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Access to 1,4-Dihydrobenzo[*e*][1,2,4]triazin-4-yl Derivatives

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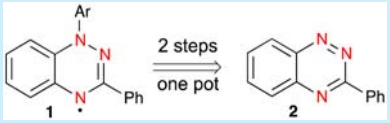
Supporting Information

ABSTRACT: A simple, one-pot method for the preparation of 1-aryl-3-phenyl-1,4-dihydrobenzo[*e*][1,2,4]triazin-4-yl radicals by addition of aryllithium to the readily available 3-phenylbenzo[*e*][1,2,4]triazine followed by aerial oxidation is described. The intermediate anion is also trapped as an *N*-benzyloxycarbonyl derivative and purified prior to deprotection and oxidation to the radical. The method was demonstrated for nine (het)arenes, and the regioselectivity of nucleophilic addition to the benzo[*e*][1,2,4]triazine and trapping of the intermediate anion with electrophiles was assessed computationally.



The electronic structure and the generally easily accessible singly occupied molecular orbital (SOMO) make stable π-delocalized radicals attractive structural elements for advanced functional materials[1−3] such as those for molecular electronics,[4,5] energy storage,[6] solar cells,[7] controlled polymerization,[8,9] and biophysical[10,11] applications. The Blatter radical[12] (**1a**, R = Ar = Ph, Figure 1) and its derivatives,

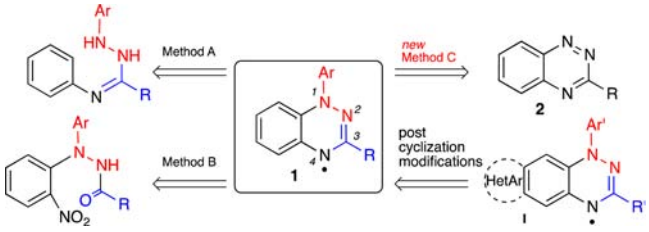


Figure 1. Comparison of two known (A and B) and new (C) methods for construction of the 1,4-dihydrobenzo[*e*][1,2,4]triazin-4-yl skeleton. Molecular fragments derived from arylhydrazine (red) and from carboxylic acid (blue) are color coded.

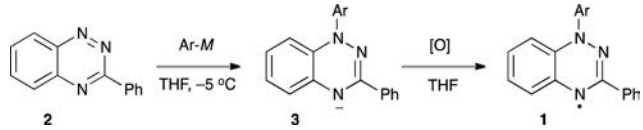
although exceptionally stable with favorable electrochemical properties,[13] were relatively little explored in this context largely due to insufficient accessibility. Only relatively recently,[14] Koutentis undertook the systematic investigation of synthetic methods, which have opened up a broader access to such derivatives. As a consequence, a number of magnetochemical and spectroscopic investigations have already appeared in the literature.[15−20]

During the past decade, the group of Koutentis has developed and optimized two practical strategies to the 1,4-dihydrobenzo[*e*][1,2,4]triazin-4-yl skeleton, all using carboxylic acids RCOOH and hydrazines $ArNHNH_2$ as the key starting materials (Figure 1). The synthesis is a multistep process involving either amidrazones (oxidative 6-π electrocyclization, method A)[14,21−24] or hydrazides (reductive cyclocondensation, method B)[23,25,26] as intermediates and frequently suffers from low reactivity and regioselectivity of *N*-acylation. For these reasons, the overall yields are often low and the methods fail for some substrates. Efficient methods have also been developed for postcyclization ring substitution,[21,22,25−27] functional group transformations,[25] and ring annulation,[16,28,29] which significantly expand the structural variety of the parent 1,4-dihydrobenzo[*e*][1,2,4]trazin-4-yl. While the substituent at the C(3) position is easily modified by the choice of appropriate carboxylic acid RCOOH,[23] the choice of substituent at the N(1) is limited to the synthetically available stable arylhydrazines. Since the N(1) position carries the positive spin density, the ability to manipulate with the N(1) substituent provides an important tool for controlling spin delocalization and, as a consequence, electrochemical properties and intermolecular spin exchange interactions.

Here, we present a one-pot, simple method for preparation of 1,4-dihydrobenzo[*e*][1,2,4]triazin-4-yl radicals **1** by adding organometallic reagents to easily available benzo[*e*][1,2,4]-triazine **2** followed by oxidation of the resulting anion **3** (Scheme 1). The method is potentially general, permits introduction of a substituent at the N(1) position post-cyclization step, and avoids the use of arylhydrazines.

Initially, we investigated the formation of the Blatter radical (**1a**) by addition of PhLi to benzo[*e*][1,2,4]triazine **2** in THF solutions (Scheme 1). We established that the complete consumption of **2** requires a small excess of PhLi (1.1 equiv),

Scheme 1. Preparation of Radical 1 from Benzo[*e*][1,2,4]triazine 2



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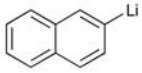
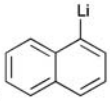
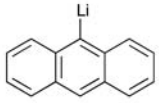
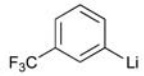
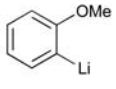
and the addition of PhLi either at −78 or at −5 °C (ice−salt bath) gives essentially the same result (Table 1). The resulting dark solution of anion **3** was exposed to air for several hours, and the generated radical **1a** was isolated by chromatography (neutral or basic Al_2O_3) in 70−78% overall yield. Oxidation of anion **3** took place within 30 min and with essentially the same yield of **1a**, when pure oxygen was used instead of air. Alternatively, addition of aqueous solution of $NaIO_4$ (2 equiv) to the reaction mixture gives radical **1a** in 68% yield after 30 min and small amounts of overoxidation product, presumably a derivative of the benzo[*e*][1,2,4]triazin-7-one.[14] Overall, the new protocol (method C in Figure 1) gives the Blatter radical **1a** in three steps from commercial materials and about 40% yield, which compares to about 25−30% (method A)[14] or 55% (method B) of **1a** obtained in three to four steps from the appropriate acid, amine, and hydrazine.[23]

Table 1. Preparation of 1-Aryl-3-phenyl-1,4-dihydrobenzo[*e*][1,2,4]triazin-4-yls 1 from Benzo[*e*][1,2,4]triazine 2[a]

	Ar–M	yield % of **1** [b]
a	Ph-Li	70–78,[1] 30[2]
	Ph-MgBr(Cl)	46–51
b		54[1], 45[2]
c		63[1]
d		25-26[1], 0[2]
e		32[1]
f		40[2]
g		(63-65)[1,c]
h		56–60[1], 35[2]
i		32–36[2]

[a]According to Scheme 1. Typical procedures: (1) ArLi prepared from 0.65 mmol of the appropriate ArBr and 1.2 mmol of *t*-BuLi in THF (5 mL) was added to 0.5 mmol of **2** in THF (2 mL) at −5 °C; (2) *t*-BuLi (1.43 mmol) was added to a solution of ArBr (0.65 mmol) and **2** (0.5 mmol) in THF (2 mL) at −78 °C. [b]Yield after chromatography. [c]Yield after crystallization.

Two modifications of the new method were briefly investigated. Thus, replacement of PhLi with PhMgCl in THF and using air as the oxidant gave **1a** in lower yields (ca. 50%, Table 1). In the second modification, we generated PhLi *in situ* from PhBr and *t*-BuLi at −78 °C.[30] In this case, the yield of the Blatter radical **1a** was only 30%.

The new method of synthesizing 1,4-dihydrobenzo[*e*]-[1,2,4]triazin-4-yl radicals was extended to other aryllithium derivatives using air as the oxidant for the intermediate anion **3**, and the results are shown in Table 1. To ensure complete consumption of **2**, the aryllithium derivatives were generated using 1.5 equiv of the appropriate bromoarene. Thus, reactions of 2-naphthyllithium and 1-naphthyllithium with **2** gave the corresponding radicals **1b** and **1c** in 54% and 63% isolated yields, respectively. Larger aryllithium derivatives, 9-anthracenyllithium and 1-pyrenyllithium, with **2** gave the corresponding radicals **1d** and **1e** in lower yields, 26% and 32%, respectively, which may be related to the sterically congested positions. The "*in situ*" method was less effective in generation of radical **1b**, and in the case of 9-bromoanthracene no radical **1d** was isolated. Two examples of substituted phenyllithium derivative were investigated. Thus, aryllithium reagents, generated from 1-bromo-3-trifluoromethybenzene and 2-bromoanisole, gave the expected radicals **1f** and **1g**, respectively, in good yields. The methoxyphenyl derivative **1g** showed low stability during chromatographic separation and was isolated by direct crystallization from the reaction mixture.

Finally two pyridine derivatives, **1h** and **1i**, were prepared from benzo[*e*][1,2,4]triazine **2**. The former radical was obtained in about 60% yield using the pre-prepared 2-pyridyllithium or 35% yield following the "*in situ*" method. This compares to about 45% of **1h** obtained in three steps from benzoic acid, 2-pyridylhydrazine, and 2-fluoronitrobenzene according to method B (Figure 1).[23] The synthesis of the 3-pyridyl isomer **1i** could not be accomplished using the preprepared 3-pyridyllithium due to its low yield and low stability.[31] Derivative **1i** was, however, prepared in 32−36% yield using the "*in situ*" method.

The low stability of the 1-(2-methoxyphenyl) derivative **1g** observed during its isolation is presumably due to the low oxidation potential of the 1,4-dihydrobenzo[*e*][1,2,4]triazin-1-yl ring resulting from the presence of an electron-donating substituent. In fact, the electron-donating ability of the N(1) substituent, 2-$MeOC_6H_4$ > C_6H_5 > 2-NC_5H_4, correlates with the observed stability of the radicals: **1h** can be purified on SiO_2 and alumina, **1a** is unstable on SiO_2 but alumina works well, and **1g** is unstable on either solid support.[32] A comparison of redox potentials for the three derivatives with electronically different substituents shows that replacement of the Ph substituent at the N(1) position in **1a** with 2-pyridyl in **1h** increases the $E_{1/2}^{0/+1}$ by 0.06 V (or 0.14 V in ref 23), while replacement with the 2-methoxyphenyl in **1g** lowers the oxidation potential by 0.04 V (Figure 2).[33] The reduction potentials $E_{1/2}^{-1/0}$ also follow the same order (Figure 2) and the lowest is measured for the 2-methoxyphenyl derivative **1g** ($E_{1/2}^{-1/0}$ = −1.01 V), while the highest for the 2-pyridyl **1h** ($E_{1/2}^{-1/0}$ = −0.76 V).

To avoid purification of oxidatively fragile radicals, such as **1g**, we focused on an alternative route in which isolation from the reaction mixture of the desired nucleophilic adduct to **2** takes place before the radical generation. Thus, treatment of anion **3a** with BnBr gave the known[34] 4-benzyl derivative ***4a-4*** as the sole product isolated by chromatography in 43% yield (Scheme 2). Unfortunately, ***4a-4*** showed limited stability on solid support, and attempts at reductive removal of the benzyl group using standard conditions (H_2 up to 55 psi, 10% Pd/C,

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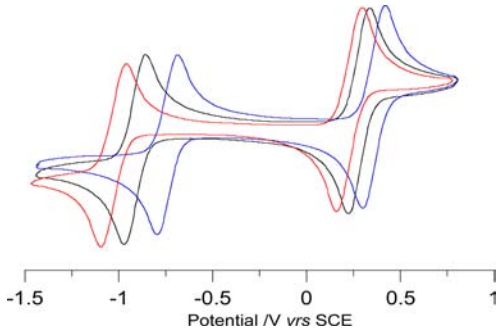
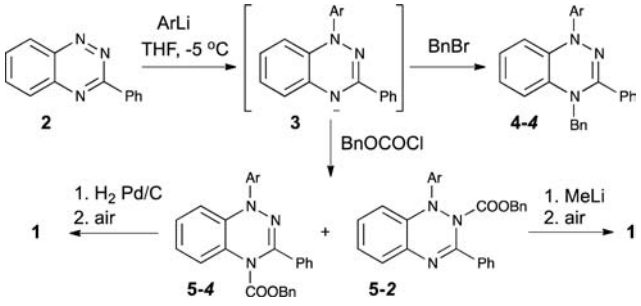


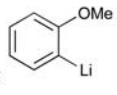
Figure 2. Cyclic voltammograms for 1-phenyl (**1a**, black), 1-(2-methoxyphenyl) (**1g**, red), and 1-(2-pyridyl) (**1h**, blue) 1,4-dihydrobenzo[*e*][1,2,4]triazin-4-yls (0.5 mM) in CH_2Cl_2 $[n\text{-}Bu_4N]^+[PF_6]^-$ (50 mM), ca. 20 °C, 50 mV s^{-1}, glassy carbon electrode.

Scheme 2. Preparation of Radical 1 from Benzo[*e*][1,2,4]triazine 2 via the Protection/Deprotection Route



rt) failed. Therefore, we focused on *N*-acyl derivatives, expecting better behavior. Thus, treatment of the anion **3a** with BnOCOCl (CBzCl) gave two isomers **5a-2** and **5a-4** in about 30% yield each (Table 2),[35] which were separated by

Table 2. Preparation of 1-Aryl-3-phenyl-1,4-dihydrobenzo[*e*][1,2,4]triazin-4-yls 1 through the Benzyloxycarbonyl (CBz) Protection/Deprotection Route[a]

R–Li	yield **2** → **5-2** + **5-4** [1)]	**5** → **1**
a Ph-Li	29 % 30 % H_2 Method:[2)]	68 %[b] and 63 %[c]
	MeLi Method:[3)]	51 %[c]
g 	7 % 42 % H_2 Method:[2)]	82 %[c]

[a]According to Scheme 2. Typical procedures: (1) 2.2 mmol of ArLi was added to 2 mmol of **2** in THF (6 mL) at −5 °C followed by CBzCl. (2) CBz-protected derivative was hydrogenated (10% Pd/C, 5 mol %) in an EtOH/THF solution and oxidized with air. (3) 3 equiv of MeLi was added to **5-2** in THF at −5 °C, stirred, and oxidized with air. [b]From the N(2) isomer. [c]From the N(4) isomer.

SiO_2 chromatography from small amounts of radical **1a** (14% yield). Removal of the CBz protecting group was accomplished quantitatively under standard conditions (H_2 1 atm, 10% Pd/C in EtOH/THF; Table 2); interestingly, the reaction was faster for the 2-isomer (**5a-2**).

After the catalyst was filtered, the resulting solution was exposed to air, and the resulting radical **1a**, formed as the only product by TLC, was isolated quantitatively by evaporation of the solution. The CBz protective group was also removed by treatment of **5a-2** with 3 equiv of MeLi in THF and exposure of the solution to air. Radical **1a** was formed as the sole product (by TLC) and isolated in 51% yield after recrystallization.

The developed two-step protocol was subsequently applied for the preparation of **1g**. Thus, the CBz-protected derivatives **5g-2** and **5g-4** were obtained in 7% and 42% yields,[35] respectively, by column chromatography. Subsequent catalytic deprotection of one of the isomers, **5g-2**, and controlled aerial oxidation gave **1g** in 82% yield after recrystallization.

From a mechanistic point of view, the reaction involves the addition of the aryl anion to the LUMO of the benzo[*e*]-[1,2,4]triazine **2** and the formation of a delocalized amidinyl-type anion **3**. Computational results suggest similar LUMO density on the nitrogen atoms (Figure 3), although condensed

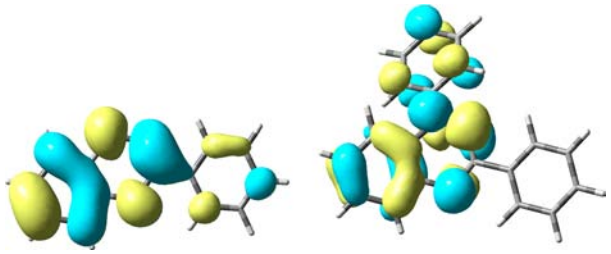


Figure 3. M062x/6-31+G(2d,p)-derived LUMO contour for 3-phenylbenzo[*e*][1,2,4]triazine (**2**, E = −1.85 eV, left) and HOMO for anion **3** (E = −4.59 eV, right) in THF dielectric medium.

electronic Fukui functions[36,37] clearly indicate the highest electrophilicity (either total f^+ or pi f_π^+) of the N(1) position in the triazinyl ring (Table 3).[33] This electronic preference for the

Table 3. Fukui Electrophilicity Indices for Selected Atoms in 3-Phenylbenzo[*e*][1,2,4]triazine (2) and Nucleophilicity Indices for Selected Atoms in Anion 3

	2		**3**	
atom	f^+	f_π^+	f^-	f_π^-
N(1)	0.22	0.24		
N(2)	0.11	0.11	0.14	0.153
C(3)	0.04	0.05		
N(4)	0.17	0.18	0.19	0.145

regioselectivity of the nucleophilic attack is also favored thermodynamically. DFT calculations in THF dielectric medium show that the addition of the Ph^- to the N(1) position is preferred by ΔH = 8.9 kcal mol^{-1} over addition to the N(4) position or ΔH = 11.3 kcal mol^{-1} over the attack on the N(2) atom. Similar analysis for anion **3a** using the more appropriate Fukui π functions (f_π^- in Table 3) shows a rather weak preference of the electrophilic attack on the N(2) atom, which is reflected in the formation of a mixture of the two isomers (Table 2).

In summary, the presented method permits the introduction of a (het)aryl substituent at the N(1) position at the post cyclization step and avoids using arylhydrazines; it shifts the dependence of the synthesis from the availability of the hydrazines to the accessibility of [1,2,4]triazines[38] and the efficiency of the generation of aryllithium reagents. The new method appears to be general, although the regioselectivity of anion addition may depend on the structure of the [1,2,4]-triazine; this, in turn, could be assessed computationally using the Fukui functions. Overall, the new procedure for making 1,4-

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dihydrobenzo[*e*][1,2,4]triazin-4-yl complements the existing methods and significantly increases the design flexibility and structural variety of the 1,4-dihydro[1,2,4]triazin-4-yl radicals in general, making them available for further transformations and incorporation into more complex architectures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03528.

Preparative and analytical details, EPR and NMR spectra, electrochemical data, and computational results (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Grzegorz Mlostoń on the occasion of his 65th birthday.

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(32) According to a reviewer's suggestion, passivation of SiO_2 with water increases the stability of benzo[*e*][1,2,4]triazinyls.

(33) For details, see the Supporting Information.

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(35) The assignment of the two isomers was based on the XRD results: Obijalska, E.; Domagała, S.; Kaszyński, P.; Woźniak, K. To be published. This work is consistent with the observed diastereotopic splitting of the CH_2 protons of the **5-2** isomer. The ratio of the two isomers varies from experiment to experiment and possibly depends on the quality of the electrophile.

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