Replacement of Tetrachloromethane with Bromotrichloromethane in Appel-type reactions

Thies Thiemann,[a*] Mazen al-Sulaibi,[a] Yosef Al-Jasem,[b] Bassam Al Hindawi[a]

Department of Chemistry, [a]Faculty of Science, and [b]Faculty of Engineering, United Arab Emirates University, Al Ain, Abu Dhabi, United Arab Emirates. E-mail: thies@uaeu.ac.ae

Keywords: tetrachloromethane, bromotrichloromethane, Appel-type reaction, cinnamic anhydrides, amidation, esterification, benzamides

Abstract: A larger number of chemical transformations have been reported using CCl_4/PPh_3. In this contribution, the possibility of replacing CCl_4 with $BrCCl_3$, as a chemical of less environmental concern, has been studied. Especially esterification and amidation reactions of cinnamic acids have been investigated, where it has been found that under the conditions cinnamic anhydrides can also be prepared with ease. Also, the dehydration of benzamides to benzonitriles and the preparation of *N*-(phenylsulfonyl)-triphenylphosphoranylideneamide using CCl_4/PPh_3 have been carried out.

Introduction.

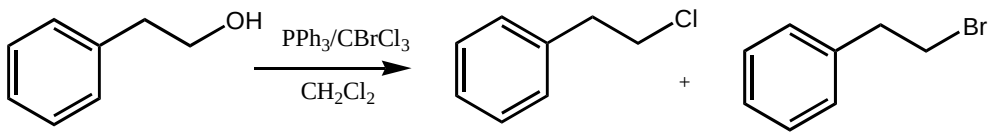
In the 1950s – 1970s, a larger number of reactions were studied that utilized the reagent combination of triphenylphosphine (PPh_3) and tetrachlorocarbon (CCl_4). The reactions range from the transformation of alkanols to chloroalkanes to the reaction of aldehyde functions to *gem.*-dichloromethylene groups. Also, PPh_3/CCl_4 has been used successfully to activate acids such as carboxylic acids and phosphoric acid derivatives and to react these under dehydrative conditions to form amides and phosphoric anhydrides. Especially in the bromination of alkanols and in the synthesis of *gem.*-dibromoolefins, CCl_4 has been exchanged for CBr_4. CBr_4 is more expensive than CCl_4 and thus does not lend itself readily as a replacement of CCl_4 in other reactions such as in activating acids for dehydrative coupling. The reactions as a whole have been reviewed extensively in 1975 by R. Appel, who has contributed significantly to the study of the reagent system CCl_4/PPh_3.[1] The halogenation of alkanols with CX_4/PPh_3 is called the Appel reaction. In the following, the authors have called transformations using the reaction system CX_4/PPh_3 Appel-type reactions, well-knowing that many of the reactions discussed below may differ mechanistically.

Today, the use of CCl_4 is looked at with great skepticism. CCl_4 is very volatile. In the time period 1980 – 1990, when CCl_4 was still used essentially without restriction, atmospheric concentrations of CCl_4 were found to be 0.5 – 1.0 g/m^3.[2,3] In the lower atmosphere, CCl_4 does not oxidize or photodegradate to an appreciable degree. As is the case for many perchlorinated chlorocarbons, CCl_4 can be carried to the stratosphere. The

average life-time of CCl_4 in the atmosphere is taken as between 45 – 50 years.[4] In the stratosphere, UV radiation leads to a homolytic fission of a C-Cl bond to create chloro radicals, which enter the well-known reaction cycle with ozone. Ozone has been listed as an ozone class 1 depletor with an ozone depletion of 1.08 (WMO 1991) to 1.1 (UNEP 1996)[5] vs. chlorofluorocarbon CFC-11.[2] Due to the provisions of the Montreal protocol of 1986 on substances that deplete the ozone layer, and its subsequent amendments, tetrachlorocarbon has been phased out in many areas. Nevertheless, recent observations have noted that the atmospheric CCl_4 concentration is still on the rise, most likely due to its long lifetime, but perhaps also due to continuing emissions.[6] This is all the more reason that CCl_4 is to be used no longer as a solvent for chemical reactions.

From this perspective, a certain interest would lie in exchanging one chloro atom in CCl_4 for a bromo atom, with the C-Br bond exhibiting a lower dissociation energy than the C-Cl bond, the photochemical induced homolytic cleavage then producing a bromo radical at a comparatively longer wavelength. While trichlorobromomethane ($BrCCl_3$) is also expected to have a long half-life (44 years)[7] in the atmosphere, it is not listed as an ozone depletor (class 1 or 2). It has been noted that were $BrCCl_3$ to reach the stratosphere, photolysis would occur but not at an environmentally important rate.[8]

Over the years, $BrCCl_3$ has been looked at in a number of Appel-type reactions, but in a desultory fashion. Initial experiments of Soulen et al. had shown that reaction of acyl cyanides with the combination $BrCCl_3/PPh_3$ leads to the corresponding 3,3-acrylonitriles at lower temperatures and with higher yields than with the reaction system CCl_4-PPh_3.[9] These results have been taken up recently by the group of M. Lautens,[10] who could show that benzaldehydes and acetophenones could be converted to the dichloromethylenated products with ease. They could also show that benzyl alcohols and cinnamyl alcohol can be chlorinated with $BrCCl_3/PPh_3$.[10] It is not self-evident that $BrCCl_3/PPh_3$ would transfer a bromo atom vs. a chloro-atom, selectively, and in our hands the reaction of alkanols such as 2-phenylethanol with $BrCCl_3/PPh_3$ in fact led to mixtures of brominated and chlorinated alkanes (Scheme 1). It may well be that in the case of the benzyl alcohols not only a higher selectivity of the substrate towards chlorination *vs*. bromination plays a role, but also the higher reactivity of benzyl bromides towards excess triphenylphosphine in the course of the reaction, as compared to benzyl chlorides.



1 **2a** **2b**

ratio: 4 : 6

Scheme 1. Halogenation of alkanols with $PPh_3/BrCCl_3$

In the following, the authors report on the use of the reaction system $BrCCl_3/PPh_3$ in the amidation of carboxylic acids **3**, in the preparation of anhydrides **6** from carboxylic acids **3** and in the esterification of carboxylic acids **3** with cholesterol (**7**), where cinnamic acids were used as acid component in all three transformations. Furthermore, the use of $BrCCl_3/PPh_3$ in the dehydration of benzcarboxamides **9** to benzonitriles **10** was studied as well as the preparation of *N*-(phenylsulfonyl)-triphenylphosphoranylideneamide (**12**) from benzenesulfonamide (**11**), the two latter reactions being known to proceed with CCl_4/PPh_3.[11,12]

Experimental

General. – Melting points were measured with a Stuart SMP10 melting point apparatus and are uncorrected. ^{1}H NMR (at 400 MHz) and ^{13}C NMR (at 100.5 MHz) spectra were taken on a Varian 400 MHz spectrometer. IR measurements were performed on a Thermo Nicolet FT-IR spectrometer, model Nexus 470. Column chromatography was carried out on silica gel S (0.2 – 0.5 mm and 0.063 – 0.1 mm, Riedel de Haen).

Triphenylphosphine (Sigma-Aldrich), phenylpropiolic acid (**3k**, Fluka), cholesterol (**7**, Fluka), benzenesulfonamide (**11**, Merck-Schuchardt), 2-hydroxybenzamide [salicylamide] (Fluka) and bromotrichloromethane (Fluka) were acquired commercially and used as obtained. 2-Methoxybenzamide (**9a**) and 2-ethoxybenzamide (**9b**) were synthesized analogous to a known procedure (i. KOH, DMSO; ii. MeI or EtI).[13] The cinnamic acids used were prepared according to the literature.[14] Triethylamine was freshly distilled over KOH. CH_2Cl_2 was distilled over P_4O_{10}.

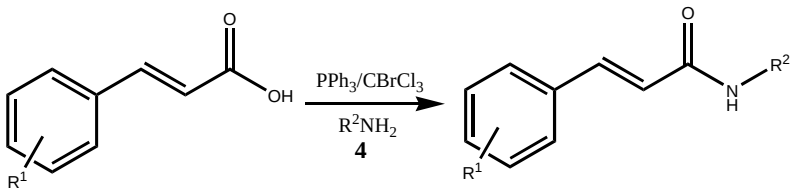
Typical procedure: To a solution of triphenylphosphine (1.3 g, 5.0 mmol) in CH_2Cl_2 (15 mL) is added bromotrichloromethane (2.0 g, 10.1 mmol), and the resulting solution is stirred for 20 min. at rt. Thereafter, 3-fluorocinnamic acid (**3c**, 595 mg, 3.58 mmol) is added to the honey-colored mixture. The solution is stirred for 30 min., then, benzylamine (**4a**, 760 mg, 7.1 mmol) is added, and the resulting reaction mixture is stirred for 24h. CH_2Cl_2 (40 mL) is added and the mixture is extracted with water (30 mL). The organic phase is washed with 15w% aq. NaOH (15 mL) and subsequently with half-conc. HCl (3 mL conc. HCl in 7 mL of H_2O). The organic phase is dried over $MgSO_4$. After concentration *in vacuo*, the organic residue is filtered over a column (M**t**BE/hexane) to give *N*-benzyl 3-fluorocinnamide (**5c**, 511 mg, 56%) as a colorless solid, mp. 112-113 ^{o}C; ν_{max} (KBr/cm^{-1}) 3291, 3063, 2922, 1652, 1616, 1582, 1543, 1247, 971, 697, 664; δ_H (400 MHz, $CDCl_3$) 4.57 (2H, d, ^3J = 5.6 Hz), 6.04 (1H, b, NH), 6.41 (1H, d, ^3J = 15.6 Hz), 7.17 (1H, bd, ^3J = 9.6 Hz), 7.24 – 7.37 (8H, m), 7.63 (1H, d, ^3J = 15.6 Hz); δ_C (100.5 MHz, $CDCl_3$) 43.9, 113.9 (d, $^2J_{CF}$ = 21.7 Hz), 116.6 (d, $^2J_{CF}$ = 20.9

Hz), 121.7, 123.9 (d, J_{CF} = 3.0 Hz), 127.7, 127.9 (2C), 128.8 (2C), 130.3 (d, ^3J = 8.2 Hz), 137.0 (d, J_{CF} = 7.5 Hz), 138.0, 140.2, 163.0 (d, $^1J_{CF}$ = 247 Hz), 165.3 (CO).

Cholester-3-yl 3,4-dimethoxycinnamate. – To a solution of triphenylphosphine (582 mg, 2.2 mmol) in CH_2Cl_2 (7.5 mL) is added bromotrichloromethane (900 mg, 4.5 mmol), and the resulting solution is stirred for 20 min. at rt. Thereafter, 3,4-dimethoxycinnamic acid (416 mg, 2.0 mmol) is added, and the solution is heated at 50 ^oC for 15 min. Cholesterol (386 mg, 1.0 mmol) is added, and after 20 min. Et_3N (200 mg, 2.0 mmol) is added dropwise with the help of a syringe. The reaction mixture is stirred at 45 ^oC for 12h. Then, it is cooled, poured into water (30 mL) and extracted with CH_2Cl_2 (3 X 15 mL). The organic phase is washed with 15w% aq. NaOH (15 mL) and subsequently with aq. HCl (1 mL conc. HCl in 7 mL of H_2O), dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. Column chromatography of the residue on silica gel (eluant M*t*BE/hexane/$CHCl_3$ 1:2:1) gives **8b** (276 mg, 48%) as a colorless solid[15] ; ν_{max} (KBr/cm^{-1}) 2941, 1705, 1634, 1594, 1462, 1256, 1157, 1026, 850, 812; δ_H (400 MHz, $CDCl_3$) 0.68 (3H, s, 3H, CH_3), 0.86 (3H, d, ^3J = 6.4 Hz, CH_3), 0.87 (3H, d, ^3J = 6.8 Hz, CH_3), 0.91 (3H, d, ^3J = 6.8 Hz, CH_3), 2.4 (2H, m), 3.91 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.76 (1H, m), 6.30 (1H, d, ^3J = 16.0 Hz), 6.86 (1H, d, ^3J = 8.4 Hz), 7.05 (1H, d, ^4J = 2.0 Hz), 7.10 (1H, dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz), 7.61 (1H, d, ^3J = 16.0 Hz); δ_C (100.5 MHz, $CDCl_3$) 11.9, 18.7, 19.3, 21.0, 22.6, 22.8, 23.8, 24.3, 27.9, 28.0, 28.2, 29.7, 31.9, 35.8, 36.2, 36.6, 37.0, 38.3, 39.5, 39.7, 42.3, 50.0, 55.8, 55.9, 56.1, 56.7, 73.9, 109.4, 110.9, 122.6, 122.7, 124.6, 127.5, 140.0, 144.6, 149.1, 151.0, 166.7.

Results and Discussion.

Due to our interest in the preparation of cinnamides with physiological activity[16] we looked into the possibility of synthesizing cinnamides directly from cinnamic acid and amine, while foregoing the use of the toxic pentafluorophenol, utilized previously.[16] Here, the idea of changing CCl_4 in the known reagent pair CCl_4/PPh_3 for the amidation of simple carboxylic acids for $BrCCl_3$ came easily. In fact, L. E. Barstow and V. J. Hruby[17] had already noted the possibility of such an exchange in the preparation of the simple dipeptide, ethyl *N*-benzyloxycarbonyl-*L*-phenylalanylglycinate. Indeed, a series of cinnamic acids could be reacted with a variety of amines in the presence of $BrCCl_3/PPh_3$ and in CH_2Cl_2 as solvent (Scheme 2). Of the cinnamic acid series surveyed, only 4-hydroxycinnamic acid did not react under the conditions (benzylamine) as the substrate is sparingly soluble in CH_2Cl_2. Also other acids such as palmitic acid (**3d**) could be subjected to the reaction with ease (Scheme 2), with the exception of oxalic acid and phenylpropiolic acid (**3k**), the latter of which led to addition products.



3a: R^1 = 3-Cl
3b: R^1 = 4-MeO
3c: R^1 = 3-F

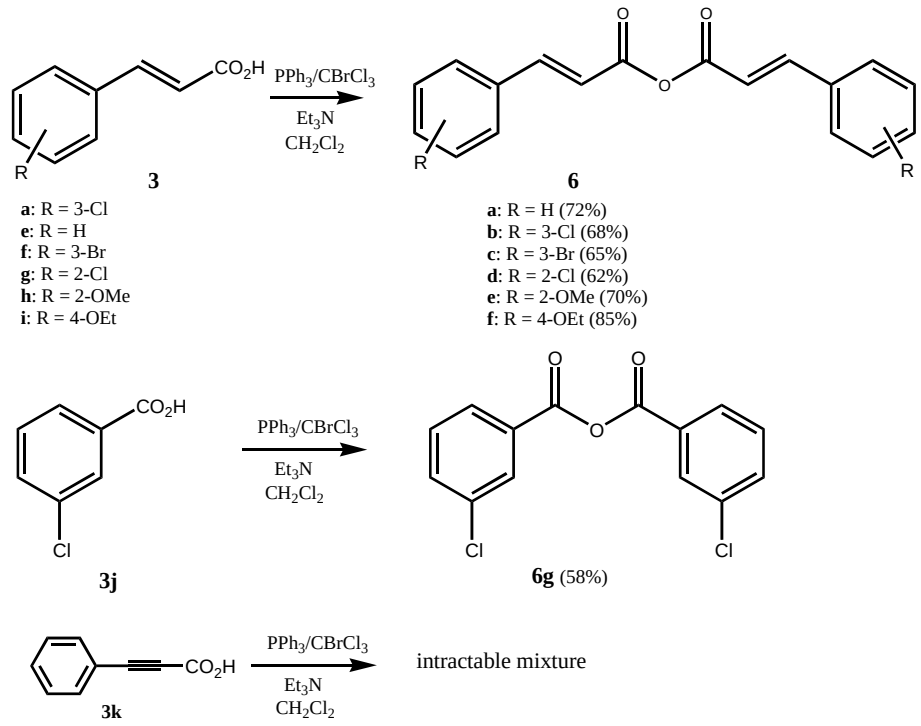
4a: R^2 = Bn
4b: R^2 = *n*-C_8H_{17}

5a: R^1 = 3-Cl; R^2 = Bn (78%)
5b: R^1 = 4-OMe; R^2 = Bn (81%)
5c: R^1 = 3-F; R^2 = Bn (56%)
5d: R^1 = 3-Cl; R^2 = *n*-C_8H_7 (60%)

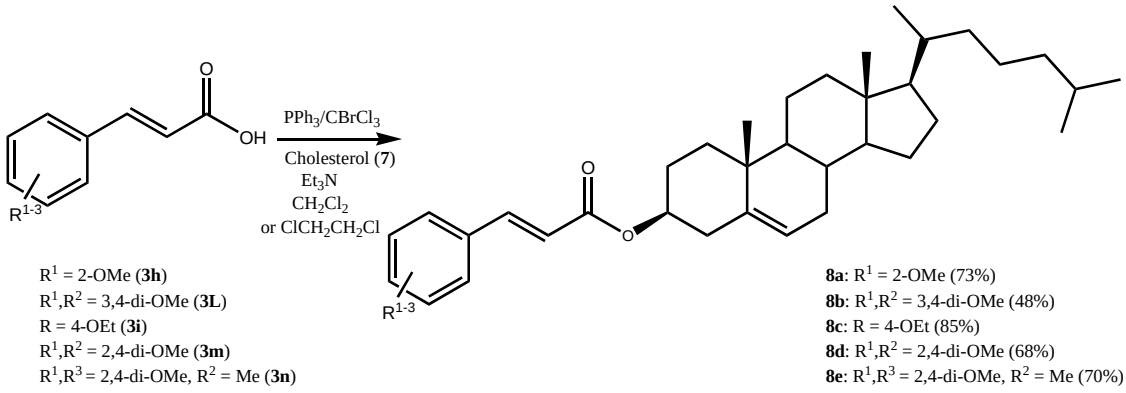
$CH_3(CH_2)_{14}CO_2H$ **3d** —($PPh_3/CBrCl_3$, $BnNH_2$ (**4a**))→ $CH_3(CH_2)_{14}CONCH_2Ph$ **5e** (68%)

Scheme 2. Amidation of cinnamic acids

When cinnamic acids **3** were reacted with $BrCCl_3/PPh_3$ in the presence of triethylamine, cinnamic anhydrides **6** could be isolated in good yield (Scheme 3). It is known that the action of CX_4/PPh_3 on carboxylic acids leads to the acyl halides.[18] It is supposed that in the present case the cinnamyl halide formed reacts with the triethylammonium cinnamate, formed from the remainder of the cinnamic acid and triethylamine, to give the cinnamyl anhydride **6**. The reaction proceeds with benzoic acid derivatives such as with **3j**, too. Reaction of phenylpropiolic acid (**3k**) under these conditions gives an intractable mixture of compounds, most likely through such reaction pathways as alkyne trimerisation, which has been noted to proceed with activated propiolic acids, already under mild conditions.
Adding cholesterol (**7**) as an alcohol component to the reaction mixture leads to cinnamyl cholesterates **8** (Scheme 4). Although cholesterol (**7**) was added after mixing the cinnamic acid **3** with $PPh_3/BrCCl_3$ prior to adding triethylamine, meaning that esterification could progress through both cinnamyl halide and a cinnamic anhydride pathway, it was found that in absence of triethylamine, under conditions which are known to produce cinnamyl halides intermittently, the yields of the cholesteryl esters were very low. In the reaction in presence of triethylamine, cinnamic anhydrides **6** were found as side products, indicating that at least a part of the esterification runs via the anhydrides. The reactions give higher yields when run in 1,2-chloroethane than in dichloromethane as solvent at higher reaction temperatures.



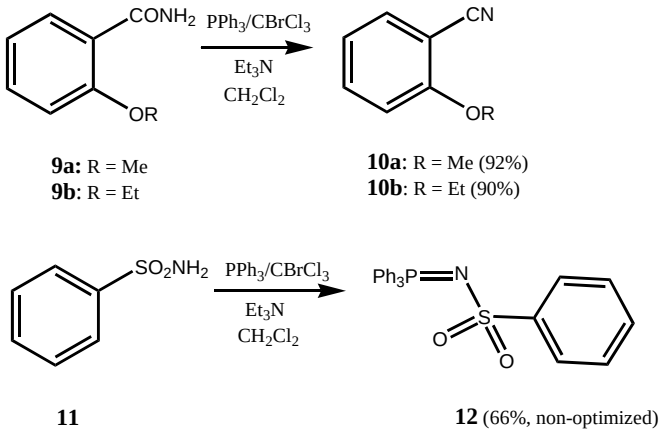
Scheme 3. Cinnamic anhydrides synthesis from cinnamic acids ($PPh_3/CBrCl_3$)



Scheme 4. Preparation of cholesteryl cinnamates

$PPh_3/BrCCl_3$ was also found to be useful in converting benzamides **9** to benzonitriles **10**. Previously, the system PPh_3/CCl_4 had been investigated for this reaction.[11] When using $PPh_3/BrCCl_3$, alkoxybenzamides **9a** and **9b** converted cleanly to the corresponding benzonitriles, **10a** and **10b** (Scheme 5).

Finally, *N*-(phenylsulfonyl)-triphenylphosphoranylideneamide (**12**) was prepared from triphenylphosphine and benzenesulfonamide (**11**) in the presence of $BrCCl_3$ (Scheme 5), again a reaction that R. Appel et al. had performed in presence of CCl_4.[12]



Scheme 5. Miscellaneous reactions with $PPh_3/CBrCl_3$

In conclusion, $BrCCl_3$ can replace CCl_4 in many reactions, in which the combination PPh_3/CX_4 is normally used. Especially noteworthy are the preparation of anhydrides from the corresponding acids and the *in situ* esterification of cholesterol utilizing $PPh_3/BrCCl_3$, which add to the scope of Appel-type reactions.

References

[1] R. Appel, *Angew. Chem. Int. Ed. Engl.*, **1975**, *14*, 801 – 811.

[2] Environmental Health Criteria 208, drafted by J. de Fouw, WHO, Geneva, **1999**.

[3] *cf.*, J. von Dueszeln and W. Thiemann, *Sci. Total Environ.*, **1985**, *41*, 187 – 194; R. Guicherit and F. L. Schulting, *Sci. Total Environ.*, **1985**, *43*, 193 – 219; R. A. Rasmussen and M. A. K. Khalil, *Science*, **1986**, *232*, 1623 – 1624.

[4] An atmospheric life time of 85 years has been ascribed to CCl_4 in: K. Dow and T. E. Downing, *The Atlas of Climate Change*, **2006**.

[5] UNEP (1996). The 1987 Montreal protocol on substances that deplete the ozone layer as adjusted and amended by the Second, Fourth and Seventh Meeting of the Parties. In: Handbook for the international treaties for the protection of the ozone layer, 4th ed. Nairobi, Kenya, United Nations Environment Programme, pp 18–39.

[6] F. Artuso, P. Chamard, S. Chiavarini, A. di Sarra, D. Meloni, S. Piacentino and M. D. Sferlazzo, *Atmos. Environ.*, **2010**, *44*, 4944 - 4953.

[7] R. Atkinson, D. L. Bauch, R. A. Cox, R. F. Hampson, J. A. Kerr and J. Troe, *Atmos. Environ.*, **1992**, *26A*, 1187 – 1230.

[8] L. Orkin and E. E. Kasimoskaya, *J. Atmos. Chem.*, **1995**, *21*, 1 - 11.

[9] B. A. Clement and R. L. Soulen, *J. Org. Chem.*, **1976**, *41*, 556 – 557.

[10] S. G. Newman, C. S. Brian, D. Perez and M. Lautens, *Synthesis*, **2011**, 342 – 346.

[11] E. Yamato and S. Sugasawa, *Tetrahedron Lett.*, **1970**, 4383; R. Appel, R. Kleinstueck and K. D. Ziehn, *Chem. Ber.*, **1971**, *104*, 1030; R. Jaunin and W. Arnold, *Helv. Chim. Acta*, **1973**, *56*, 2569.

[12] R. Appel, R. Kleinstueck, and K. D. Ziehn, *Chem. Ber.*, **1971**, *104*, 2250; R. Appel and H. Einig, *Z. Naturforschg.*, **1975**, *30B*, 134.

[13] R. A. W. Johnstone and M. E. Rose, *Tetrahedron*, **1979**, *35*, 2169.

[14] T. Thiemann, M. Elshorbagy, M. Salem, M. al-Sulaibi, B. al-Hindawi, contribution to ECSOC-14, **2010**: a021.

[15] I. J. Elkenov, D. I. Todorova, V. S. Bankova, T. S. Milkova, *J. Nat. Prod.*, **1995**, 58, 280.

[16] G. R. Morais, M. Watanabe, Y. Tanaka and T. Thiemann, *J. Chem. Res.*, **2005**, *29*, 802 – 807.

[17] L. E. Barstow and V. J. Hruby, *J. Org. Chem.*, **1971**, *36*, 1305 – 1306.

[18] J. B. Lee, *J. Am. Chem. Soc.*, **1966**, *88*, 3440.