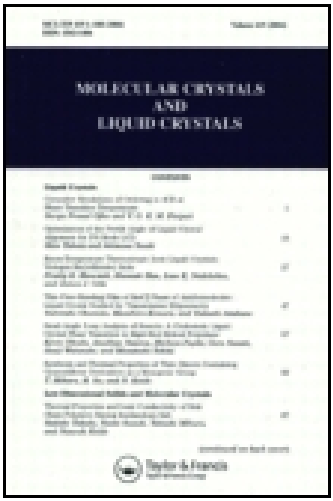


Molecular Crystals and Liquid Crystals

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl20

Crystal and Molecular Structure Analysis of (2-((6-Chloro pyridin-3-yl)methoxy)-5-methylphenyl)(p-tolyl)Methanone

B. N. Lakshminarayana [a], J. Shashidhara Prasad [a], T. D. Venu [b], B. K. Manuprasad [b], M. A. Sridhar [a] & Sheena Shashikanth [b]

[a] Department of Studies in Physics, University of Mysore, Mysore, India

[b] Department of Studies in Chemistry, University of Mysore, Mysore, India

Published online: 17 Dec 2009.

To cite this article: B. N. Lakshminarayana, J. Shashidhara Prasad, T. D. Venu, B. K. Manuprasad, M. A. Sridhar & Sheena Shashikanth (2009) Crystal and Molecular Structure Analysis of (2-((6-Chloro pyridin-3-yl)methoxy)-5-methylphenyl)(p-tolyl)Methanone, Molecular Crystals and Liquid Crystals, 515:1, 207-214, DOI: 10.1080/15421400903359116

To link to this article: http://dx.doi.org/10.1080/15421400903359116

Mol. Cryst. Liq. Cryst., Vol. 515, pp. 207–214, 2009

ISSN: 1542-1406 print/1563-5287 online
DOI: 10.1080/15421400903359116

Crystal and Molecular Structure Analysis of (2-((6-Chloro pyridin-3-yl)methoxy)-5-methylphenyl) (p-tolyl)Methanone

B. N. Lakshminarayana[1], J. Shashidhara Prasad[1], T. D. Venu[2], B. K. Manuprasad[2], M. A. Sridhar[1], and Sheena Shashikanth[2]

[1]Department of Studies in Physics, University of Mysore, Mysore, India
[2]Department of Studies in Chemistry, University of Mysore, Mysore, India

The title compound, (2-((6-chloropyridin-3-yl)methoxy)-5-methylphenyl)(p-tolyl) methanone, was synthesized and characterized spectroscopically and finally confirmed by (XRD) study. The title compound crystallizes in the monoclinic space group $P2_1/c$ with cell parameters $a = 9.4420(1)\,\text{Å}$, $b = 7.9810(6)\,\text{Å}$, $c = 23.777(4)\,\text{Å}$, $\alpha = 90^\circ$, $\beta = 90.883(3)^\circ$, $\gamma = 90^\circ$, $V = 1791.5(4)\,\text{Å}^{-3}$, and $Z = 4$. The structure exhibits intermolecular hydrogen bond of the type $C{-}H\cdots O$.

Keywords: anti-cancer; anti-inflammatory; benzophenone; crystal structure; pyridine ring

INTRODUCTION

Functionalized phenols, such as 2-hydroxy benzophenones, represent important building blocks in organic [1] and medicinal chemistry [2]. Benzophenone is a prototypical aromatic carbonyl compound that has been extensively studied [3]. The great importance of these substances is fundamentally due to the diverse biological and chemical properties that they possess [4–13]. Benzophenones are usually obtained from natural products [14–17] or by synthetic methods. Subsequently, benzophenones are frequently used in medicine and industry [18,19].

The proficiency of benzophenone analogues as chemotherapeutic agent, especially as anti-inflammatory, is well documented [20]. Benzophenone analogues which are synthesized by several scientists

Address correspondence to Prof. J. Shashidhara Prasad, Department of Studies in Physics, Manasagangotri, University of Mysore, Mysore 570 006, India. Fax: +91-821-2419333. E-mail: jsp@physics.uni-mysore.ac.in

have been reported as effective anti-inflammatory agents [21–24]. Recently, synthesis and structural activity relationship of benzophenones as novel class of p38 MAP kinase inhibitors with high anti-inflammatory activity have been reported [25]. The in-vitro and in-vivo studies of novel nitro and amino substituted benzophenones have been investigated as potential anticancer agents with low cytotoxicity [26].

These observations and our exploration for new molecules with anti-inflammatory activity, encouraged us to integrate 2-chloro-5-chloromethyl pyridine moiety in benzophenone framework, since these systems possess well-documented anti-inflammatory activity.

EXPERIMENTAL

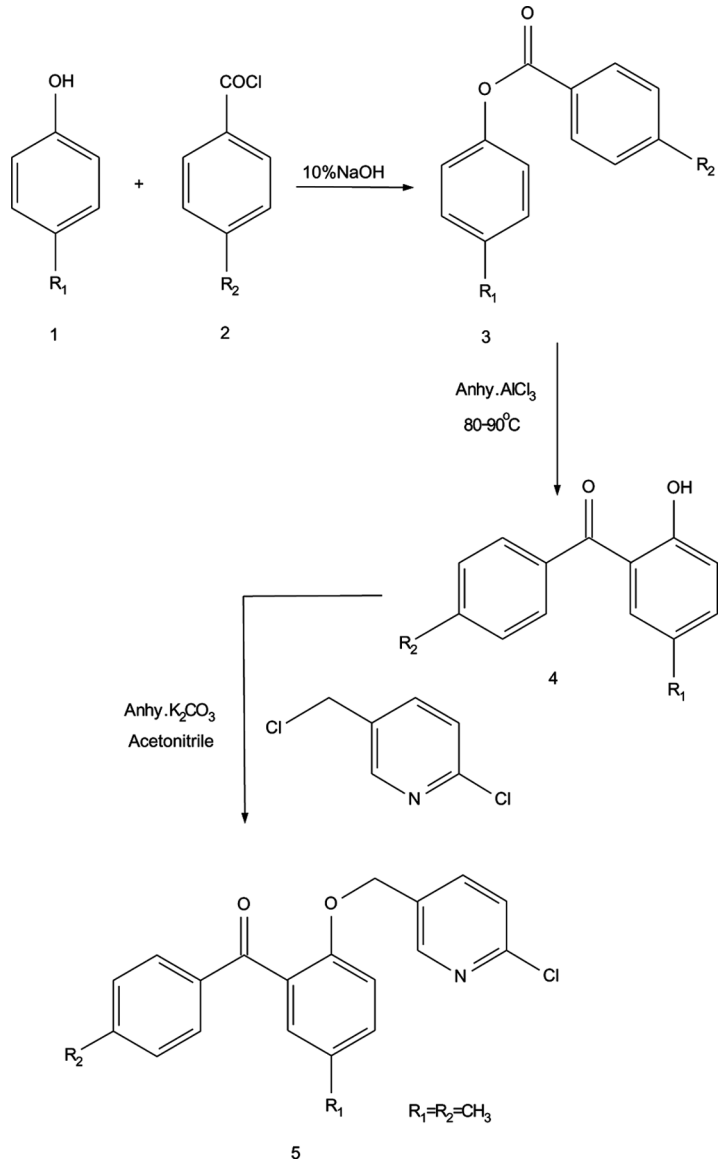
Synthesis of (2-((6-Chloropyridin-3-yl)methoxy)-5-methylphenyl)(p-tolyl)methanone

4-Methyl-benzoic acid 4-methyl-phenyl ester (3) was synthesized by benzoylation of 4-methyl-phenol (1) with 4-methyl benzoyl chloride (2) using 10% sodium hydroxide solution. (5-Methyl-2-hydroxy-phenyl)-(4-methyl-phenyl)-methanone (4) was synthesized by Fries rearrangement of the above ester in presence of anhydrous aluminium chloride. A mixture of 4 (1 g, 4.41 mM) and 2-chloro-5-chloromethyl pyridine (0.95 g, 4.41 mM) was refluxed in dry acetonitrile for 5 h, in presence of anhydrous potassium carbonate (1.83 g, 13.25 mM). When the reaction was completed (TLC), the reaction mass was cooled, and the solvent was removed under reduced pressure. The residual mass was triturated with ice-cold water to remove potassium carbonate and then extracted with dichloromethane (3×20 ml). The organic layer was washed with 10% sodium hydroxide solution (3×10 ml) followed with water wash (3×15 ml) and then dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure to obtain the crude solid, which upon recrystallization with ethanol afforded (2-((6-chloropyridin-3-yl) methoxy)-5-bromophenyl) (4-chlorophenyl) methanone (5) as pale yellow crystals, in good yield. A schematic diagram of the molecule is shown in Figure 1.

Yield 1.40 g (88%): M.p. 165°C; IR (Nujol): 1718 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 2.31(s, 3 H, CH_3), 2.41(s, 3 Hm CH_3), 4.91 (s, 2 H, CH_2), 6.70–8.71 ppm (m, 10 H, $J = 7$ Hz, Ar-H). Anal. Calc. for $C_{21}H_{18}ClNO_2$: C, 71.69; H, 5.16; N, 3.98. Found: C, 71.68; H, 5.13; N, 3.98%.

CRYSTAL STRUCTURE DETERMINATION

Single crystals of suitable size were chosen for X-ray diffraction (XRD) studies. The data were collected at room temperature on a DIPLabo



SCHEME 1 Schematic diagram of the molecule.

Image Plate system with graphite monochromated radiation MoK_α. Each exposure of the image plate was set to a period of 400 s. Thirty-six frames of data were collected in the oscillation mode with an oscillation range of 5° and processed using Denzo [27]. The reflections were

merged with Scalepack. All the frames could be indexed using a primitive monoclinic lattice. The structure was solved by direct methods using SHELXS-97 [28]. Least-squares refinement using SHELXL-97 [28] with isotropic displacement parameters for all the non-hydrogen atoms converged the residual to 0.1659. Subsequent refinements were carried out with anisotropic thermal parameters for non-hydrogen atoms. After eight cycles of refinement the residuals converged to 0.0583. The hydrogen atoms were fixed at chemically acceptable positions and were allowed to ride on their parent atoms.

RESULTS AND DISCUSSION

The details of crystal data and refinement are given in Table 1. The bond lengths and bond angles of all the non-hydrogen atoms are given

TABLE 1 Crystal Data and Structure Refinement Table

CCDC Deposition Number	CCDC 719332
Empirical formula	$C_{21}H_{18}NO_2Cl$
Formula weight	351.81
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Cell dimensions	$a = 9.4420(15)$ Å
	$b = 7.9810(6)$ Å
	$c = 23.777(4)$ Å
	$\beta = 90.883(3)$
Volume	1791.5(4) Å^3
Z	4
Density (calculated)	1.304 Mg/m^3
Absorption coefficient	0.227 mm^{-1}
F_{000}	736
Crystal size	$0.3 \times 0.27 \times 0.25$ mm
Theta range for data collection	2.69° to 25.02°
Index ranges	$-9 \le h \le 9$
	$-8 \le k \le 7$
	$-28 \le l \le 28$
Reflections collected	4451
Independent reflections	2500 [R(int) = 0.0254]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2500/0/230
Goodness-of-fit on F^2	1.073
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0583$, $wR2 = 0.1599$
R indices (all data)	$R1 = 0.0729$, $wR2 = 0.1775$
Extinction coefficient	0.020(5)
Largest diff. peak and hole	0.186 and -0.274 e·Å^{-3}

TABLE 2 Selected Bond Lengths (Å) and angles (°)

Atoms	Length	Atoms	Length
Cl16–C13	1.737(3)	C2–C17	1.500(4)
O18–C17	1.224(3)	C10–C15	1.364(4)
O8–C3	1.375(3)	C10–C11	1.373(4)
O8–C9	1.413(4)	C23–C22	1.385(4)
N14–C13	1.315(5)	N14–C15	1.340(4)
C19–C17	1.482(4)	C1–C6	1.384(4)
C2–C1	1.385(4)		
C3–O8–C9	119.0(2)		
C20–C19–C17	120.5(2)	C13–N14–C15	116.4(3)
C24–C19–C17	121.2(2)	C6–C1–C2	121.8(3)
O8–C9–C10	107.8(2)	N14–C13–C12	124.1(3)
O8–C3–C4	124.8(3)	N14–C13–Cl16	116.3(3)
O8–C3–C2	115.5(2)	C12–C13–Cl16	119.6(3)
C1–C2–C3	119.2(3)	C23–C22–C25	121.0(3)
C1–C2–C17	119.5(3)	C3–C2–C17	121.2(2)
O18–C17–C19	121.0(2)	N14–C15–C10	124.5(3)
O18–C17–C2	119.3(2)	C19–C17–C2	119.7(2)

in Table 2, which are in good agreement with the standard values. Figure 2 represents the ORTEP [29] diagram of the molecule with thermal ellipsoids drawn at 50% probability.

In the title compound, (2-((6-chloropyridin-3-yl)methoxy)-5-methyl phenyl)(p-tolyl) methanone, the ring twist angle of 70.29(1)° between the phenyl rings bridged by the keto carbonyl is less compared with the corresponding value of 83.72(6)° reported for [2-amino-2′,5-dichlorobenzophenone] [30], and high as compared with other reported compounds [30]. The dihedral angle between the pyridine ring and phenyl ring (C19–C20–C21–C22–C23–C24) is 82.97(1)°, which

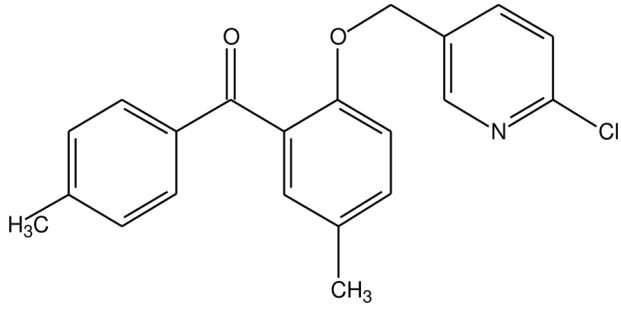


FIGURE 1 Schematic diagram of the title compound.

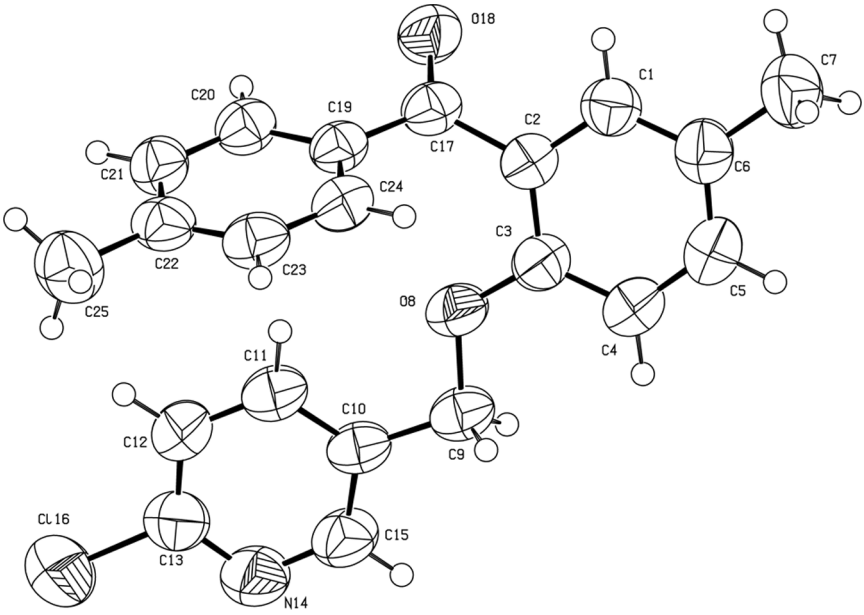


FIGURE 2 ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

shows that it is an indication of equatorial conformation. The pyridine ring is at axial position to the phenyl ring (C1–C2–C3–C4–C5–C6) as indicated by the dihedral angle of 16.22(1)° between them. The bond length O18=C17 = 1.244(3) Å is comparable with other reported compounds [30]. Another indication of the conformation is the values of the torsion angles for C1–C2–C17–O18 and C20–C19–C17–O18 are 53.5(4)° and 24.4(4)°, respectively, and these values vary with the other reported compounds [30]. For benzophenone, these torsion angles take the same sign and are each reported to be 30% in energy minimized benzophenones [31]. The C9–O8 bond is in an *+anti-periplanar* conformation, as indicated by the torsion angle value of 174.2(3)° for C10–C9–O8–C3. The structure exhibits an intermolecular hydrogen bond of the type C–H···O which holds the molecules together in the crystal lattice resulting in a hydrogen bonded dimer as shown in Fig. 3. The intermolecular hydrogen bond C23–H23···O18 is between the central methyl phenyl ring and the keto carbonyl group. The C23–H23···O18 has a distance of 0.93 Å and a distance of 2.51 Å to the acceptor atom with a bond length of 3.427(4) Å and a bond angle of 167° with symmetry code x, $1+y$, z.

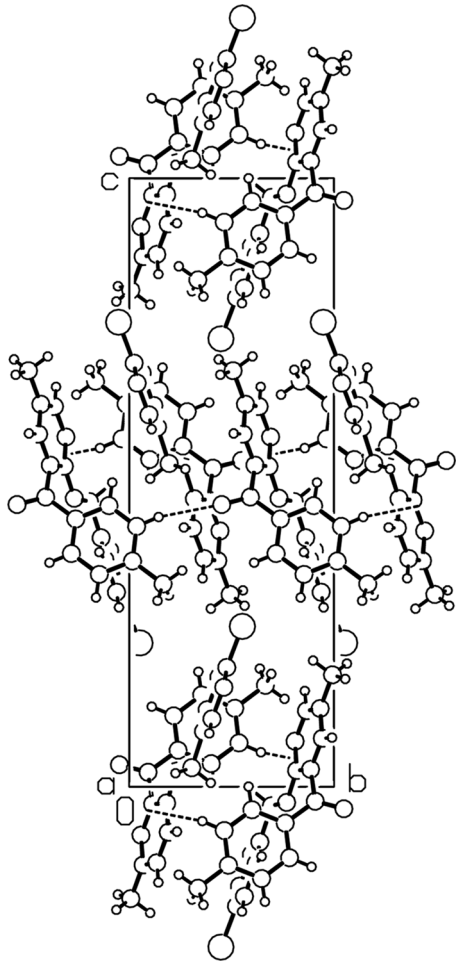


FIGURE 3 Packing of the molecules down *a* axis.

ACKNOWLEDGMENTS

The authors are grateful to DST and Government of India project SP/I2/FOO/93 and University of Mysore, Mysore for financial assistance.

REFERENCES

[1] Martin, R., *et al*. (2005). *Handbook of Hydroxyacetophenones; Preparation and Physical Properties*, 2nd Ed., Springer: Berlin.
[2] Vane, J. R., *et al*. (1992). *Aspirin and Other Salicylates*, Chapman and Hall Medical: London.

[3] Du, Y., Ma, C., Kwok, W. M., Xue, J., & Philips, D. L. (2007). *J. Org. Chem.*, *72*, 7149.
[4] Moffett, R. B., & Sey, P. P. H. (1964). *J. Med. Chem.*, *7*, 178.
[5] Wiesner, J., Kettler, K., Sakowski, J., Ortmann, R., Jomaa, H., & Schlitzer, M. (2003). *Bioorg. Med. Chem.*, *13*, 361.
[6] (a) Winter, Walter, R., Riscoe, Kerin, M., Hinrich, & David, J. (1997). *PCT Int.*, 9707790; (b) Winter, Walter, R., Riscoe, Kerin, M., Hinrich, & David, J. (1997). *Through Chem. Abstr.*, *126*, 248760.
[7] (a) Sanji, H., Susumce, K., Yasushi, M., Nobuhiro, H., Yasunobu, & Toshiro, K. (1995). *PCT Int.*, 9521856; (b) Sanji, H., Susumce, K., Yasushi, M., Nobuhiro, H., Yasunobu, & Toshiro, K. (1995). *Through Chem. Abstr.*, *124*, 56716j.
[8] Saettone, M. F., Alderigi, C., Giannaccini, B., Anselmi, C., Rosselt, M. G., Schot-ton, M., Gerini, R. (1998). *Int. J. Cosmet. Sci.*, *10*, 99.
[9] Bernadi, A. P. M., Ferraz, A. B. F., Albring, D. V., Birdignon, S. A. L., Schripsema, J., Bridi, R., Dutra-Filho, C. S., Henriques, A. T., & Von Poser, G. L. (2005). *J. Nat. Prod.*, *68*, 784.
[10] Saharia, G. S., & Sharma, H. R. (1979). *Sci. Cult.*, *45*, 139.
[11] (a) Pierre, D., Jacques, B., Matthias, K., & Corina, B. (2002). *PCT Int.*, 2002092552; (b) Pierre, D., Jacques, B., Matthias, K., & Corina, B. (2002). *Through Chem. Abstr.*, *137*, 384655.
[12] Singh, N. A., Indra, D., Setty, B. S., & Ray, S. (1994). *Indian J. Pharm. Sci.*, *56*, 105.
[13] Bakana, P., Claeys, M., Totte, J., Pieters, L. A., Van Hoof, L., Vemba, Y., Berghe, V. D. A., & Vlietinck, A. J. (1987). *J. Ethnopharmacol.*, *21*, 75.
[14] (a) Leonard, D. M., et al. (1997). *J. Med. Chem.*, *40*, 2971; (b) Williams, T. M., & Dinsmore, C. (1999). *J. Adv. Med. Chem.*, *4*, 273.
[15] Palomer, A., Pascual, J., Cabre, M., Borras, L., Gonzalez, G., Aparici, M., Carabaza, A., Cabre, F., Garcia, M. L., & Mauleon, D. (2002). *Bioorg. Med. Chem. Lett.*, *12*, 533.
[16] (a) Jaques, M., & Walter, S. (1983). *Eur. Pat.*, *79*, 499; (b) Jaques, M., & Walter, S. (1983). *Through Chem. Abstr.*, *99*, 83726j.
[17] Hejaz, A. A. M., Woo, L. W., Purohit, A., Reed, M. J., & Potter, B. V. L. (2004). *Bioorg. Med. Chem.*, *12*, 2759.
[18] Mitsch, A., Wibner, P., Sibler, K., Haebel, P., Satler, I., Klebe, G., & Schlitzer, M. (2004). *Bioorg. Med. Chem.*, *12*, 4585.
[19] Katsuichi, S., & Massaki, T. (1992). *Chem. Abstr.*, *116*, 128368g.
[20] Ottosen, E. R., Sorensen, M. D., Bjorkling, F., Skak-Nielsen, T., Fjording, M. S., Aaes, H., & Binderup, L. (2003). *J. Med. Chem.*, *46*, 5651.
[21] Khanum, S. A., Shashikanth, S., & Deepak, A. V. (2004). *Bioorg. Chem.*, *32*, 211.
[22] Khanum, S. A., Shashikanth, S., & Sudha, B. S. (2004). *Heteroatom Chem.*, *15*, 37.
[23] Khanum, S. A., Shashikanth, S., & Sudha, B. S. (2004). *Pestmanag. Sci*, *60*, 1119.
[24] Mahendra, M., Doreswamy, B. H., Sridhar, M. A., Shashidhara Prasad, J., Khanum, S. A., Shashikanth, S., & Venu, T. D. (2005). *J. Chem. Cryst.*, *35*, 463.
[25] Kumazawa, E., Hirotani, K., Burford, S. C., Kawagoe, K., Miwa, T., Mitsul, I., & Ejima, A. (1997). *Chem. Pharm. Bull.*, *45*, 1470.
[26] Winter, C. A., Risley, E. A., & Nuss, G. W. (1962). *Proc. Soc. Exp. Biol. New York*, *111*, 544.
[27] Otwinowski, V., & Minor, W. (1997). In: *Methods in Enzymology*, 276, Carter, C. W., Jr. & Sweet, R. M. (Eds.), Academic Press: New York, 307–326.
[28] Sheldrick, G. M. (2008). *Acta Cryst.*, *A64*, 112–122.
[29] Spek, A. L. (2003). *J. Appl. Cryst.*, *36*, 7–13.
[30] Philip, J. (2008). *Cox, Dimitrious Kechagias, Orla Kelly. Acta Cryst.*, *B64*, 206–216.
[31] Rappoport, Z., Biali, S. E., & Kaftory, M. (1990). *J. Am. Chem. Soc.*, *112*, 7742.