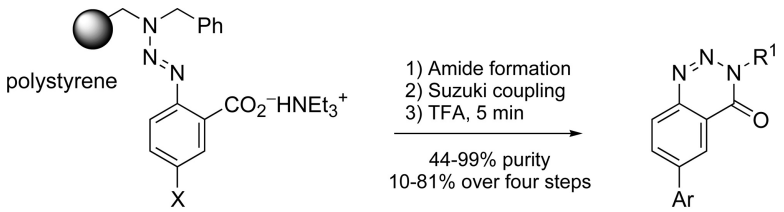
JOURNAL OF combinatorial CHEMISTRY

Report

The Synthesis of 3-Substituted 6-Aryl-3 *H*-benzo[*a*][1,2,3]triazinones Using Polymer-Bound Triazenes

Carmen Gil, Anja Schwgler, and Stefan Brse

J. Comb. Chem., **2004**, 6 (1), 38-42• DOI: 10.1021/cc0340271 • Publication Date (Web): 05 December 2003



T1 linker

42 examples

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

The Synthesis of 3-Substituted 6-Aryl-3 *H*-benzo[*a*][1,2,3]triazinones Using Polymer-Bound Triazenes

Carmen Gil,[†] Anja Schwögler,[‡] and Stefan Bräse*[,§]

Kekulé-Institut für Organische Chemie und Biochemie der Rheinischen Friedrich-Wilhelms-Universität Bonn, Gerhard-Domagk-Strasse 1, D-53121 Bonn, Germany, BASF AG, Agrochemical Research GVA/FC, D-67056 Ludwigshafen, Germany, and Institut für Organische Chemie, Universität Karlsruhe (TH), Fritz-Haber-Weg 6, D-76131 Karlsruhe, Germany

Received July 7, 2003

Introduction. Solid-phase combinatorial chemistry has frequently been employed for the rapid generation of libraries because of the increasing demand for new molecules with pharmacological and medicinal properties or biological activity.[1−3]

Many such compounds that possess biological activity are derived from heterocyclic structures that frequently appear in natural products. Therefore, the one way to ensure the success of organic synthesis in the drug development process is to first achieve the synthesis of such heterocyclic structures.[4,5] Benzoannelated nitrogen heterocycles have been especially well-recognized for their pharmacological properties.[6] Among them, benzotriazinones have displayed a broad range of biological activities, including their affinity for 5-HT_{1A} receptors;[7] cytotoxicity;[8] antipsychotic,[9] antimicrobial, and antitumor effects.[10] Related structures have other such interesting properties displayed as antiinflammatory agents,[11] thromboxane synthetase inhibitors, and antihypertension agents.[12] In addition, 3-phenyl-1,2,3-benzotriazin-4-ones show herbicidal activity.[13]

The benzotriazinone core structure is, in contrast to open-chained triazenes,[14] less susceptible to ring cleavage under acidic conditions. This skeleton is a useful intermediate for the synthesis of new fungicides.[15] In addition, the cytotoxic and mutagenic properties of antitumor triazene compounds are well-known.[16] Dacarbazine (DTIC)[17] has been used in the treatment of malignant melanoma and Hodgkin tumors. Recent studies have been developed new triazine prodrugs such as the novel agent Temozolomide (TMZ, Temodar),[18,19] which is used against malignant melanoma and brain tumors. Mitozolomide[20] is another example of an antitumor imidazotetrazine (Figure 1).

Despite their usefulness, however, a combinatorial access to this benzoannelated heterocycle using solid-phase methods has not yet been reported. In this paper, we present the synthesis of 3-substituted 6-aryl-(1,2,3)-benzotriazin-4-ones using polymer-bound triazenes.

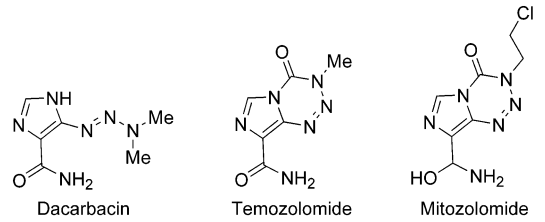


Figure 1. Antitumor imidazotetrazines.

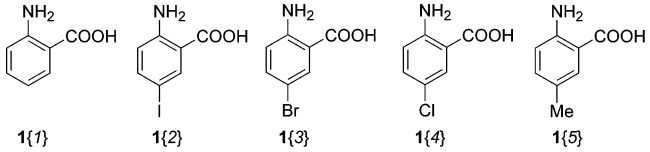


Figure 2. Anthranilic acids **1**{*1*−*5*} used for library synthesis.

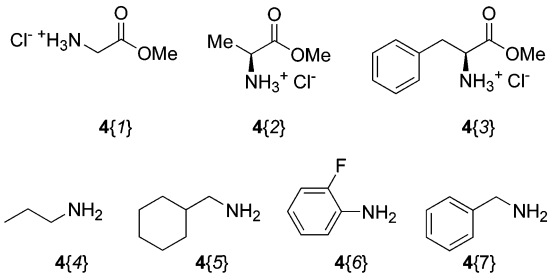
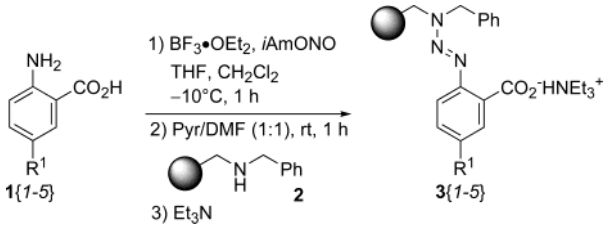


Figure 3. Amines **4** used for library synthesis.

Scheme 1. Synthesis of the Triazene Resins **3**



Recently, we introduced the triazene T1 linker system as a viable method for the construction of arenes libraries using the flexible chemistry of the diazonium group.[21−23] In addition, cinnolines[24] and benzotriazole[25] libraries have been synthesized using ortho-substituted arenes. Therefore, we intended to expand the scope of the triazene linkers to the important class of benzotriazin-4-ones.

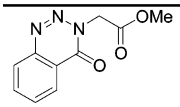
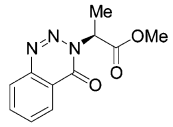
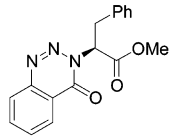
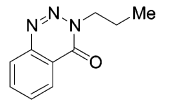
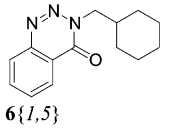
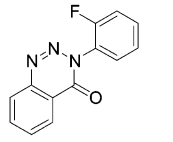
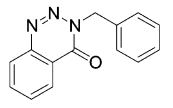
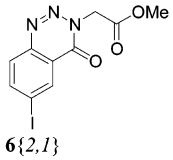
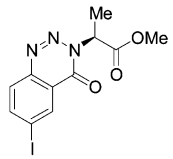
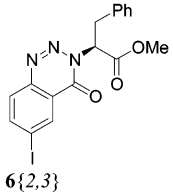
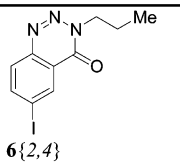
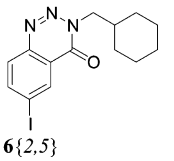
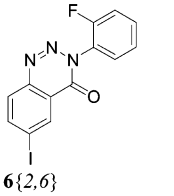
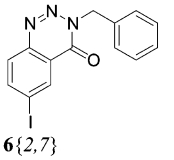
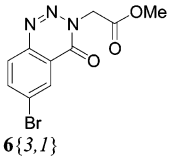
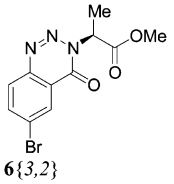
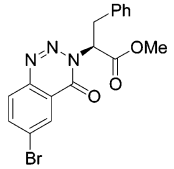
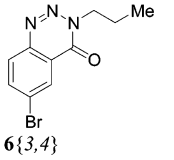
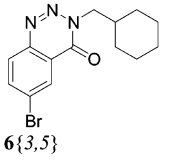
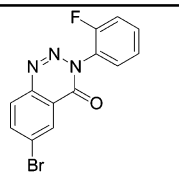
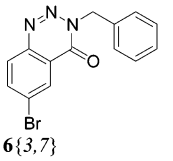
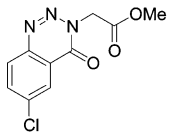
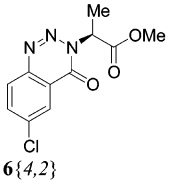
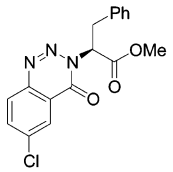
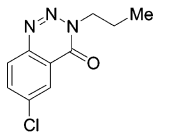
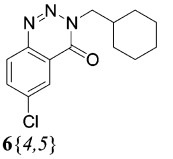
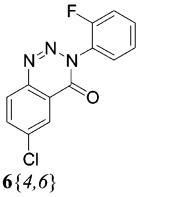
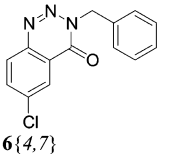
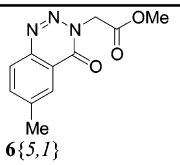
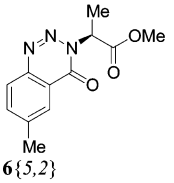
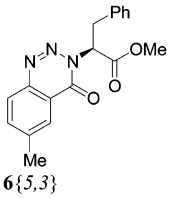
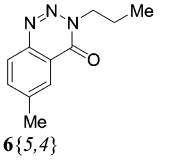
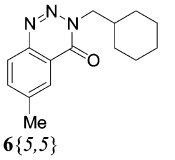
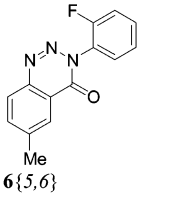
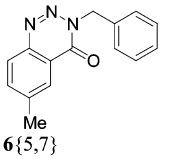
Results and Discussion. Starting from anthranilic acids **1**{*1*−*5*} (Figure 2) and benzylaminomethyl polystyrene (**2**), triazene carboxylate resins **3**{*1*−*5*} were prepared on a 5-g scale. This was achieved by diazotation of the aminobenzoic acids with *iso*-amyl nitrite, coupling to the benzylamine resin **2**, and subsequent treatment with triethylamine according to the synthesis of polymer-bound 4-aminobenzoates[26,27] (Scheme 1). The resins are indefinitely stable at room temperature. The only exception is the iodo-substituted resin **3**{*2*}, which should be stored at low temperatures and in the absence of light.

The triazene carboxylate resins **3**{*1*−*5*} were coupled with different amino acids and amines **4**{*1*−*7*} (Figure 3), employing 2-chloro-1-methylpyridinium iodide as a coupling

* To whom correspondence should be addressed. Braese@ioc.uka.de.
† Kekulé-Institut für Org. Chemie, University Bonn.
‡ BASF AG, Ludwigshafen.
§ Institut für Org. Chemie, University Karlsruhe.

10.1021/cc0340271 CCC: $27.50
Published on Web 12/05/2003

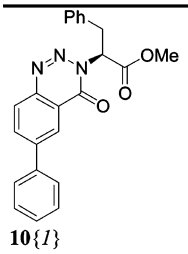
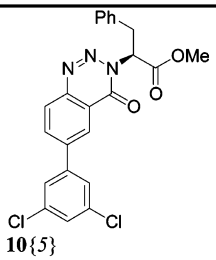
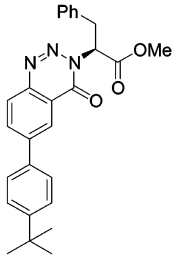
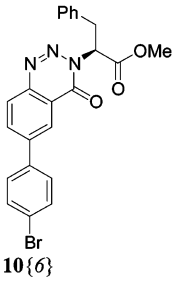
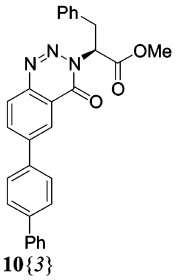
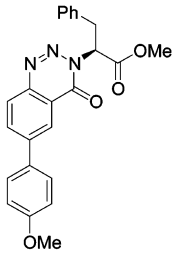
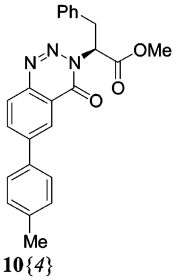
Table 1. Benzotriazinones **6**{*1-5,1-7*} Prepared[a]

	Yield (%)	Purity (%)
 **6**{*1,1*}	38	97
 **6**{*1,2*}	38	95
 **6**{*1,3*}	27	>99
 **6**{*1,4*}	70	93
 **6**{*1,5*}	31	>99
 **6**{*1,6*}	34	90
 **6**{*1,7*}	42	>99
 **6**{*2,1*}	49	>99
 **6**{*2,2*}	45	>99
 **6**{*2,3*}	61	98
 **6**{*2,4*}	70	>99
 **6**{*2,5*}	67	>99
 **6**{*2,6*}	49	82
 **6**{*2,7*}	64	67
 **6**{*3,1*}	56	92
 **6**{*3,2*}	57	>99
 **6**{*3,3*}	45	>99
 **6**{*3,4*}	45	>99
 **6**{*3,5*}	55	>99
 **6**{*3,6*}	68	>99
 **6**{*3,7*}	57	58
 **6**{*4,1*}	56	94
 **6**{*4,2*}	57	93
 **6**{*4,3*}	52	89
 **6**{*4,4*}	81	78
 **6**{*4,5*}	76	99
 **6**{*4,6*}	65	88
 **6**{*4,7*}	65	>99
 **6**{*5,1*}	32	>99
 **6**{*5,2*}	35	>99
 **6**{*5,3*}	33	>99
 **6**{*5,4*}	49	78
 **6**{*5,5*}	27	96
 **6**{*5,6*}	43	76
 **6**{5,7}	63	>99

[a] Purities determined by GC. Identification by $^{1}H/^{13}C$ NMR spectroscopy and MS.

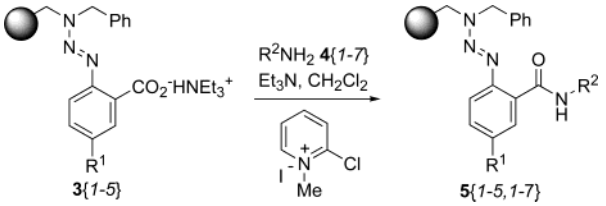
reagent[26,27] (Scheme 2). This reaction has been carried out with different amino acid methyl esters and alkyl and aryl primary amines **4**{*1*−*7*} to introduce another point of diversity. Even amines with a low degree of nucleophilicity, such as 2-fluoroaniline (**4**{*6*}), can be used. In general, hydrochlorides of the corresponding amines are tolerated.

Table 2. Benzotriazinones **10** Prepared[a]

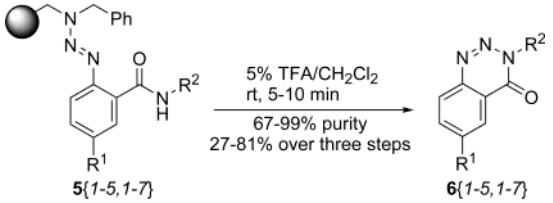
	Yield (%)	Purity (%)		Yield (%)	Purity (%)
 **10**{*1*}	29	66	 **10**{*5*}	11	61
 **10**{*2*}	13	57	 **10**{*6*}	10	53
 **10**{*3*}	17	44	 **10**{*7*}	16	37 (58)[b]
 **10**{*4*}	18	75			

[a] Purities determined by GC. Identification by $^1H/^{13}C$ NMR spectroscopy and MS. [b] Order of coupling is reversed.

Scheme 2. Amide Coupling on Solid Support



Scheme 3. Cleavage-Cyclization of Benzotriazinones 6{*1-5,1-7*}



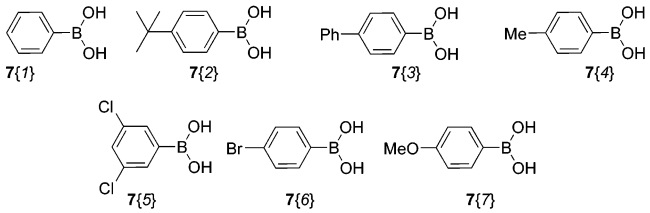
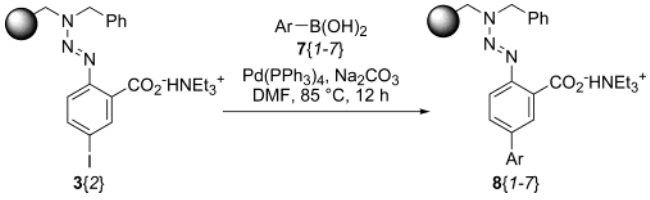


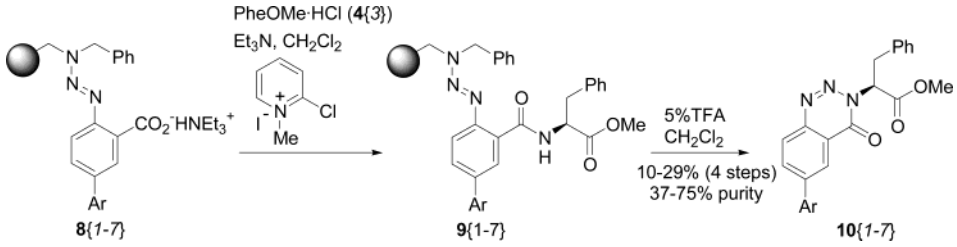
Figure 4. Boronic acids **7**{*1*−*7*} used for library production.

Scheme 4. Suzuki Coupling on a Solid Support

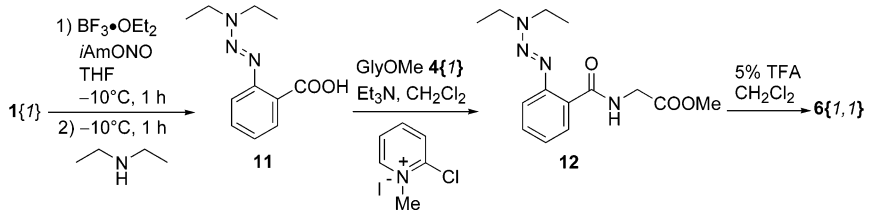


The benzotriazinones, **6**{*1*−*5,1*−*7*}, were obtained in solution by cyclization after acidic cleavage. Thus, after treatment of the triazenes, **5**{*1*−*5,1*−*7*} with 5% TFA in dichloromethane at room temperature, the mixture was filtered, and the solvent was removed by evaporation. The benzotriazinones **6**{*1*−*5,1*−*7*} were isolated in good overall

Scheme 5. Amide and Subsequent Benzotriazinone Formation on Solid Support



Scheme 6. Liquid-Phase Synthesis of Benzotriazinones



yields (27−81% over three steps) and sufficient purities (67−99%) without any further purification (Scheme 3).

The mild cleavage conditions allow the synthesis of various functionalized arenes with halo and ester functionalities (Table 1).

The next modification on the bead was exemplified by a Suzuki coupling[28,29] to introduce an arene functionality in the 4-position. The polymer-bound aryl iodide **3**{*2*} was coupled with arylboronic acids **7**{*1*−*7*} (Figure 4) via Suzuki reaction to form the triazene biaryl resins **8**{*1*−*7*}. Different palladium catalysts, $Pd_2(dba)_3$, $Pd(OAc)_2$, and $Pd(PPh_3)_4$, were tested. Among them, $Pd(PPh_3)_4$ with dimethylformamide (DMF) as the solvent gave the best results after 12 h at 85 °C (Scheme 4). It is remarkable that the carboxylate moiety remains intact during the coupling. However, since the nitrogen content of the resin decreases to 70−80% of its initial value, the counterion may be exchanged.

Finally, the triazene carboxylate resins, **8**{*1*−*7*}, were coupled with phenylalanine methyl ester, **4**{*3*} and finally cleaved from the resin with diluted TFA to provide the benzotriazinones, **10**{*1*−*7*} (Scheme 5) in acceptable yields and purities.

The order of the coupling steps (amide formation, Suzuki coupling) was reversed for one case. Thus, the polymer-bound aryliodide, **3**{*2*}, was first reacted with phenylalanine methyl ester under improved reaction conditions to yield the corresponding amide and subsequently coupled with 4-methoxybenzeneboronic acid via the Suzuki reaction. The purity of the benzotriazinone, **10**{*7*}, obtained after cleavage with TFA, was 58%. In this case, the purity of the corresponding benzotriazinone is slightly higher when the amide formation is made prior to the Suzuki coupling.

In addition, the benzotriazinone **6**{*1,1*} was synthesized in liquid phase to compare the efficiency of the solid-phase approach (Scheme 6). According to the solid-phase procedure, diazotation of anthranilic acid with *iso*-amyl nitrite, and coupling to diethylamine gave the triazene, **11**. The latter was then coupled with glycinemethylester. Finally, the benzotriazinone **6**{*1,1*} was obtained by cyclization after acidic cleavage of **12** in a 62% yield. When the synthesis was carried out in solution, the purification of the intermediates required tedious purification by chromatography, and the final product was contaminated with diethylamine hydrotrifluoroacetate. Sidestepping the handling of the quite carcinogenic triazenes is an additional advantage to the solid-phase procedure.[30]

Conclusion. We have demonstrated a new synthesis for the T1 triazene linker[31] to yield benzotriazinones. Since this moderately sensitive heterocycle is formed on (at) the final step, this synthesis is applicable to various transformations on the arene core. Further applications toward the synthesis of other heterocycles are currently being investigated and will be reported in due course.

Acknowledgment. Our research was supported by the Deutsche Forschungsgemeinschaft (BR1750-2/3), the Fonds der Chemischen Industrie, and by a Marie Curie Fellowship (C. Gil) of the European Community program "Improving Human Research Potential and the Socio-economic Knowledge Base" (Contract No. HPMF-CT-2002-01644). We also thank the BASF AG for the donation of chemicals and for financial support. Special thanks to Sven Steingrüber and Anna Klein for experimental support.

Supporting Information Available. Experimental details and data are available as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Thompson, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 324−337.
(2) War, W. A. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 134−140.
(3) Lou, B. *Drug Discovery Today*, **2001**, *6*, 1288−1294.
(4) Nicolaou, K. C.; Pfefferkorn, J. A. *Biopolymers* **2001**, *60*, 171−193.
(5) Hall, D. G.; Manku, S.; Wang, F. *J. Comb. Chem.* **2001**, *3*, 125−150.
(6) Bräse, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415−2437.
(7) (a) Caliendo, G.; Fiorino, F.; Grieco, P.; Perissutti, E.; Santagada, V.; Severino, B.; Bruni, G.; Romeo, M. R. *Bioorg. Med. Chem.* **2000**, *8*, 533−538. (b) Caliendo, G.; Fiorino, F.; Perissutti, E.; Severino, B.; Gessi, S.; Cattabriga, E.; Borea, P. A.; Santagada, V. *Eur. J. Med. Chem.* **2001**, *36*, 873−886.

(8) Clark, A. S.; Deans, B.; Stevens, M. F. G.; Tisdale, M. J.; Wheelhouse, R. T.; Denny, B. J.; Hartley, J. A. *J. Med. Chem*. **1995**, *38*, 1493−1504.
(9) Norman, M. H.; Rigdon, G. C.; Navas III, F.; Cooper, B. R. *J. Med. Chem*. **1994**, *37*, 2552−2563.
(10) Daidone, G.; Plescia, S.; Raffa, D.; Schillaci, D.; Maggio, B.; Benetollo, F.; Bombieri, G. *Heterocycles* **1996**, *43*, 2385−2396.
(11) Kathawala, F. G. 1,2,3-Benzotriazin-4(3*H*)-ones. U.S. Patent 3,818,001; June 1974.
(12) Wright, W. B.; Tomcufcik, A. S.; Chan, P. S.; Marsico, J. W.; Press, J. B. *J. Med. Chem.* **1987**, *30*, 2277−2283.
(13) Li, B.; Chi-Tung Hsu, A. Herbicidal 3-substituted-phenyl-1,2,3-benzotriazin-4-ones. U.S. Patent 6,303,542 B1; October, 2001.
(14) Schmidt, B. F.; Snyder, E. J.; Carroll, R. M.; Farnsworth, D. W.; Michejda, C. J.; Smith, R. H., Jr. *J. Org. Chem*. **1997**, *62*, 8660−8665.
(15) Raffa, D.; Daidone, G.; Maggio, B.; Schillaci, D.; Plescia, F.; Torta, L. *Farmaco* **2002**, *57*, 183−187.
(16) Lacal, P. M.; D'Atri, S.; Orlando, L.; Bonmassar, E.; Graziani, G. *J. Pharmacol. Exp. Ther*. **1996**, *279*, 416−422.
(17) Serrone, L.; Zeuli, M.; Sega, F.; Cognetti, J. *J. Exp. Clin. Cancer Res.* **2000**, *19*, 21−34.
(18) (a) Newlands, E. S.; Stevens, M. F. G.; Wedge, S. R.; Wheelhouse, R. T.; Brock, C. *Cancer Treat. Rev*. **1997**, *23*, 35−61. (b) Danson, S. J.; Middleton, M. R. *Expert Rev. Anticancer Ther*. **2001**, *1*, 13−19.
(19) Vaughan, K.; Wilman, D. E. V.; Wheelhouse, R. T.; Stevens, M. F. G. *Magn. Reson. Chem.* **2002**, *40*, 300−302.
(20) Horspool, K. R.; Stevens, M. F.; Newton, C. G.; Lunt, E.; Walsh, R. J.; Pedgrift, B. L.; Baig, G. U.; Lavelle, F.; Fizames, C. *J. Med. Chem.* **1990**, *33*, 1393−1399.
(21) Bräse, S.; Lormann, M.; Vogt, H. Scope and Limitation of a Tin Promoted Amidation on Solid Phase: A New Monitoring for the T1 Triazene Linker. Proceedings of ECSOC-4, The Third International Electronic Conference on Synthetic Organic Chemistry, September 1−30, 2000. See also: http://www.mdpi.org/ecsoc-4.htm.
(22) (a) Lormann, M.; Dahmen, S.; Bräse, S. *Tetrahedron Lett.* **2000**, *41*, 3813−3816. (b) Bräse, S.; Enders, D.; Köbberling, J.; Avemaria, F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3413−3415; *Angew. Chem.* **1998**, *110*, 3614−3615.
(23) (a) Bräse, S.; Schroen, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1071−1073. *Angew. Chem.* **1999**, *111*, 1139−1142. (b) de Meijere, A.; Nüske, H.; Es-Sayed, M.; Labahn, T.; Schroen, M.; Bräse, S. *Angew. Chem., Int. Ed*. **1999,** *38*, 3669−3672; *Angew. Chem.* **1999**, *111*, 3881−3884.
(24) Bräse, S.; Dahmen, S.; Heuts, J. *Tetrahedron Lett*. **1999**, *40*, 6201−6203.
(25) Lormann, M. P. E.; Walker, C. H.; Es-Sayed, M.; Bräse, S. *Chem. Comm*. **2002**, 1296−1297.
(26) Schunk, S.; Enders, D. *Org. Lett.* **2000**, *2*, 907−910.
(27) Schunk, S.; Enders, D. *J. Org. Chem*. **2002**, *67*, 8034−8042.
(28) (a) Bräse, S.; Köbberling, J.; Griebenow, N. In *Handbook of Organo-Palladium Chemistry*, Negishi, E.-i., Ed.; Wiley: New York, 2002; pp 3031−3128. (b) Bräse, S.; Kirchhoff, J. H.; Köbberling, J. *Tetrahedron* **2003**, *59*, 885−939.
(29) Franzén, R. *Can. J. Chem*. **2000**, *78*, 957−962.
(30) Kimball, D. B.; Haley, M. M. *Angew. Chem., Int. Ed*. **2002**, *41*, 3338−3351; *Angew. Chem*. **2002**, *114*, 3484−3498.
(31) Bräse, S. *Chim. Oggi* **2000**, *18*, 14−19.

CC0340271