C. R. Chimie 15 (2012) 384–388

Contents lists available at SciVerse ScienceDirect

Comptes Rendus Chimie

www.sciencedirect.com

Preliminary communication/Communication

# Efficient BOP-mediated synthesis of fulgimides

## *Synthèse efficace de fulgimides en utilisant le réactif BOP*

Krzysztof K. Krawczyk [a], Daria Madej [a], Jan K. Maurin [b], Zbigniew Czarnocki [a,*]

[a] *Faculty of Chemistry, University of Warsaw, Pasteura 1, 02-093 Warszawa, Poland*
[b] *National Drug Institute, Chełmska 30/34, 00-725 Warszawa, Poland*

ARTICLE INFO

*Article history:*
Received 6 December 2011
Accepted after revision 7 February 2012
Available online 10 March 2012

*Keywords:*
Amides
Chirality
Cyclization
Strained molecules

ABSTRACT

A mild and efficient method for the synthesis of fulgimides is presented in which the peptide coupling reagent BOP is employed for dehydratation of fulgenic acid monoamides (succinamic acids). The disclosed method proved to be superior to those described in the literature.



RÉSUMÉ

Une méthode douce et efficace pour la synthèse de fulgimides est présentée, dans laquelle le réactif de couplage peptidique BOP est utilisé pour la déshydratation de monoamides d'acide fulgenique (acides succinamiques). Le procédé décrit ici s'est avéré être supérieur à ceux décrits dans la littérature.



## 1. Introduction

Fulgide family compounds are the subject of numerous publications, mainly due to their photochromic properties and applications in the synthesis of lignans [1,2]. From the fulgide-related compounds, fulgimides appear to be the most interesting for data storage applications because of their increased fatigue resistance, higher chemical stability compared to the parent fulgides and the possibility of functionalisation at the nitrogen atom.

*N*-substituted fulgimides can be synthesized by functionalisation of simple *N*-*H* imides or by the dehydratation of related succinamic acids. The latter can be obtained either by the reaction of a fulgide with a primary amine or by the reaction of a succinic half-ester with the Grignard salt of the amine [1,3].

Amongst available dehydrating agents, the most common is acetyl chloride [4], acetic anhydride [5] and thionyl chloride [6] but there are also literature reports about the use of carbonyldiimidazole (CDI) [7], carbodiimides [1,8] and recently also hexamethyldisilazane (HMDS) [9].

It is known that DCC (*N*,*N*′-dicyclohexylcarbodiimide) and CDI (1,1′-carbonyldiimidazole) may give unsatisfactory results due to the formation of isofulgimides instead of fulgimides [1,8].

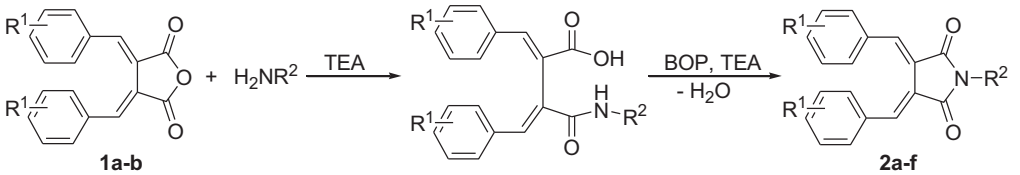
The use of acetyl chloride or acetic anhydride proved not always effective due to the formation of acidic byproducts, which can lead to decomposition of the material.

Otto et al. [10] have developed another interesting method for fulgimide formation, where the succinamic acid is esterified to give a phenacyl ester, which is then cyclized to the imide by treatment with a base. The disadvantage of this approach is that it requires additional steps and the treatment with a strong base (*t*-BuLi) is sometimes necessary. Nevertheless, the obtained yields are much better compared to other methods.

We have already successfully used benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP; Castro's reagent) for the coupling of amines

* Corresponding author.
*E-mail address:* czarnoz@chem.uw.edu.pl (Z. Czarnocki).

1631-0748/$ – see front matter 
doi:10.1016/j.crci.2012.02.001




| | $R^1$ |
|---|---|
| **1a** | 3,4,5-trimethoxyphenyl |
| **1b** | H |

| | $R^1$ | $R^2$ |
|---|---|---|
| **2a** | 3,4,5-trimethoxyphenyl | methyl |
| **2b** | 3,4,5-trimethoxyphenyl | phenyl |
| **2c** | 3,4,5-trimethoxyphenyl | 4-methoxyphenyl |
| **2d** | 3,4,5-trimethoxyphenyl | 4-bromophenyl |
| **2e** | 3,4,5-trimethoxyphenyl | (*R*)-1-phenylethyl |
| **2f** | H | 2-naphthyl |

**Scheme 1.** General procedure for the BOP-mediated synthesis of fulgimides **2a-f**.

or alcohols with carboxylates, and we usually obtained excellent results [11,12].

As none of the methods described in the literature proved successful in the case of the synthesis of chiral imide **2e** due to its instability, we decided to employ BOP. The good yield of dehydratation and a short reaction time encouraged us to check this method on a broader scope of substrates.

## 2. Results and discussion

The used synthetic procedure is presented in Scheme 1. Fulgides **1a** and **1b** were prepared according to the literature protocols [2b, 2h], involving a double Stobbe condensation followed by saponification of the 2,3-bisarylidene succinic acid ester and subsequent treatment with acetyl chloride. It is noteworthy that BOP could also successfully be used for the dehydratation of fulgenic acids to produce fulgides. The yield obtained using this methodology was always higher than obtained by the treatment with acetyl chloride and similar to those observed when DCC was used. In contrast to DCC, the purification process was much easier. Nevertheless, in the case of most fulgides, the use of somewhat more expensive and toxic BOP does not seem to be reasonable.

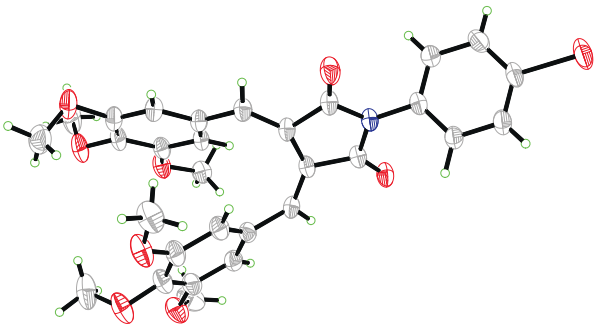


**Figure 1.** Oak Ridge Thermal Ellipsoid Plot (ORTEP) diagram of molecule **2d**.

Fulgides react almost quantitatively with primary amines in the presence of one equivalent of tertiary amine (triethylamine, TEA). TEA can compete in salt formation between the succinamic acid and the primary amine, thus its addition was found to be beneficial to the rate of the reaction and the obtained yield.

Rigorous drying of the resulted amide acid is essential for the next step, since even traces of residual humidity significantly lowers the yield of the BOP-mediated reactions. The mixture of the amide acid with 1.05 eq of BOP in dry tetrahydrofuran (THF) was then treated with 1.1 eq of TEA, first at −45 °C and then at room temperature. We found that final warming up of the reaction mixture to 35 °C slightly increased the yield. The usual work-up affords the product pure enough to crystallize out of the ethereal solution without additional purification by column chromatography. However, in the case of the oily imide **2e**, this operation was necessary.

The described method proved to be the only applicable for the synthesis of this compound.

Attempted synthesis using acetyl chloride or DCC gave only trace amounts of the product **2e**.

It is also noteworthy that in the case of *N*-(4-bromo)-phenyl fulgimide **2d**, the yield was increased significantly, comparing to the obtained by traditional methods (48%). We found *p*-bromophenyl fulgimides of particular interest due to a possibility to introduce other structural modifications at the *N*-phenyl ring e.g. via the Suzuki-Miyaura cross coupling. The X-ray structure of fulgimide **2d** proves the (*E*,*E*) configuration of the double bonds which causes helical chirality of the molecule (Fig. 1), that can be further elaborated in stereoselective transformations [12].

The described method will be evaluated for the synthesis of thermally irreversible heterocyclic fulgimides.

## 3. Conclusion

We have developed a mild method for the preparation of fulgimides which can be used for the synthesis of bisarylidenefulgimides having different *N*-substituents.

**Table 1**
Structure of products **2a**–**f**, the obtained yields and analytical data.

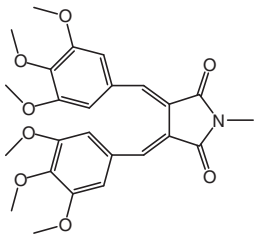
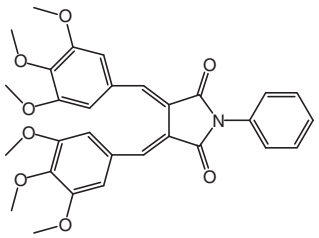
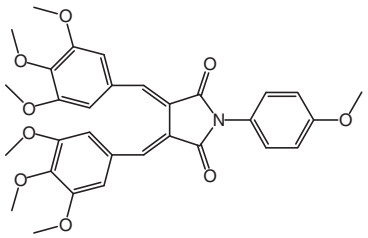
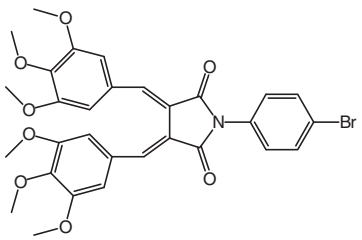
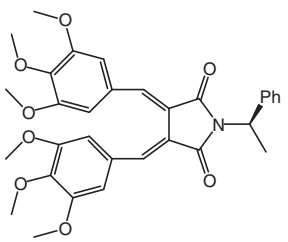
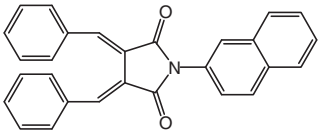
| Compound | Isolated yield and analytical data |
|---|---|
| **2a**  | 76%, 78 mg of dense, deep yellow oil, which slowly solidifies to form dark yellow crystals; Mp 152–154 °C<br>$^1$H NMR: 3.25 (s, 3H), 3.64 (s, 12H), 3.76 (s, 6H); 6.29 (s, 4H), 7.68 (s, 2H),<br>$^{13}$C NMR: 25.09, 55.93, 61.43, 107.87, 122.47, 130.14, 134.65, 140.53, 152.28, 170.67<br>HRMS: *m/z* $[M+Na]^+$ calcd for $C_{25}H_{27}NNaO_8$ 492.1634; found 492.1626 |
| **2b**  | 92%, 107 mg of fine yellow crystals; Mp 174–175 °C<br>$^1$H NMR: 3.66 (s, 12H), 3.78 (s, 6H), 6.35 (s, 4H), 7.51 (m, 5H), 7.79 (s, 2H)<br>$^{13}$C NMR: 55.89, 61.41, 107.93, 122.07, 126.65, 128.59, 129.27, 130.11, 132.16, 135.44, 140.66, 152.24, 169.53<br>HRMS: *m/z* $[M+Na]^+$ calcd for $C_{30}H_{29}NNaO_8$ 554.1791; found 554.1782 |
| **2c**  | 94%; 116 mg of fine yellow crystals; Mp 217–219 °C<br>$^1$H NMR: 3.65 (s, 12H), 3.78 (s, 6H), 3.87 (s, 3H), 6.34 (s, 4H), 7.05 (d, J = 4.5 Hz, 2H), 7.41 (d, J = 4.5 Hz, 2H), 7.77 (s, 2H)<br>$^{13}$C NMR: 55.67, 55.93, 61.41, 108.00, 114.63, 122.20, 124.82, 127.89, 130.16, 135.26, 140.69, 152.28, 159.59, 169.82,<br>HRMS: *m/z* $[M+Na]^+$ calcd for $C_{31}H_{31}NNaO_9$ 584.1897; found 584.1901 |
| **2d**  | 82%; 110 mg of fine yellow crystals; Mp 190–191 °C<br>$^1$H NMR: 3.63 (s, 12H), 3.76 (s, 6H); 6.31 (s, 4H); 7.42 (d, J = 4.4 Hz, 2H), 7.66 (d, J = 4.4 Hz, 2H), 7.76 (s, 2H)<br>$^{13}$C NMR: 55.92, 61.44, 108.00, 121.79, 122.35, 128.10, 130.00, 131.19, 132.43, 135.77, 140.81, 152.27, 169.21<br>HRMS: *m/z* $[M+Na]^+$ calcd for $C_{30}H_{28}BrNNaO_8$ 632.0896; found 632.0878<br>CCDC nr 847340 |
| **2e**  | 73%, 89 mg of dense, deep yellow oil; $[\alpha]_D^{20}$ +94 (*c* 1, $CHCl_3$)<br>$^1$H NMR: 1.97 (d, J = 7.4 Hz, 3H), 3.62 (s, 12H); 3.75 (s, 6H); 5.25 (q, J = 7.4 Hz, 1H); 6.25 (s, 4H); 7.26–7.42 (m, 3H); 7.58 (m, 2H); 7.61 (s, 2H)<br>$^{13}$C NMR: 27.58, 50.59, 55.97, 61.47, 107.88, 117.13, 122.47, 127.89, 127.91, 128.69, 130.24, 134.66, 140.90, 152.28, 171.20<br>HRMS: *m/z* $[M+Na]^+$ calcd for $C_{32}H_{33}NNaO_8$ 582.2104; found 582.2099 |

**Table 1** (*Continued*)

| Compound | Isolated yield and analytical data |
|---|---|
| **2f**  | 60%, 87 mg of fine, yellowish crystals; Mp 234–237 °C<br>$^1$H NMR: 6.80–6.95 (m, 8H), 7.04–7.13 (m, 2H), 7.51–7.56 (m, 2H), 7.62 (dd, $J_1$ = 2.0 Hz, $J_2$ = 8.8 Hz, 1H), 7.87–7.97 (m, 2H), 7.93 (s, 2H), 7.99 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 1.8 Hz, 1H)<br>$^{13}$C NMR: 122.59, 124.18, 125.74, 126.66, 126.90, 127.25, 127.89, 128.43, 129.05, 129.66, 129.87, 129.99, 132.90, 133.35, 134.81, 135.87, 169.71<br>HRMS: *m/z* $[M + Na]^+$ calcd for $C_{28}H_{19}NNaO_2$ 424.1313; found 424.1313 |

The yields are superior to those obtained with traditional dehydratation with AcCl or CDI. For unstable fulgimide **2e**, the BOP-mediated dehydratation proved to be the only applicable procedure.

## 4. Experimental

The NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 200 MHz for $^1$H NMR and at 50 MHz for $^{13}$C NMR. The spectra were measured in $CDCl_3$ and are given as δ values (in ppm) relative to TMS. Mass spectra were collected on Quattro LC Micromass and LCT Micromass TOF HiRes apparatus. Optical rotations were measured on Perkin-Elmer 241 polarimeter. TLC analyses were performed on silica gel plates (Merck Silica Gel 60 F254) and visualized using UV-light. Column chromatography was carried out at atmospheric pressure using Silica Gel 60 (230–400 mesh, Merck). Melting points were determined by a Boetius hot-plate microscope and were uncorrected. Solvents used in the reactions were anhydrous. $CH_2Cl_2$ was dried with anhydrous $CaCl_2$. THF was dried with $CaH_2$ and distilled under argon directly into the reaction vessel. The single-crystal X-ray measurements were carried out on Oxford Diffraction Xcalibur R κ-axis diffractometer with CCD Ruby detector. In all cases, Cu Kα characteristic radiation was applied. After initial corrections and data reduction, intensities of reflections were used to solve and consecutively refine structures using SHELXS97 [13] and SHELXL97 [14] programs. Further absorption corrections were applied in final steps of refinement. BOP and all other reactants were purchased from Aldrich.

The anhydrides **1a** and **1b** were prepared according to literature protocols, via double Stobbe condensation/esterification sequences, followed by saponification and dehydratation with AcCl at reflux. The analytical data were in accordance with those presented in the literature for **1a** [2b] and **1b** [2g].

### 4.1. General synthesis of fulgimides 2

Fulgide **1a** (100 mg, 0.22 mmol) or **1b** (100 mg, 0.36 mmol) was dissolved in a minimal amount of $CH_2Cl_2$ and 1.05 eq of primary amine was added in dry $CH_2Cl_2$. In the case of the synthesis of **2a**, methylamine was cooled to −78 °C, and 2.5 eq were added directly to the cooled solution of the fulgide in dry $CH_2Cl_2$. It was not necessary to use TEA in this preparation. In all other cases, 2 eq of TEA were added and the solution was stirred at room temperature or refluxed until bleaching of the solution indicated complete turnover of the coloured fulgide. The solvents were evaporated, and the residue dissolved in AcOEt and washed with 10% aqueous citric acid solution and brine. The organic layer was dried with $Na_2SO_4$, filtered and evaporated in vacuo to give the appropriate succinamic acid as an oily residue. Dry THF was distilled directly into the reaction mixture (approx. 1 mL/20 mg) and 1.05 eq of BOP was added under argon. The mixture was stirred and cooled to −45 °C. Then 1.1 eq of TEA was added at this temperature and the solution was left to reach room temperature and then was warmed to 35 °C. During the time of the reaction, a color change from slightly yellow to deep yellow or deep orange was observed. After 30 more minutes of reaction time, the solvent was evaporated, the residue dissolved in AcOEt and washed with 10% citric acid solution (2 ×), then 5% $NaHCO_3$ solution (4 ×), water (1 ×) and brine (1 ×). The solution was dried over $Na_2SO_4$, filtered and evaporated to dryness.

Fulgimides **2a–d** and **2f** started to crystallize after immediate treatment with diethyl ether.

Fulgimide **2e** was subjected to flash column chromatography on $Al_2O_3$ (it decomposed immediately on silica) using diethyl ether as an eluent.

Yields and analytical data for fulgimides **2a–f** are presented in Table 1.

## Acknowledgment

The authors kindly acknowledge the financial support from the Polish Ministry of Science and Higher Education (grant No. N204 030636).

## References

[1] J.C. Crano, R.J. Gulielmetti, Organic photchromic and thermochromic compounds, 1, Plenum Press, New York, 1999, Main Photochromic Families.
[2] (a) Y. Yokoyama, Chem. Rev. 100 (5) (2000) 1717;
(b) A.S.R. Anjaneyulu, D. Santi Kumar, C.V.M. Sastry, P. Umasundari, Indian Journal of Chemistry, Sect. B: Organic Chemistry Including Medicinal Chemistry 33B (9) (1994) 839;
(c) H.D. Ilge, C. Drawert, J. Suehnel, R. Paetzold, Journal für Praktische Chemie (Leipzig) 326 (2) (1984) 233;
(d) P.A. Ganeshpure, Indian Journal of Chemistry, Sect. B: Organic Chemistry Including Medicinal Chemistry 17B (3) (1979) 202;
(e) H.D. Ilge, J. Suehnel, R. Paetzold, Journal für Signalaufzeichnungsmaterialien 5 (3) (1977) 177;
(f) R. Paetzold, H.D. Ilge, Journal für Signalaufzeichnungsmaterialien 3 (2) (1975) 93;
(g) G.D. Brown, H.-F. Wong, Tetrahedron 60 (2004) 5439;
(h) A.M. Asiri, J. Photochem. Photobiol. 159 (2003) 1.
[3] (a) A.P. Glaze, H.G. Heller, J. Whittall, J. Chem. Soc. Perkin Trans. 2 (1992) 591;
(b) H.G. Heller, R.M. Megit, J. Chem. Soc. Perkin Trans. 1 (1974) 923;
(c) P.J. Darcy, H.G. Heller, S. Patharakorn, R.D. Piggott, J. Whittall, J. Chem. Soc. Perkin Trans. 1 (1986) 315.

[4] R. Matsushima, H. Sakaguchi, J. Photochemistry Photobiology A: Chemistry 108 (1997) 239.
[5] P.J. Darcy, H.G. Heller, S. Patharakorn, R.D. Piggott, J. Whittall, J. Chem. Soc. Perkin Trans. 1 (1986) 315.
[6] H. Sai, T. Ogiku, H. Ohmizu, A. Ohtani, Chem. Pharm. Bull. 54 (12) (2006) 1686.
[7] I.G. Ilyina, V.V. Mel'nikov, S.I. Luyksaar, M.M. Krayushkin, A.Y. P'yankov, V.A. Barachevsky, I.V. Fedyanin, Russ. Chem. Bull., Int. Ed. 57 (7) (2008) 1444.
[8] H.G. Heller, K. Koh, C. Elliot, J. Whittall, Mol. Cryst. Liq. Cryst. 246 (1994) 79–86.
[9] (a) M. Köse, E. Orhan, Turk. J. Chem. 33 (2009) 579;
(b) Y.C. Liang, A.S. Dvornikov, P.M. Rentzepis, Tetrahedron Lett. 40 (1999) 8067;
(c) Y. Liang, A.S. Dvornikov, P.M. Rentzepis, Res. Chem. Intermed. 25 (1998) 905;
(d) Y. Liang, A.S. Dvornikov, P.M. Rentzepis, J. Mater. Chem. 10 (2000) 2477.
[10] B. Otto, K. Rück-Braun, Eur. J. Org. Chem. 13 (2003) 2409.
[11] K. Piwowarczyk, A. Zawadzka, P. Roszkowski, J. Szawkało, A. Leniewski, J.K. Maurin, D. Kranz, Z. Czarnocki, Tetrahedron: Asymmetry 19 (2008) 309.
[12] K.K. Krawczyk, D. Madej, J.K. Maurin, Z. Czarnocki, Tetrahedron: Asymmetry 22 (10) (2011) 1103.
[13] G.M. Sheldrick, SHELXS97. Program for solving crystal structures, University of Goettingen, Germany, 1997.
[14] G.M. Sheldrick, SHELXL97. Program for crystal structure refinement, University of Goettingen, Germany, 1997.