimental data and AM1 calculations. *J. Heterocycl. Chem.* **2001**, *38*, 397–402; (d) Miki, Y.; Nakamura, N.; Yamakawa, R.; Hachiken, H.; Matsushita, K. Reaction of 3-ethoxycarbonylindolizine-1,2-dicarboxylic anhydride: synthesis of 2-acylindolizines and quinones. *Heterocycles* **2000**, *53*, 2143–2150; (e) Kohara, T.; Tanaka, H.; Kimura, K.; Fujimoto, T.; Yamamoto, I.; Arita, M. Synthesis of a benzo[5,6]cyclohepta[1,2-b]thiophene and thieno[3,2-c]benzazepine derivatives. *Synthesis* **2002**, *3*, 355–360.
2. (a) Yamamoto, A.; Kakino, R.; Shimizu, I. Synthetic design of carbonyl-group-containing compounds based on C–O bond cleavage promoted by Pd complexes. *Helv. Chim. Acta* **2001**, *84*, 2996–3014 (for review); (b) Bercot, E.A.; Rovis, T. A mild and efficient catalytic alkylative monofunctionalization of cyclic anhydrides. *J. Am. Chem. Soc.* **2002**, *124*, 174–175; (c) Kakino, R.; Yasumi, S.; Shimizu, I.; Yamamoto, A. Synthesis of unsymmetrical ketones by palladium-catalyzed cross-coupling reaction of carboxylic anhydrides with organoboron compounds. *Bull.*

- Chem. Soc. Japan **2002**, 75, 137–148; (d) Frosch, W.; Back, S.; Lang, H. C–C-bond formation in reactions of [(h5-C5H4SiMe3)2Ti (CYCR1)2]CuR with acyl chlorides and anhydrides. *J. Organometall. Chem.* **2001**, 625, 140–147; (e) Song, R.; Kim, K.M.; Lee, S.S.; Sohn, Y.S. Electrophilic substitution of (diamine)tetrahydroxoplatinum(IV) with carboxylic anhydrides. Synthesis and characterization of (diamine)platinum(IV) complexes of mixed carboxylates. *Inorg. Chem.* **2000**, 39, 3567–3571; (f) Orita, A.; Tanahashi, Ch.; Kakuda, A.; Otera, J. Highly powerful and practical acylation of alcohols with acid anhydride catalyzed by Bi(OTf)₃. *J. Org. Chem.* **2001**, 66, 8926–8934; (g) Sabitha, G.; Srividya, R.; Yadav, J.S. Ring opening of cyclic anhydrides: synthesis of achiral half-esters using lewis acids. *Tetrahedron* **1999**, 55, 4015–4018; (h) Frost, Ch.G.; Wadsworth, K.J. Rhodium catalyzed addition of boronic acids to anhydrides: a new method for the synthesis of ketones. *Chem. Commun.* **2001**, 22, 2316–2317.
- Shintani, R.; Fu, G.C. Highly enantioselective desymmetrization of anhydrides by carbon nucleophiles: reaction of grignard reagents in the presence of (–)-sparteine. *Angew. Chem. Int. Ed.* **2002**, 114, 1099.
 - (a) Cesar, J.; Sollner, D.M. Trimethylsilyldiazomethane in the preparation of diazoketones via mixed anhydride and coupling reagent methods: a new approach to the Arndt-Eistert synthesis. *Tetrahedron Lett.* **2001**, 42, 7099–7102; (b) Stamatov, S.D.; Stawinski, J. A simple and efficient method for direct acylation of acetals with long alkyl-chain carboxylic acid anhydrides. *Tetrahedron* **2000**, 56, 9697–9703; (c) Uozumi, Y.; Yasoshima, K.; Miyachi, T.; Nagai, S. Enantioselective desymmetrization of meso-cyclic anhydrides catalyzed by hexahydro-1H-pyrrolo[1,2-c]imidazolones. *Tetrahedron Lett.* **2001**, 42, 411–414; (d) Clarke, P.A. Selective mono-acylation of meso- and C2-symmetric 1,3- and 1,4-diols. *Tetrahedron Lett.* **2002**, 43, 4761–4763; (e) Shiina, I.; Ibuka, R.; Kubota, M. A new condensation reaction for the synthesis of carboxylic esters from nearly equimolar amounts of carboxylic acids and alcohols using 2-methyl-6-nitrobenzoic anhydride. *Chem. Lett.* **2002** (3), 286–287.
 - (a) Kamiński, Z.J. A new reaction of 2-chloro-4,6-dimethoxy-(diaryl-oxy)-1,3,5-triazines with carboxylic acids leading to hitherto unknown 2-acyloxy-4,6-dimethoxy-(diaryl-oxy)-1,3,5-triazines. *J. Prakt. Chem.* **1990**, 332, 579–581; (b) Kamiński, Z.J. Synthesis of 2,4-diacyloxy-6-methoxy-1,3,5-triazines. *Pol. J. Chem.* **1991**, 65, 2077–2079.
 - Keshavamurthy, K.S.; Vankar, Y.D.; Dhar, D.N. Preparation of acid anhydrides, amides, and esters using chlorosulfonyl isocyanate as a dehydrating agent. *Synthesis* **1982**, 6, 506–508.

7. Stahlke, K.R.; Heime, H.G.; Hartmann, W. Zur photochemie aryl-substitueierte vinylcarbonate. *Liebigs Ann. Chem.* **1972**, *764*, 116–124.
8. Newmann, M.S.; Cella, J.A. Intramolecular aromatic and aliphatic Ullman reactions. *J. Org. Chem.* **1974**, *39*, 2084–2087.
9. Beckwith, A.L.J.; Cross, R.T.; Gream, G.E. The mechanism of lead tetraacetate decarboxylation. II. 2,3,3-trimethylbutanoic and adamantane-2-carboxylic acids. *Aust. J. Chem.* **1974**, *27*, 1693–1710.
10. Wang, J.-X.; Hu, Y.; Cui, W. Solid–liquid phase transfer and cobalt or palladium complex catalyzed synthesis of anhydrides from acyl chlorides. *Synth. Commun.* **1994**, *24*, 3261–3268.
11. Plusquellec, D.; Roulleau, F.; Lefeuvre, M.; Brown, E. A new synthesis of carboxylic and carbonic acid anhydrides using phase transfer reactions. *Tetrahedron* **1988**, *44*, 2471–2476.
12. Bleyberg, W.; Ulrich, H. Synthese hochmolekularer fettsauren und ihrer anhydride. *Chem. Ber.* **1931**, *64*, 2504–2513.
13. Bellucci, G.; Berti, G.; Bianchini, R.; Vecchiani, S. Enantioface differentiating additions of protected hexoses to prochiral ketenes: synthesis of optically active α -arylpropanoic acids. *Gazz. Chim. Ital.* **1988**, *118*, 451–456.
14. Kamiński, Z.J.; Kolesińska, B.; Kamińska, J.E.; Góra, J. Coupling reagents of the novel generation. Enantiodifferentiating coupling reagents prepared *in situ* From 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and chiral tertiary amines. *J. Org. Chem.* **2001**, *63*, 4248–4255.
15. Kamiński, Z.J.; Kolesinska, B. An application of chiral triazine condensing reagents for facile synthesis of *mezo*-anhydrides directly from racemic carboxylic acids (in preparation).

Received in the UK March 30, 2004