Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 5228

www.rsc.org/obc

PAPER

1,3-Diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one: Selected Chemistry at the C-6, C-7 and C-8 Positions†

Panayiotis A. Koutentis,* Harry Krassos and Daniele Lo Re

Received 15th March 2011, Accepted 13th April 2011
DOI: 10.1039/c1ob05410d

1,3-Diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**6**) reacts with tetracyanoethylene (TCNE) or tetracyanoethylene oxide (TCNEO) to give the deep green 2-[1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-ylidene]propanedinitrile (**11**) in 17 and 15% yields, respectively. Nucleophiles such as amines, alkoxides, thiols and Grignard reagents all reacted with the 1,3-diphenylbenzotriazinone **6** regioselectively at C-6, while halogenating agents reacted exclusively at C-8. Furthermore, 8-iodo-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**32**) undergoes palladium-catalysed Suzuki–Miyaura and Stille coupling reactions to give 8-aryl- or heteroaryl-substituted benzotriazinones. By combining both the C-6 and C-8 chemistries 1,3,6,8-tetraphenylbenzo[*e*]-[1,2,4]triazin-7(1*H*)-one (**42**) and 1,3-diphenyl-6,8-di(thien-2-yl)-benzo[*e*][1,2,4]triazin-7(1*H*)-one (**43**) can be prepared. All new compounds are fully characterized.

1. Introduction

1,2,4-Triazines are a well know class of heterocycle, several of which are particularly important as agrochemicals.[1] Commercial herbicides include 4-amino-6-*tert*-butyl-3-(methylthio)-1,2,4-triazin-5(4*H*)-one (**1a**) (Metribuzin or Sencor®) and 4-amino-3-methyl-6-phenyl-1,2,4-triazin-5(4*H*)-one (**1b**) (Metamitron or Goltix®).[2] Several benzo-fused 1,2,4-triazines also show interesting properties: 4-hydroxy-1-oxido-1,2,4-benzotriazin-1-ium-3-imine (**2**) (Tirapazamine) is a bioreductive prodrug which attacks chemo- and radio-resistant hypoxic tumor cells.[3] Furthermore, 1,2,4-benzotriazinyls are stable organic radicals (*e.g.*, Blatter's radical **3**),[4] which display a range of magnetic behaviours,[5] and were the inspiration behind the preparation of the unusual zwitterionic biscyanine tetraphenylhexaazaanthracene **4** (TPHA)[6] (Fig. 1). The synthesis and chemistry of 1,2,4-triazines and their benzo derivatives has been extensively reviewed.[7]

We recently developed a high yielding route to a potentially useful 1,2,4-benzotriazine scaffold, 1,3-diphenylbenzo[*e*]-[1,2,4]triazin-7(1*H*)-one (**6**) from readily available Blatter's radical **3** or directly from an amidrazone precursor **5** *via* oxidation using either MnO_2 (20 equiv., 8 d) or $KMnO_4$ (10 equiv., 3 d) in 68 and 82% yields, respectively.[4c] The benzotriazinone **6**, which is a deep purple in color [λ_{max}(DCM) 544 nm (log ε 3.82)], possesses a quinonimine functionality that renders it redox active (Scheme 1).

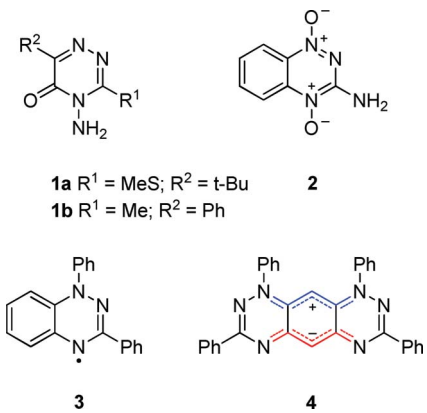
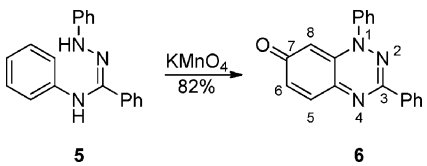


Fig. 1 Some 1,2,4-triazines that display either important biological and/or physical properties.



Scheme 1 Oxidation of amidrazone **5** to give benzotriazinone **6**.

Planar polycyclic quinones can intercalate DNA by binding strongly between the base pairs through hydrogen bond and π interactions.[8] Several polycyclic quinonimines have interesting anticancer[9] and antibiotic activities.[10] For example, Actinomycin D (**7**), isolated from *Streptomyces parvulus*,[9c] is a strong antitumor agent but has limited use due to side effects such as myelosuppression and cardiotoxicity; the synthetic 7-(benzylamino)-1,3,4,8-tetrahydropyrrolo[4,3,2-*de*]quinolin-8(1*H*)-one (**8**, BA-TPQ) is

Department of Chemistry, University of Cyprus, P.O. Box 20537, 1678 Nicosia, Cyprus. E-mail: koutenti@ucy.ac.cy

† Electronic supplementary information (ESI) available: Experimental procedures, analytical and spectroscopic data for all new compounds. ^{1}H and ^{13}C NMR spectra of all new compounds, and computational data for the benzotriazinone **6** are provided. See DOI: 10.1039/c1ob05410d

active against a variety of human cancer cell lines through multiple mechanisms of action (inhibition of MDM2 oncoprotein, induction of DNA damage response, and induction of endoplasmic reticulum stress).[11] In addition, several polycyclic quinonimines such as Endophenazine B (**9**) [λ_{max}(MeOH) 516 nm (log ε 3.89)], isolated from *Streptomyces anulatus*[12] and 10-phenylphenazin-2(10*H*)-one (**10**, aposafranone),[13] are highly colored. The latter have been investigated as dyes and incorporated in organic photovoltaic devices[14] (Fig. 2).

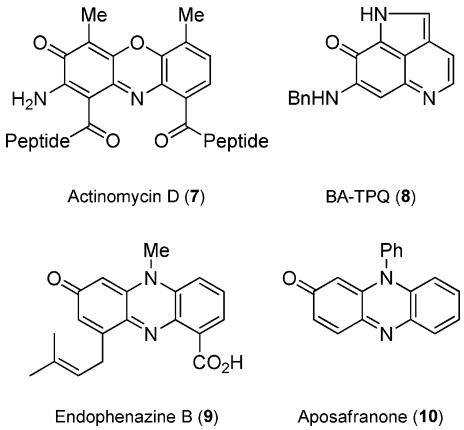


Fig. 2 Selected natural and synthetic quinonimines.

In light of the above, we have been investigating the chemistry of the readily accessible benzotriazinone **6** to determine its potential as a new heterocyclic quinonimine scaffold. Below we report the preparation of the highly colored ylidenemalononitrile and the regioselective nucleophilic and electrophilic substitution reactions of benzotriazinone **6** which occur at C-6 and C-8, respectively.

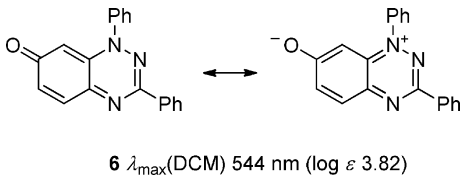
2. Results and discussion

Benzotriazinone **6** was first identified by Huisgen *et al.*,[15] in 1969 as a minor byproduct during the preparation of 1,4-dihydro-7-methoxy-1,3-diphenyl-1,2,4-benzotriazin-4-yl from diphenylnitrilimine and 4-methoxyphenyliminotriphenylphosphorane. Later, in 1980, Neugebauer *et al.*[16] attempted a direct synthesis of benzotriazinone **6** by treating 1,4-dihydro-1,3-diphenyl-1,2,4-benzotriazinyl (**3**) (Blatter's radical) with oxygen in the presence of active charcoal. Both routes, however, were very low yielding, preventing the study of this quinonimine. In light of our ability to access benzotriazinone **6** in multigram quantities we proceeded to study the chemistry of this potentially useful quinonimine.[4c]

2.1. Preparation of the (benzotriazinylidene)malononitrile 11

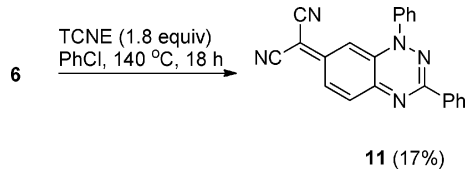
1,3-Diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**6**) has a deep purple color presumably owing to a strong contribution of a zwitterionic resonance form (Scheme 2). In an attempt to build a "chromophore" with a longer wavelength absorption possibly extending into the near infrared we considered the synthesis of the ylidenemalononitrile **11**. Furthermore, ylidenemalononitriles are also useful scaffolds for the preparation of a wide range of other heteroarenes.[17]

However, all attempts to condense malononitrile with the benzotriazinone **6**, led to complex highly colored reaction mixtures, from



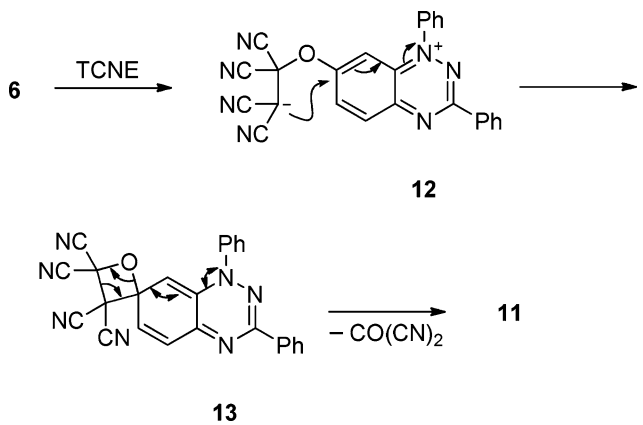
Scheme 2 Important resonance forms of quinonimine **6**.

which no stable product could be isolated. As such, alternative strategies were followed that included treating the benzotriazinone **6** with other dicyanomethylene sources.[18] Fortunately, a PhCl solution of benzotriazinone **6** treated with tetracyanoethylene (TCNE) at *ca.* 140 °C gave the desired 2-[1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-ylidene]propanedinitrile (**11**) in low yield (17%) (Scheme 3).



Scheme 3 Synthesis of the ylidenemalononitrile **11**.

Recrystallisation of the ylidenemalononitrile **11** afforded dark green plates mp 306–311 °C ($CHCl_3$) that gave a deep blue-green solution λ_{max}(DCM) 702 nm (log ε 3.08) supporting a highly conjugated and possibly charge separated system. Attempts to improve the yield of this reaction by using additional equivalents of TCNE or prolonged reaction times led to a drop in yield. Replacing TCNE for tetracyanoethylene oxide (TCNEO) led to similar yields (15%). In light of these low yields, further chemistry on the ylidenemalononitrile **11** was not considered worthwhile. Nevertheless, the failure to condense malononitrile onto the carbonyl at C-7 and the lack of any identifiable ν(C═O) stretch in the IR spectrum of quinonimine **6** supported the strong contribution of the charge separated resonance form. As such it was unlikely that TCNE reacts with benzotriazinone *via* a concerted 2 + 2 cycloaddition but rather the benzotriazinone **6** added to the highly electrophilic TCNE in a stepwise manner to give first the zwitterion **12**, which subsequently cyclises to afford the spirocyclic oxetane **13** that eliminated unstable carbonyl cyanide to give the ylidene **11** (Scheme 4).



Scheme 4 Plausible mechanism for the formation of the ylidenemalononitrile **11**.

In addition, benzotriazinone **6** was reacted with PCl_5 (1 equiv.) in $POCl_3$ at *ca.* 20 °C to give presumably the 7-chloro-1,3-diphenylbenzo[*e*][1,2,4]triazin-1-ium *in situ.* Subsequent treatment of this cation with aniline (3 equiv.) gave a deep blue compound that gave a mass spectrum molecular ion peak of *m*/*z* 374 Da, potentially corresponding to *N*-(1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-ylidene)benzenamine. However, after chromatographic purification, the ^{1}H NMR was complex, indicating mixtures that could not be separated. This work remains on going.

2.2. Regioselective nucleophilic addition

Further chemistry of the benzotriazinone **6** was discovered when an ethanolic solution of Blatter's radical **3** treated with MnO_2 gave not only the expected benzotriazinone **6** (14%) but also a deep red colored [λ_{max}(DCM) 520 nm (log ε 2.83)] ethoxy-substituted benzotriazinone **14** in low yield (15%). ^{1}H NMR spectroscopy of the ethoxybenzotriazinone **14** identified two clear singlets at δ_H 7.01 and 6.31 ppm that tentatively corresponded to the H-5 and H-8 hydrogens, respectively. These assignments were based on the anticipated shielding effects of the N-1 phenyl which should lead to H-8 appearing more up-field than H-5[19] and supported the structure to be the 6-ethoxy-substituted benzotriazinone **14** and not the isomeric 5-ethoxy-substituted analogue. Additional support for this tentative assignment came from a comparison of the structurally related aposafranone **10** which suffers regioselective nucleophilic addition at C-3,[10a] and electrophilic substitution at C-1 (Fig. 3).[20] As such, we initiated the "semi-independent" synthesis of the red 6-ethoxybenzotriazinone **14** followed by a broader investigation of regioselective nucleophilic substitution involving N, S and C nucleophiles.

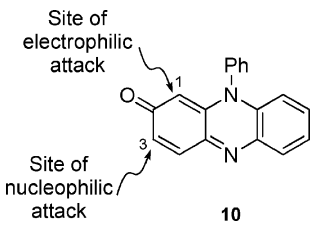
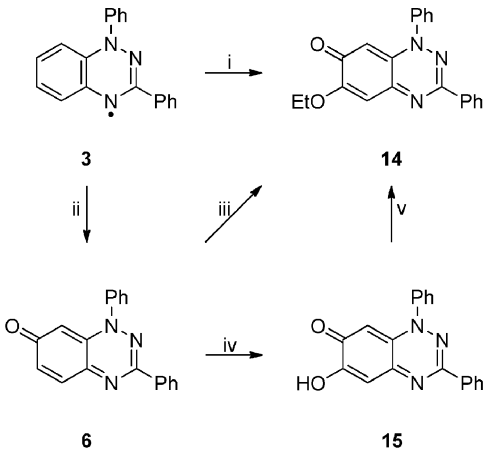


Fig. 3 Regioselectivity of aposafranone **10**.

Treating benzotriazinone **6** with 2 N EtONa (2 equiv.) in EtOH at *ca.* 20 °C or at *ca.* 78 °C gave only intractable material (baseline on TLC); however, treatment in EtOH with Hünig's base (20 equiv.) at *ca.* 78 °C gave 6-ethoxybenzotriazinone **14** in moderate yield (44%) identical to that described above. The compound can also be prepared in somewhat higher yield *via* a two-step synthesis. Treating benzotriazinone **6** with KOH (3 equiv.) in THF/H_2O (4 : 1) at *ca.* 90 °C for 18 h gave 6-hydroxy-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**15**), in good yield (92%) without the need for chromatographic isolation. Subsequent *O*-ethylation using EtI (4 equiv.) and Hünig's base (8 equiv.) in refluxing MeCN for 2 d gave the identical 6-ethoxybenzotriazinone **14** in 71% yield (Scheme 5).

In light of the observed regioselectivity, additional nucleophiles were investigated: attempts to prepare the 6-phenoxybenzotriazinone failed since treatment of benzotriazinone **6** with PhONa (1 equiv.) or PhOH/NaH (5 equiv.) in THF gave only an intractable baseline material. Alkyl, benzyl



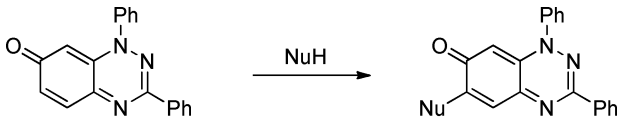
Reagents and conditions: i) EtOH, MnO_2 (5 equiv), reflux, 36 h, 15%; ii) DCM, MnO_2 (10 equiv), RT, 7 d, 82%; iii) EtOH, i-Pr_2NEt (20 equiv), reflux, 2 d, 44%; iv), THF/H_2O 4:1, KOH (3 equiv), reflux, 18 h, 92%; v) EtI (4 equiv), i-Pr_2NEt (8 equiv), MeCN, reflux, 19 h, 71%.

Scheme 5 Preparation of 6-ethoxybenzotriazinone **14**.

and phenyl mercaptans reacted readily with the benzotriazinone **6** to give the corresponding 6-substituted analogues **16–18** (Table 1, entries 3–5). A wide range of nitrogen and carbon nucleophiles could also be introduced with ease (Table 1). Monoalkyl amino derivative 6-ethylaminobenzotriazinone **20** (entry 7), was obtained in good yield (72%) using excess 2 N ethylamine in THF heated to reflux, while 6-anilinobenzotriazinone **21** (entry 8) was prepared in 67% yield using aniline (1.5 equiv.) in the presence of Hünig's base (1.5 equiv.) in EtOH heated to reflux. In both cases the products could be isolated without the need for chromatography. Several 6-dialkylamino- or 6-alkylarylamino-substituted benzotriazinones **23–27** were prepared in high yields (81–99%) using neat amine as solvent (entries 10–14). However, secondary dialkylamines that are more costly can also be used in less quantity (2 equiv.) using THF as solvent (entry 9). More interestingly, powerful carbon nucleophiles as phenyl- and thien-2-ylmagnesium bromide (entries 15 and 16) also gave the 6-phenyl and 6-thien-2-yl benzotriazinones **28** and **29** in 82 and 63% yields, respectively (Table 1). Both 1,2- and 1,4-additions of Grignards to 1,4-quinones are known,[21] but the high isolated yields of 6-substituted benzotriazinones further supported the hypothesis of a strong contribution of the charge separated resonance form.

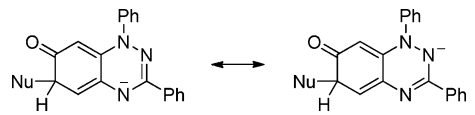
The regioselectivity observed was not altogether surprising, although the C-5, C-6 and C-8 positions are all β to either imine or carbonyl functionality, making them potentially active towards nucleophilic attack. However, attack at C-5 would leave an anion that was stabilized only by the carbonyl oxygen while attack at either C-6 or C-8 left intermediates that had the anion doubly stabilized by both the triazine nitrogens N-2 and N-4. The C-6 position was preferred over the C-8 since the latter was strongly influenced by the electron releasing enamine-like triazine nitrogen N-1 and was more sterically crowded owing to the N-1 phenyl substituent (Scheme 6). The regioselectivity was also supported by computational studies (see the ESI†) which indicated the LUMO of the benzotriazinone **6** had considerable orbital density at C-6.

Table 1 Regioselective nucleophilic addition reactions of benzotriazinone **6**



6 **14-29**

Entry	NuH (equiv.)	*i*-Pr_2NEt (equiv.)	Solvent	Temp. (°C)	Time (h)	Yields (%)
1	EtOH	20	EtOH	78	48	**14** (44)
2	KOH (3)	—	THF/H_2O 4 : 1	90	18	**15** (92)
3	*i*-BuSH (3)	1.1	THF	20	0.50	**16** (91)
4	BnSH (3)	1.1	THF	20	0.30	**17** (83)
5	PhSH (3)	1.1	EtOH	78	0.50	**18** (100)
6	NH_3(g)	—	DMF	120	12	**19** (64)
7	$EtNH_2$ (20)	—	THF	20	2	**20** (72)
8	$PhNH_2$ (1.5)	1.5	EtOH	78	12	**21** (67)
9	4-Ph-piperazine (2)	—	THF	20	9	**22** (91)
10	PhNHMe	—	neat	80	72	**23** (93)
11	*N*-Me-cyclohexylamine	—	neat	20	20	**24** (87)
12	Piperidine	—	neat	20	0.17	**25** (99)
13	1,2,3,4-Tetrahydroisoquinoline	—	neat	50	0.50	**26** (81)
14	4-Me-piperazine	—	neat	50	0.25	**27** (84)
15	PhMgBr (4)	—	THF	20	12	**28** (82)
16	Thien-2-ylMgBr (4)	—	THF	20	18	**29** (63)



Scheme 6 Resonance structures supporting the regioselective addition of nucleophiles to C-6.

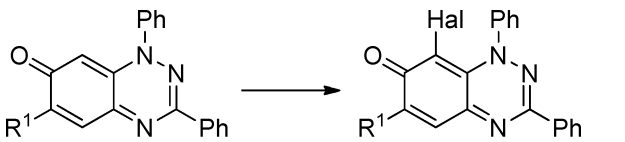
It is worth noting that the "substitution" at C-6 is in reality an addition reaction and that oxidation is needed to transform the adduct back into the quinonimine form *via* a formal loss of hydride. Presumably this step is catalysed by oxygen present in the reaction mixture. Attempts to carry out the reaction of benzotriazinone **6** with piperidine in either dry deoxygenated THF under an argon atmosphere or in non-deoxygenated THF under air atmosphere at *ca.* 20 °C gave the expected 6-piperidinobenzotriazinone **25** rapidly (3 h) and in high yield (93%), which indicated that either the oxidation step was very facile and required only traces of molecular oxygen or that another species present in the reaction mixture was responsible for the oxidation.

Another interesting feature of substitution at C-6 was the blue shifts observed in the UV/vis spectra on introducing strongly donating amino or oxy groups. The λ_{max} of benzotriazinone **6** shifted from 544 nm to 430–504 nm on introduction of an amino group at C-6 and to 508–520 nm on introduction of hydroxyl or ethoxy groups, as such all these compounds were colored deep red. Introduction of alkyl or aryl thiols or phenyl and thien-2-yl substituents led to a red shift in the UV/vis spectra and the compounds were either deep purple or brown in color. Presumably, the electron releasing groups undermined the contribution of the charge separated zwitterionic resonance form.

2.3. Electrophilic regioselective substitution and Pd coupling on C-8

Aposafranone chemistry suggests that the benzotriazinone **6** should also react with electrophiles in a very regioselective manner.[20] Reaction of benzotriazinone **6** with different sources of electrophiles such NIS, NBS, Br_2 and NCS in DCM at *ca.* 20 °C afforded the desired 8-halobenzotriazinones **30–32** in quantitative yields (Table 2, entries 1–4). In addition, regioselective halogenation of 6-substituted benzotriazinones also occurred in good yield (Table 2, entries 5 and 6).

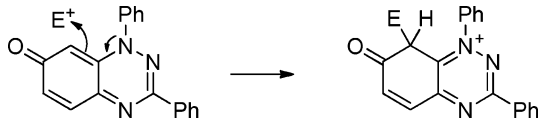
Table 2 C-8 Halogenation of benzotriazinone **6** in DCM at RT



6, 28, 29 **30-34**

Entry	R^1	Reagent (equiv.)	Time (h)	Hal	Yields (%)
1	H	NCS(1.1)	12	Cl	**30** (99)
2	H	NBS(5)	12	Br	**31** (100)
3	H	Br_2 (2)	0.5	Br	**31** (100)
4	H	NIS (5)	12	I	**32** (100)
5	Ph	NIS (5)	12	I	**33** (76)
6	Thien-2-yl	NIS (5)	12	I	**34** (67)

The selectivity of substitution at C-8 was supported by the loss of the up-field H-8 signal in the ^{1}H NMR spectrum. Interestingly, halogenation at C-8 also led to significant red shifts in the UV/vis spectroscopy affording in all cases deep blue colored products (568–602 nm). Furthermore, understanding the regioselectivity of the electrophilic substitution was less complex than that of the nucleophilic substitution since the C-8 position was enamine-like with respect to the N-1 position. The triazine N-1 nitrogen releases electron density to both the C-8 and the carbonyl oxygen. However, only substitution at C-8 readily provides the opportunity for the loss of the C-8 proton to neutralize the intermediate triazinium cation (Scheme 7). The rationale is presumably very similar to



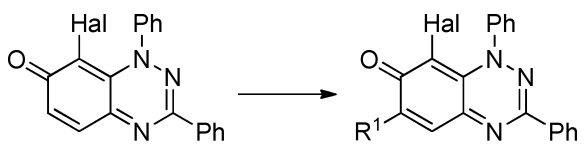
Scheme 7 Rationale for regioselective addition of electrophiles at C-8.

that which governs the analogous electrophilic substitution of aposafranones at C-1. The regioselectivity was also supported by computational studies (see the ESI†) which indicated the HOMO of the benzotriazinone **6** had considerable orbital density at C-8.

With a good leaving group at C-8 we then investigated the reactivity of the 8-bromo- and 8-iodobenzotriazinones **31** and **32** towards nucleophiles (Table 3). In all cases (entries 1–3) substitution occurred regioselectively at C-6 and displacement of the halogen at C-8 was not observed. Nevertheless, the reactions between the 8-iodobenzotriazinone **32** and the Grignard reagents (entries 1 and 2) gave slightly more complex reactions and the desired product can be obtained only in low to moderate yields, while the reaction with 8-bromobenzotriazinone **31** with the 'softer' pyrrolidine nucleophile gave the desired compound **35** in good yield (entry 3).

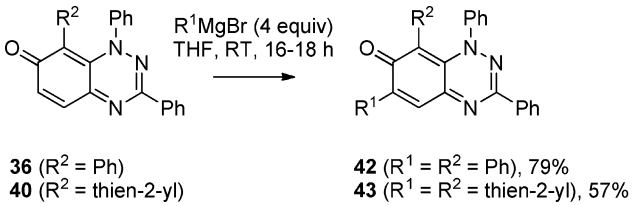
Despite the preference of nucleophiles to react regioselectively at C-6 even in the presence of a potentially reactive halogen at C-8, we considered arylation of the C-8 position by involving Suzuki–Miyaura or Stille coupling chemistry (Table 4). The Suzuki–Miyaura reaction of 8-chlorobenzotriazinone **30** [Pd(dppf)Cl_2·DCM (10 mol%), $PhB(OH)_2$ (2 equiv.), K_2CO_3 (2 equiv.) dioxane/water 3 : 1, at reflux] gave no reaction while 8-bromobenzotriazinone **31** only gave 1,3,8-triphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**36**) in a moderate yield (51%) and with a considerable amount (34%) of unreacted bromobenzotriazinone **31**. Fortunately, 8-iodobenzotriazinone **32** under similar conditions gave 1,3,8-triphenylbenzotriazinonone **36** in 78% yield (Table 4, entry 1). In a similar manner, 8-(4-chlorophenyl)- and 8-(3-methoxyphenyl)benzotriazinones **37** and **38** could be prepared in 91 and 96% yield, respectively. Unfortunately, the use of either 2-bromophenyl- or 2-chloro-4-(trifluoromethyl)-phenylboronic acids gave only protodehalogenated benzotriazinone **6** probably due to steric hindrance. Similar reactivities were also observed with the Stille coupling reaction: treating 8-bromobenzotriazinone **31** with tributyl(furan-2-yl)stannane (3 equiv.) and $Pd(OAc)_2$ (15%) in DMF at 100 °C for 24 h gave no reaction and the starting 8-bromobenzotriazinone **31** was completely recovered, while under the same conditions, 8-iodobenzotriazinone **32** gave the desired 8-(furan-2-yl)-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**39**) in 71% yield. In a similar manner, the 8-(thien-2-yl)- and 8-vinylbenzotriazinones **40** and **41** were obtained in 79 and 51% yields, respectively. Suzuki and Stille couplings were also successfully achieved on the 6-substituted benzotriazinones **30** and **31** obtaining 1,3,6,8-tetraaryl analogues **42** and **43** (entries 7 and 8).

Table 3 Nucleophilic addition reactions of 8-halobenzotriaziones **31** (Hal = Br) and **32** (Hal = I) at RT



	31 & 32		**33-35**	
Entry	Hal	Conditions	R^1	Yields (%)
1	I	PhMgBr (4 equiv.) THF, 18 h	Ph	**33** (22)
2	I	(Thien-2-yl)MgBr (4 equiv.), THF, 18 h	Thien-2-yl	**34** (49)
3	Br	Pyrrolidine (2 equiv.) DCM, 36 h	Pyrrolidinyl	**35** (74)

These 1,3,6,8-tetraarylbenzotriazinones **42** and **43** could alternatively be prepared from the 8-arylbenzotriazinones *via* C-6 nucleophilic substitution (Scheme 8).



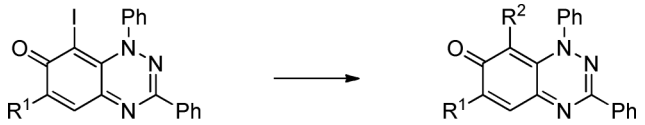
Scheme 8 1,3,6,8-Tetraarylbenzotriazinones *via* C-6 Substitution Reactions with Aryl Grignards.

With this result in hand there were now three available routes to the 1,3,6,8-tetraphenylbenzotriazinone **42**: Route 1) C-6 Grignard mediated phenylation followed by C-8 electrophilic iodination and subsequent Suzuki–Miyaura reaction with phenylboronic acid to give in 3 steps the 1,3,6,8-tetraphenylbenzotriazinone **42** in an overall yield of 48%; Route 2) C-8 electrophilic iodination, followed by Suzuki–Miyaura C-8 arylation and subsequent C-6 Grignard mediated phenylation to give in 3 steps the tetrasubstituted benzotriazinone **42** in a 62% overall yield; and finally, Route 3) C-8 electrophilic iodination, followed by Grignard mediated C-6 phenylation and finally Suzuki–Miyaura C-8 arylation that provided benzotriazinone **42** in the overall lowest yield of 17%. Similar overall yields were obtained for the 1,3-diphenyl-6,8-dithien-2-ylbenzotriazinone **43**, supporting Route 2 as the most efficient for the preparation of tetraarylbenzotriazinones.

3. Conclusions

1,3-Diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**6**) on heating with TCNE affords the ylidinemalononitrile **11** in low yield. Furthermore, benzotriazinone **6** readily undergoes high yielding and regioselective nucleophilic substitution at C-6 and electrophilic halogenations at C-8. 8-Iodobenzotriazinones participate in both Suzuki–Miyaura and Stille coupling reactions to give 1,3,8-triarylbenzotriazinones. By combining the above chemistries, 1,3,6,8-tetraarylbenzotriazinones can also be prepared. The above demonstrated the versatility of benzotriazinone **6** as a useful heterocyclic scaffold that can be used for the preparation of small libraries of potentially biological active quinonimines. The biological activity of these new benzotriazinones will be reported in the near future.

Table 4 Suzuki–Miyaura [Pd(dppf)Cl_2·DCM (10 mol %), K_2CO_3 (2 equiv.), $ArB(OH)_2$ (2 equiv.), dioxane/water 3 : 1, *ca.* 90 °C] and Stille [$ArSnBu_3$ (3 equiv.), $Pd(OAc)_2$ (15 mol %), DMF, *ca.* 100 °C, Ar atmosphere] C–C coupling reactions of 8-iodobenzotriaziones **32–34**



32-34 **36-43**

Entry	R^1	Reaction type	Reagent	Time (h)	R^2	Yields (%)
1	H	Suzuki	$PhB(OH)_2$	2.5	Ph	**36** (78)
2	H	Suzuki	$4\text{-}ClC_6H_4B(OH)_2$	1.5	$4\text{-}ClC_6H_4$	**37** (91)
3	H	Suzuki	$3\text{-}MeOC_6H_4B(OH)_2$	1	$3\text{-}MeOC_6H_4$	**38** (96)
4	H	Stille	Fur-2-ylSnBu_3	21	Fur-2-yl	**39** (71)
5	H	Stille	Thien-2-ylSnBu_3	25	Thien-2-yl	**40** (79)
6	H	Stille	VinylSnBu_3	24	Vinyl	**41** (51)
7	Ph	Suzuki	$PhB(OH)_2$	2.5	Ph	**42** (77)
8	Thien-2-yl	Stille	Thien-2-ylSnBu_3	15	Thien-2-yl	**43** (81)

4. Experimental

4.1. General procedures

Acetonitrile was distilled over CaH_2 and THF was distilled over Na before use. Reactions were protected by $CaCl_2$ drying tubes. Anhydrous Na_2SO_4 was used for drying organic extracts and all volatiles were removed under reduced pressure. All reaction mixtures and column eluents were monitored by TLC using commercial glass backed thin layer chromatography (TLC) plates (Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The technique of dry flash chromatography was used throughout for all non-TLC scale chromatographic separations using silica gel 60 (less than 0.063 mm). Melting points were determined using a hot stage microscope apparatus. Solvents used for recrystallization are indicated after the melting point. Inflections in the UV spectra are identified by the abbreviation "inf". FTIR spectra were recorded using a Ge ATR accessory and strong, medium and weak peaks are represented by s, m and w respectively. ^{1}H NMR spectra were recorded at either 300 or 500 MHz and ^{13}C NMR spectra were recorded at either 75 and 125 MHz, respectively. DEPT 135 NMR studies identified quaternary and tertiary carbons, which are indicated by (s) and (d) notations, respectively. Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Low resolution (EI) mass spectra were recorded on a GCMS with direct inlet probe.

4.2. Preparation of (benzotriazinylidene)malononitrile

4.2.1. 2-(1,3-Diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-ylidene)propanedinitrile (11). To a stirred solution of 1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**6**) (30 mg, 0.1 mmol) in PhCl (1 ml), TCNE (23 mg, 0.18 mmol) was added and the mixture heated to *ca.* 140 °C for 18 h. TLC (*t*-BuOMe/hexane, 2 : 1) showed the absence of the starting material and the presence of a new less polar green product. The mixture was diluted with THF (2 ml) and cooled until *ca.* 0 °C. The precipitate was filtered and dissolved in DCM (5 ml). To this solution was added silica gel (100 mg) and the mixture stirred for 10 min and then filtered. The solvent was evaporated *in vacuo* and the residue crystallized to afford the *title compound* **11** (6 mg, 17%) as green plates, mp 306–311 °C (from $CHCl_3$), R_f 0.61 (*t*-BuOMe/hexane, 3 : 1); (found: C, 75.9; H, 3.7; N, 20.1. $C_{22}H_{13}N_5$ requires C, 76.1; H, 3.8; N, 20.2%); λ_{max}(DCM)/nm 277 (log ε 3.06), 345 inf (3.24), 360 (3.37), 377 (3.42), 421 (2.98), 610 inf (2.90), 647 (3.04), 702 (3.08), 774 inf (2.84); ν_{max}/cm^{-1} 3063w (Ar CH), 2203 m (C≡N), 1612w, 1551w, 1508 s, 1489w, 1472w, 1454w, 1449w, 1427w, 1402w, 1377 m, 1364w, 1341w, 1306 m, 1267 m, 1227w, 1207w, 1188w, 1153w, 1136w, 1069w, 1028w, 1003w, 983w, 989w, 924w, 887w, 860w, 841 m, 833w 816w, 800w, 781w; δ_H(300 MHz, $CDCl_3$) 8.28–8.25 (2H, m, Ar *H*), 7.94 (1H, d, *J* 9.5, 1.9, *H*-6), 7.72–7.59 (6H, m, Ar *H*), 7.52–7.46 (3H, m, Ar *H*), 6.59 (1H, d, *J* 2.0, *H*-8); δ_H(125 MHz; $CDCl_3$) 156.5 (s), 154.1 (s), 153.1 (s), 140.7 (s), 137.8 (d), 134.7 (s), 133.3 (s), 131.5 (d), 131.2 (d), 130.6 (d), 130.6, (d), 129.1 (d), 127.2 (d), 125.4 (d), 116.1 (s), 116.0 (s), 95.1 (d); *m*/*z* (EI) 348 (M^+ + 1, 26%), 347 (M^+, 100), 319 (3), 244 (4), 215 (6), 188 (3), 139 (16), 112 (11), 103 (6), 91 (6), 77 ($C_5H_5^+$, 41), 51 (21).

4.3. C-6 substituted benzotriazinones

4.3.1. 6-Hydroxy-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (15). To a stirred solution of 1,3-diphenylbenzo[*e*][1,2,4]-triazin-7(1*H*)-one (**6**) (29.9 mg, 0.1 mmol) in THF/H_2O (4 : 1) (1 ml), KOH (16.8 mg, 0.3 mmol) was added and the reaction mixture was heated at 90 °C for 18 h. TLC (*t*-BuOMe) showed the absence of the starting material and the presence of a very polar red compound. Conc. HCl was added (51 µl, 0.61 mmol), followed by an excess of hexane (10 ml) and the precipitate that formed was filtered, washed (water) and recrystallized to afford the *title compound* **15** (28.9 mg, 92%) as light red plates, mp 250–255 °C (from PhH), R_f 0.74 (DCM/MeOH, 5 : 1); (found: C, 72.3; H, 4.1; N, 13.4. $C_{19}H_{13}N_3O_2$ requires C, 72.4; H, 4.2; N, 13.3%); λ_{max}(DCM)/nm 251 (log ε 3.41), 309 (3.72), 366 inf (2.91), 386 inf (2.83), 508 (2.82); ν_{max}/cm^{-1} 3161w (OH), 1580 s, 1555 s, 1495 m, 1470 m, 1404 m, 1385 s, 1364 m, 1314 s, 1290 m, 1261w, 1229 m, 1190 m, 1163 m, 1070w, 1026w, 1003w, 984w, 928w, 854 m, 818w, 781 m, 750w, 717m; δ_H(300 MHz; TFA-d_1) OH peak missing 8.32 (2H, d, *J* 7.7, Ar *H*), 7.83–7.61 (7H, m, Ar *H*), 7.53 (2H, dd, *J* 7.5, 7.5, Ar *H*), 7.19 (1H, m, Ar *H*); δ_C(75 MHz; TFA-d_1) 167.1 (Ar *C*═O), 161.5 (s), 158.7 (s), 148.5 (s), 142.2 (s), 140.1 (s), 135.4 (d),

134.3 (d), 131.7 (d), 130.9 (s), 130.7 (d), 129.3 (d), 126.3 (d), 108.1 (d), 100.2 (d); *m/z* (EI) 316 ($M^+ + 1$, 24%), 315 (M^+, 100), 298 (4), 287 (26), 277 (6), 258 (2), 184 (13), 155 (9), 144 (17), 128 (10), 117 (8), 104 (12), 89 (5), 77 (62), 51 (33).

4.3.2. 6-Ethoxy-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (14) (Method 1). To a stirred solution of 1,3-diphenylbenzo-[*e*][1,2,4]triazin-7(1*H*)-one (**6**) (30 mg, 0.1 mmol) in EtOH (1 ml), Hünig's base (342 μl, 2 mmol) was added, and the reaction mixture was heated at reflux for 48 h. TLC (*t*-BuOMe) showed the absence of the starting material and the presence of a new red compound. The mixture was diluted with DCM (8 ml) and adsorbed onto silica gel. Dry flash chromatography (*t*-BuOMe) gave the *title compound* **14** (15 mg, 44%) as red needles, mp 212–214 °C (from PhH), R_f 0.29 (*t*-BuOMe); (found: C, 73.6; H, 4.9; N, 12.2. $C_{21}H_{17}N_3O_2$ requires C, 73.5; H, 5.0; N, 12.2%); λ_{max}(DCM)/nm 246 (log ε 3.39), 311 (3.72), 363 inf (3.03), 381 inf (2.77), 520 (2.83); ν_{max}/cm^{-1} 3107w, 3061w and 3036w (Ar CH), 2990w, 1607 s, 1591 m, 1560 s, 1516 m, 1493 m, 1458w, 1447w, 1408w, 1393w, 1379w, 1352w, 1314w, 1281 m, 1256 m, 1242 m, 1227w, 1206w, 1196w, 1155w, 1136w, 1107w, 1084w, 1067w, 1024 m, 986w, 970w, 926w, 901w, 866w, 849 m, 824m; δ_H(300 MHz; $CDCl_3$) 8.32–8.29 (2H, m, Ar *H*), 7.62–7.57 (4H, m, Ar *H*), 7.51–7.48 (4H, m, Ar *H*), 7.01 (1H, s, *H*-5), 6.31 (1H, s, *H*-8), 4.34 (2H, q, *J* 6.8, O*CH*$_2$), 1.62 (3H, t, *J* 7.0, *CH*$_3$); δ_C(75 MHz; $CDCl_3$) 175.3 (*C*═O), 163.4 (s), 155.3 (s), 151.4 (s), 141.5 (s), 135.2 (s), 134.6 (s), 130.6 (d), 130.2 (d), 130.1 (d), 128.9 (d), 126.9 (d), 125.9 (d), 104.6 (d), 97.3 (d), 65.9 (O*C*H$_2$), 14.3 (*C*H$_3$); *m/z* (EI) 344 ($M^+ + 1$, 10%), 343 (M^+, 31), 328 (100), 314 (9), 300 (48), 271 (7), 195 (3), 184 (2), 168 (11), 155 (8), 144 (12), 128 (5), 116 (10), 103 (9), 89 (7), 77 (72), 57 (12), 51 (22).

4.3.3. 6-(Isobutylthio)-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (16) (typical procedure). To a stirred solution of 1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**6**) (30 mg, 0.1 mmol) in THF (1 ml), 2-methylpropane-1-thiol (32 μl, 0.3 mmol) and Hünig's base (19 μl, 0.11 mmol) were added. The mixture was stirred at *ca.* 20 °C for 30 min. TLC (*t*-BuOMe) showed the absence of the starting material and the presence of a less polar brown compound. The mixture was diluted with DCM (5 ml) and adsorbed onto silica gel. Dry flash chromatography (*t*-BuOMe/hexane, 1 : 2) of the residue gave the *title compound* **16** (35.3 mg, 91%) as brown needles, mp 205–209 °C (from DCM/MeOH, 1 : 2); R_f 0.76 (*t*-BuOMe/hexane, 3 : 1); (found: C, 71.2; H, 5.3; N, 10.7. $C_{23}H_{21}N_3OS$ requires C, 71.3; H, 5.5; N, 10.8%); λ_{max}(DCM)/nm 267 (log ε 3.23), 324 (3.37), 341 inf (3.26), 425 (3.15), 519 inf (2.50), 550 (2.55), 603 inf (2.27); ν_{max}/cm^{-1} 2955w, 2922w, 2855w, 1580 s, 1522 s, 1508 s, 1493 m, 1452w, 1429w, 1371w, 1339w, 1314 m, 1287w, 1215w, 1198w, 1171w, 1144w, 1069w, 1024w, 1009 m, 928w, 847 m, 812w; δ_H(300 MHz, $CDCl_3$) 8.29–8.26 (2H, m, Ar *H*), 7.63–7.55 (5H, m, Ar *H*), 7.47–7.45 (3H, m, Ar *H*), 7.36 (1H, s, *H*-5), 6.15 (1H, s, *H*-8), 2.88 (2H, d, *J* 6.5, SC*H*$_2$), 2.13 (1H, hept, *J* 6.8, C*H*Me$_2$), 1.16 [6H, d, *J* 6.8, CH(C*H*$_3$)$_2$]; δ_C(75 MHz, $CDCl_3$) 177.4 (*C*═O), 160.5 (s), 151.8 (s), 151.5 (s), 141.5 (s), 136.1 (s), 134.5 (s), 130.6 (d), 130.3 (d), 130.1 (d), 128.9 (d), 126.9 (d), 125.9 (d), 119.9 (d), 95.7 (d), 39.9 (S*C*H$_2$), 27.6 (*C*H), 22.6 (2 × *C*H$_3$); *m/z* (EI) 387 (M^+, 13%), 372 (10), 354 (100), 344 (92), 331 (52), 313 (10), 303 (16), 299 (5), 200 (6), 180 (9), 168 (8), 160 (6), 116 (16), 103 (6), 94 (11), 77 (71), 69 (6), 51 (15).

4.3.4. 6-Amino-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (19). To a stirred solution of 1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**6**) (30 mg, 0.1 mmol) in DMF (2 ml) at *ca.* 120 °C, a steady stream of NH_3 (g) was passed through for 6 h. After an additional 6 h at *ca.* 120 °C TLC (*t*-BuOMe) showed the disappearance of the starting material. The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (20 ml) and washed with H_2O (15 ml). The organic layer was separated, dried (Na_2SO_4) and adsorbed onto silica. Dry flash chromatography (*t*-BuOMe) gave the *title compound* **19** (20 mg, 64%) as a light orange needles, mp 279–282 °C (from PhH); R_f 0.21 (*t*-BuOMe/hexane, 3 : 1); (found: C, 72.7; H, 4.4; N, 17.9. $C_{19}H_{14}N_4O$ requires C, 72.6; H, 4.5; N, 17.8%); λ_{max}(DCM)/nm 274 (log ε 3.49), 302 inf (3.46), 312 (3.48), 332 inf (3.29), 401 inf (3.25), 417 (3.30), 504 (2.60); ν_{max}/cm^{-1} 3416w (Ar NH), 3283w, 3221br w, 3154br w (Ar CH), 1639w, 1581 m, 1566 m, 1555 s, 1541 s, 1491 m, 1449w, 1422w, 1391w, 1360w, 1312w, 1292w, 1275w, 1231w, 1190w, 1173w, 1098w, 1067w, 1026w, 1003w, 980w, 916w, 854w, 835w,m, 824 m, 812w; δ_H(300 MHz; TFA-d_1) NH peak missing 8.09 (2H, d, *J* 7.6, Ar *H*), 7.78–7.64 (7H, m, Ar *H*), 7.58–7.48 (3H, m, Ar *H*); δ_C(75 MHz; TFA-d_1) 161.8 (*C*═O), 158.9 (s), 154.1 (s), 143.7 (s), 142.0 (s), 141.2 (s), 136.8 (d), 134.9 (d), 131.9 (d), 131.4 (d), 129.5 (d), 127.8 (s), 126.5 (d), 101.8 (d), 99.0 (d); *m/z* (EI) 315 ($M^+ + 1$, 23%), 314 (M^+, 100), 297 (3), 286 (12), 183 (9), 155 (9), 143 (7), 116 (8), 104 (13), 89 (7), 77 (100), 67 (9), 63 (5), 51 (61).

4.3.5. 6-(Ethylamino)-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (20). To a stirred solution of 1,3-diphenylbenzo[*e*]-[1,2,4]triazin-7(1*H*)-one (**6**) (30 mg, 0.1 mmol) in $EtNH_2$ 2 M in THF (1 ml, 20 mmol) was added and the mixture was stirred at *ca.* 20 °C for 2 h. The solution was cooled to *ca.* 0 °C and filtered to afford the *title compound* **20** (24.8 mg, 72%) as orange plates, mp 297–301 °C (from PhH), R_f 0.69 (*t*-BuOMe); (found: C, 73.6; H, 5.4; N, 16.2. $C_{21}H_{18}N_4O$ requires C, 73.7; H, 5.3; N, 16.4%); λ_{max}(DCM)/nm 280 inf (log ε 3.44), 287 (3.46), 301 (3.45), 311 inf (3.41), 336 inf (3.06), 352 inf (2.94), 412 inf (3.29), 430 (3.39); ν_{max}/cm^{-1} 3240br w (NH), 2980w, 2864w, 1562w, 1547 s, 1518w, 1489 m, 1477 m, 1449w, 1383w, 1354w, 1312 m, 1298w, 1271w, 1200w, 1171w, 1134w, 1070w, 1051w, 1024w, 989w, 924w, 866w, 843w, 816w, 806w, 779w; δ_H(300 MHz; TFA-d_1) NH peak missing 7.99 (2H, d, *J* 8.0, Ar *H*), 7.70–7.56 (6H, m, Ar *H*), 7.52–7.47 (2H, m, Ar *H*), 7.24 (1H, s, *H*-5 or 8), 6.96 (1H, s, *H*-5 or 8), 3.75 (2H, q, *J* 7.1, NC*H*$_2$), 1.40 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz; TFA-d_1) 155.8 (*C*═O), 153.4 (s), 144.1 (s), 144.1 (s), 142.0 (s), 141.0 (s), 136.7 (d), 134.7 (d), 132.0 (d), 131.4 (d), 129.4 (d), 127.9 (s), 126.5 (d), 100.9 (d), 95.2 (d), 42.4 (N*C*H$_2$), 13.1 (*C*H$_3$); *m/z* (EI) 343 ($M^+ + 1$, 24%), 342 (M^+, 100), 327 (26), 300 (17), 284 (4), 271 (5), 197 (4), 180 (8), 134 (11), 118 (7), 104 (10), 89 (5), 77 (60), 64 (7), 51 (17).

4.3.6. 1,3,6-Triphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (28) (typical procedure). To a stirred solution of 1,3-diphenylbenzo[*e*]-[1,2,4]triazin-7(1*H*)-one (**6**) (30 mg, 0.1 mmol) in dry THF (0.6 ml) at *ca.* 20 °C under an Ar atmosphere, PhMgBr 1 M in THF (0.4 ml, 0.4 mmol) was added and the mixture was stirred for 12 h. TLC (*t*-BuOMe/hexane, 3 : 1) showed the absence of the starting material and the presence of a new less polar purple product. The mixture was diluted with MeOH (1 ml) and stirred for 10 min. Dry flash chromatography (*t*-BuOMe) gave the *title compound* **28** (30.8 mg, 82%) as purple needles, mp 262–265 °C

(from DCM/MeOH, 1 : 3), R_f 0.60 (*t*-BuOMe/hexane, 3 : 1); (found: C, 79.9; H, 4.4; N, 11.1. $C_{25}H_{17}N_3O$ requires C, 80.0; H, 4.6; N, 11.2%); λ_{max}(DCM)/nm 253 (log ε 3.39), 272 inf (3.32), 327 (3.56), 405 inf (2.73), 568 (2.72), 617 inf (2.54); ν_{max}/cm^{-1} 3061w (Ar CH), 1611w, 1601w, 1585 m, 1541 s, 1520 s, 1489 m, 1456w, 1439w, 1396w, 1373w, 1344w, 1314 m, 1281w, 1267w, 1202 m, 1179w, 1169w, 1157w, 1136w, 1078w, 1067w, 1028w, 1001w, 989w, 930w, 916w, 905w, 849 m, 839 m, 829 m, 785 m, 777 m, 762s; δ_H(300 MHz; $CDCl_3$) 8.30–8.27 (2H, m, Ar *H*), 7.84 (1H, s, *H*-5 or 8), 7.78–7.75 (2H, m, Ar *H*), 7.63–7.57 (5H, m, Ar *H*), 7.48–7.47 (6H, m, Ar *H*), 6.23 (1H, s, *H*-5 or 8); δ_C(75 MHz; $CDCl_3$) 180.7 (*C*═O), 155.1 (s), 151.6 (s), 151.1 (s), 141.3 (s), 136.1 (s), 135.7 (s), 134.2 (s), 130.6 (d), 130.2 (d), 130.2 (d), 129.8 (d), 129.7 (d), 128.9 (d), 128.4 (d), 126.8 (d), 125.8 (d), 98.4 (d); *m*/*z* (EI) 376 (M^+ + 1, 19%), 375 (M^+, 72), 374 (M^+-1, 100), 347 (4), 270 (9), 243 (8), 188 (4), 166 (7), 139 (14), 103 (3), 89 (7), 77 (42), 63 (4), 51 (13).

4.4. Halogenation at C-8 using NXS

4.4.1. 8-Chloro-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (30) (typical procedure). To a solution of 1,3-diphenylbenzo[*e*]-[1,2,4]triazin-7(1*H*)-one (**6**) (30 mg, 0.1 mmol) in dry DCM (2 ml), NCS (15 mg, 0.11 mmol) was added. The mixture was stirred at *ca.* 20 °C for 12 h or until all the starting material was consumed. The reaction mixture was then adsorbed onto silica using DCM. Dry flash chromatography (*t*-BuOMe) of the residue gave the *title compound* **30** (33 mg, 99%) as shiny blue crystals, mp 187–189 °C (from cyclohexane); R_f 0.80 (*t*-BuOMe/hexane, 3 : 1); (found: C, 68.3; H, 3.7; N, 12.5. $C_{19}H_{12}ClN_3O$ requires C, 68.4; H, 3.6; N, 12.6%); λ_{max}(DCM)/nm 241 (log ε 3.07), 301 (3.30), 313 inf (3.26), 358 (2.96), 568 (2.55); ν_{max}/cm^{-1} 3054w (Ar CH), 1615 m, 1605 m, 1536w, 1517 s, 1490w, 1455w, 1430w, 1389w, 1376w, 1312w, 1198w, 1175w, 1137w, 1108 m, 1088w, 1073w, 1027w, 1000w, 946w, 921w, 903w, 840 m, 811w, 799w; δ_H(300 MHz, $CDCl_3$) 8.29–8.26 (2H, m, Ar *H*), 7.77 (1H, d, *J* 9.7, Ar *H*), 7.54–7.47 (9H, m, Ar *H*); δ_C(75 MHz, $CDCl_3$) 176.2 (*C*═O), 154.8 (s), 150.8 (s), 143.3 (s), 140.5 (d), 133.0 (s), 131.8 (s), 131.8 (d), 130.9 (d), 129.3 (d), 128.8 (d), 126.7 (d), 125.3 (d), 105.4 (*C*-8); *m*/*z* (EI) 335 (M^+ + 2, 24%), 333 (M^+, 54), 298 (100), 270 (6), 167 (12), 139 (16), 114 (4), 104 (6), 97 (24), 77 (70), 62 (10), 51 (27).

4.5. Reaction of 8-halobenzotriazinones with nucleophiles

4.5.1. 8-Bromo-1,3-diphenyl-6-(pyrrolidin-1-yl)benzo[*e*][1,2,4]-triazin-7(1*H*)-one (35). To a stirred solution of 8-bromo-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**31**) (37.8 mg, 0.100 mmol) in DCM (2 ml), at *ca.* 20 °C, protected with a $CaCl_2$ drying tube, pyrrolidine (18.2 µl, 0.200 mmol) was added and the reaction mixture was stirred at this temperature for 36 h until no starting material remained (TLC). The reaction mixture was then diluted (DCM) and washed (5% HCl) to remove unreacted amine. The organic layer was separated, dried (Na_2SO_4) and evaporated to afford the *title compound* **35** (33.1 mg, 74%) as red crystals, mp 254–255 °C (from cyclohexane); (Found C, 61.9; H, 4.2 N, 12.6. $C_{23}H_{19}BrN_4O$ requires C, 61.8; H, 4.3; N, 12.5%); λ_{max}(DCM)/nm 283 inf (log ε 3.53), 307 (3.69), 327 inf (3.53), 354 inf (3.10), 368 inf (3.02), 440 inf (3.49), 459 (3.60); ν_{max}/cm^{-1} 2968w, 2924w (Ar CH), 2878w (Ar CH), 2849w, 1609 m, 1584 m (Ar C-C), 1564 s, 1531 s, 1495 m, 1468 m, 1454 m, 1443w, 1404 m, 1371 m, 1302 s, 1290 m, 1256w, 1225w, 1200w, 1171w, 1157w, 1119w, 1107w, 1092w, 1069w, 1026w, 993w, 937 m, 922w, 905w, 883w, 856w, 843w, 816 m, 782w, 768m; δ_H(300 MHz; $CDCl_3$) 8.27≥8.24 (2H, m, Ph C*H*), 7.50≥7.42 (8H, m, Ph C*H*), 6.57 (1H, s, Ph C*H*), 4.335 (2H, s, CH_2), 3.533 (2H, s, CH_2), 2.00 (4H, s, CH_2); δ_C(75 MHz; $CDCl_3$) 172.0 (*C*═O), 153.1, 152.05, 150.6, 144.2, 135.2, 133.8, 130.5 (d), 129.25 (d), 129.2 (d), 128.9 (d), 127.4 (d), 126.8, 100.15, 27.3 (CH_2); *m*/*z* (EI) 448 (M^++1, 55), 447 (M^+, 14), 446 (M^+ + 1, 57), 393 (4), 367 (M^+ + Br, 4), 339 (M^+-C_2H_4Br, 20), 298 (M^+ – C_4H_8NBr, 4), 238 (13), 180 (7), 167 (5), 152 (5), 140 (7), 116 (7), 103 (12), 91 (13), 77 (100), 70 (12).

4.5.2. 8-Iodo-1,3,6-triphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (33) (typical procedure). To a stirred solution of 8-iodo-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**32**) (42.5 mg, 0.1 mmol) in dry THF (0.6 ml) at *ca.* 20 °C in Ar atmosphere, PhMgBr 1 M in THF (0.4 ml, 0.4 mmol) was added and the mixture was stirred for 18 h. TLC (*t*-BuOMe/hexane, 1 : 1) showed the absence of the starting material and the presence of a new less polar blue product. The mixture was diluted with MeOH (1 ml), stirred for 10 min, adsorbed onto silica gel and dry flash chromatography (EtOAc/hexane, 1 : 2) gave the *title compound* **33** (11 mg, 22%) as blue needles, mp 96–101 °C (DCM/MeOH, 1 : 3), R_f 0.43 (*t*-BuOMe/hexane, 1 : 4), identical to that describe above.

4.6. C–C coupling reactions

4.6.1. Suzuki coupling at C-8.

*4.6.1.1. 1,3,8-Triphenylbenzo[e][1,2,4]triazin-7(1H)-one (**36**) (typical procedure).* To a stirred solution of 8-iodo-1,3-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**32**) (42.5 mg, 0.1 mmol) in dioxane/water 3 : 1 (0.8 ml), $Pd(dppf)Cl_2$·DCM (8 mg, 0.01 mmol), K_2CO_3 (27.6 mg, 0.2 mmol) and phenylboronic acid (24.4 mg, 0.2 mmol) were added and the mixture was heated at reflux for 2.5 h. TLC (*t*-BuOMe/hexane, 1 : 1), showed the absence of the starting material and the presence of a new slightly more polar blue product. The mixture was dried (Na_2SO_4) filtered, adsorbed onto silica gel and dry flash chromatography (*t*-BuOMe/hexane, 1 : 2) gave the *title compound* **36** (29.4 mg, 78%) as shiny blue needles, mp 219–222 °C (from DCM/MeOH 1 : 1); R_f 0.70 (*t*-BuOMe/hexane 3 : 1); (found: C, 80.1; H, 4.5; N, 11.1. $C_{25}H_{17}N_3O$ requires C, 80.0; H, 4.6; N, 11.2%); λ_{max}(DCM)/nm 230 inf (log ε 3.46), 240 (3.47), 256 (3.44), 288 (3.58), 309 inf (3.47), 360 (3.28), 584 (2.76); ν_{max}/cm^{-1} 3055w (Ar CH), 2920w, 2849w, 1624w, 1599w, 1582 m, 1537 m, 1524 m, 1483 m, 1456 m, 1435 s, 1396w, 1373 m, 1321w, 1310 m, 1287w, 1234 m, 1175 m, 1132 m, 1107 m, 1088 m, 1074 m, 1026w, 989w, 951 m, 910w, 891w, 835m; δ_H(300 MHz, $CDCl_3$) 8.31–8.28 (2H, m, Ar *H*), 7.78 (1H, d, *J* 9.7, Ar *H*), 7.52–7.48 (3H, m, Ar *H*), 7.42 (1H, d, *J* 9.7, Ar *H*), 7.16–7.11 (2H, m, Ar *H*), 7.05–6.95 (6H, m, Ar *H*), 6.92–6.88 (2H, m, Ar *H*); δ_C(75 MHz, $CDCl_3$) 181.2 (*C*═O), 155.9 (s), 150.7 (s), 143.5 (s), 141.6 (d), 133.8 (s), 133.6 (s), 132.6 (s), 132.2 (d), 131.0 (d), 130.7 (d), 128.9 (d), 128.5 (d), 128.1 (d), 127.7 (d), 127.0 (d), 126.7 (d), 124.8 (d), 112.7 (s); *m*/*z* (EI) 376 (M^+ + 1, 29%), 375 (M^+, 100), 346 (38), 330 (5), 298 (23), 284 (6), 271 (42), 243 (15), 215 (14), 187 (6), 180 (9), 166 (9), 139 (26), 114 (9), 104 (11), 89 (22), 77 (54), 63 (10), 51 (21).

4.6.2. Stille coupling at C-8.

*4.6.2.1. 8-(Furan-2-yl)-1,3-diphenylbenzo[e][1,2,4]triazin-7(1H)-one (**39**) (typical procedure).* To a stirred solution of 8-iodo-1,3-diphenylbenzo[*e*][1,2,4]-triazin-7(1*H*)-one (**32**) (42.5 mg, 0.1 mmol) in DMF (2 ml), 2-(tributylstannyl)furan (91 μl, 0.29 mmol) and $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) were added and the solution was heated at *ca.* 100 °C under an Ar atmosphere for 21 h. TLC (*t*-BuOMe/hexane, 1 : 1) showed the absence of the starting material and the presence of a new more polar product. The reaction mixture was cooled, filtered, diluted with EtOAc (10 ml) and washed with water (15 ml). The combined organic layers were dried (Na_2SO_4), filtered and the residue dry flash chromatographed (*t*-BuOMe/hexane, 1 : 2) to give the *title compound* **39** (25.9 mg, 71%) as shiny blue needles, mp 189–192 °C (from cyclohexane); R_f 0.65 (*t*-BuOMe/hexane, 3 : 1); (found: C, 75.5; H, 4.1; N, 11.4. $C_{23}H_{15}N_3O_2$ requires C, 75.6; H, 4.1; N, 11.5%); λ_{max}(DCM)/nm 218 (log ε 3.83), 252 (3.11), 298 (3.14), 378 (2.72), 602 (2.53); ν_{max}/cm^{-1} 3140w, 3113w, 3065w (Ar CH), 1626 m, 1599 m, 1585 m, 1539w, 1514 m, 1485w, 1470 m, 1454w, 1437 s, 1391w, 1364 m, 1329 m, 1317 m, 1277w, 1232 m, 1215w, 1188w, 1169 m, 1155 m, 1126 m, 1101 m, 1088w, 1076 m, 1024 m, 1003w, 986w, 949 m, 935w, 883w, 858w, 831s; δ_H(300 MHz, $CDCl_3$) 8.33–8.30 (2H, m, Ar *H*), 7.76 (1H, d, *J* 9.7, Ar *H*), 7.54–7.48 (3H, m, Ar *H*), 7.41–7.37 (3H, m, Ar *H*), 7.24–7.17 (3H, m, Ar *H*), 6.78–6.77 (1H, m, Ar *H*), 6.57 (1H, dd, *J* 3.1, 0.7, Ar *H*), 6.11 (1H, dd, *J* 3.3, 1.9, Ar *H*); δ_C(75 MHz, $CDCl_3$) one Ar CH missing 179.8 (*C*=O), 155.3 (s), 151.5 (s), 145.3 (s), 143.2 (s), 141.8 (d), 141.4 (d), 133.7 (s), 132.2 (d), 131.9 (s), 130.8 (d), 128.9 (d), 128.5 (d), 128.3 (d), 127.0 (d), 123.2 (d), 113.1 (d), 111.3 (d), 102.8 (s); *m/z* (EI) 366 (M^+ + 1, 28%), 365 (M^+, 100), 336 (80), 322 (40), 308 (17), 260 (5), 232 (10), 219 (5), 205 (25), 191 (5), 176 (17), 169 (7), 152 (12), 129 (15), 103 (18), 88 (4), 77 (87), 63 (7), 51 (52).

4.7. Preparation of 1,3,6,8-tetraarylbenzotriazinones *via* Grignard reaction at C-6

4.7.1. 1,3,6,8-Tetraphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (42) (typical procedure). To a stirred solution of 1,3,8-diphenylbenzo[*e*][1,2,4]triazin-7(1*H*)-one (**28**) (37.5 mg, 0.1 mmol) in dry THF (0.6 ml) at *ca.* 20 °C in Ar atmosphere, PhMgBr 1 M in THF (0.4 ml, 0.4 mmol) was added and the mixture stirred for 18 h. TLC (*t*-BuOMe/hexane, 1 : 1) showed the absence of the starting material and the presence of a new less polar blue product. The mixture was diluted with MeOH (1 ml) and stirred for 10 min. Dry flash chromatography (EtOAc/hexane, 1 : 2) gave the *title compound* **42** (35.5 mg, 79%) as blue needles, mp 205–209 °C (from DCM/MeOH, 1 : 3), R_f 0.37 (*t*-BuOMe/hexane, 1 : 4); (found: C, 82.3; H, 4.7; N, 9.2. $C_{31}H_{21}N_3O$ requires C, 82.5; H, 4.7; N, 9.3%); λ_{max}(DCM)/nm 230 inf (log ε 3.62), 255 (3.70), 285 inf (3.57), 339 (3.76), 585 (2.93); ν_{max}/cm^{-1} 3055w (Ar CH), 2963w, 2916w, 1601 m, 1587 s, 1547 s, 1524 s, 1487 s, 1454w, 1445w, 1431 m, 1369w, 1335w, 1310 m, 1285 s, 1258 m, 1209 m, 1182w, 1146w, 1124w, 1076w, 1069w, 1028w, 1005w, 953w, 920w, 907w, 883w, 839w, 802m; δ_H(500 MHz; $CDCl_3$) 8.33–8.31 (2H, m, Ar H), 7.95 (1H, s, Ar H), 7.81–7.82 (2H, m, Ar H), 7.53–7.45 (6H, m, Ar H), 7.20–7.18 (2H, m, Ar H), 7.08–7.04 (3H, m, Ar H), 7.00–6.94 (5H, m, Ar H); δ_C(125 MHz; $CDCl_3$) one Ar *C*H missing 179.8 (s), 155.9 (s), 151.0 (s), 150.3 (s), 143.6 (s), 136.0 (s), 134.3 (s), 134.1 (s), 132.2 (s), 131.3 (d), 130.6 (d), 130.0 (d), 129.7 (d), 128.9 (d), 128.5 (d), 128.3 (d), 128.1 (d), 127.6 (d), 126.9 (d), 126.8 (d), 125.0 (d), 112.9 (s); *m/z* (EI) 452 (M^+ + 1, 31%), 451 (M^+, 100), 450 (M^+ – 1, 46), 423 (35), 374 (18), 347 (18), 319 (13), 285 (3), 242 (8), 216 (14), 189 (9), 180 (11), 165 (6), 104 (7), 89 (15), 77 (33), 69 (7), 51 (10).

Acknowledgements

The authors wish to thank Dr Georgia Loizou and Miss Marina Demetriadou for early experiments and the Cyprus Research Promotion Foundation [Grant No. ΥΓΕΙΑ/βΙΟΣ/0308(βΙΕ)/13] and the University of Cyprus (Medium Sized Grants) for financial support. Furthermore, the authors thank the following organizations in Cyprus for generous donations of chemicals and glassware: the State General Laboratory, the Agricultural Research Institute, the Ministry of Agriculture, and Biotronics Ltd. Finally, we thank the A. G. Leventis Foundation for helping to establish the NMR facility in the University of Cyprus.

References

1 In *The Triazine Herbicides, 50 Years Revolutionizing Agriculture*, J. E. McFarland and O. E. Burnside, ed., H. M. LeBaron, Ed-in-Chief, Elsevier, Oxford, 2008.
2 H. O. Esser, G. Depuis, E. Ebert, G. Nacro and C. Vogel, in *Herbicides Chemistry, Degradation and Mode of Action*, P. C. Kearney and D. D. Kaufmann, ed., Dekker, New York, 1976, Vol. 3, p 191.
3 Y. Chen and L. Hu, *Med. Res. Rev.*, 2009, **29**, 29 and references cited herein.
4 (*a*) H. M. Blatter and H. Lukaszewski, *Tetrahedron Lett.*, 1968, **9**, 2701; (*b*) H. Blatter, *U.S. Pat.* 3 423 409, 1969; (*c*) P. A. Koutentis and D. Lo Re, *Synthesis*, 2010, 2075; (*d*) C. P. Constantinides, P. A. Koutentis and G. Loizou, *Org. Biomol. Chem.*, 2011, **9**, 3122.
5 (*a*) K. Mukai, K. Inoue, N. Achiwa, J. B. Jamali, C. Krieger and F. A. Neugebauer, *Chem. Phys. Lett.*, 1994, **224**, 569; (*b*) C. Krieger and F. A. Neugebauer, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **52**, 3124; (*c*) C. P. Constantinides, P. A. Koutentis, H. Krassos, J. M. Rawson and A. J. Tasiopoulos, *J. Org. Chem*, 2011, **76**, 2798; (*d*) B. Yan, J. Cramen, R. McDonald and N. L. Frank, *Chem. Commun.*, 2011, **47**, 3201.
6 K. Hutchison, G. Srdanov, R. Hicks, H. Yu and F. Wudl, *J. Am. Chem. Soc.*, 1998, **120**, 2989.
7 (*a*) V. Charushin, V. Rusinov and O. Chupakhin, in *Comprehensive Heterocyclic Chemistry III*, ed. K. Turnbull, (Eds in Chief A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor), Elsevier, Oxford, 2008, vol. 9, ch. 9.02, p. 95-196; (*b*) H. Neunhoeffer, in *Comprehensive Heterocyclic Chemistry II*, ed. A. J. Boulton, (Eds in Chief A. R. Katritzky, C. W. Rees and E. F. V. Scriven), Elsevier, Oxford, 1996, vol. 6, ch. 6.11, p. 507-573; (*c*) H. Neunhoeffer, in *Comprehensive Heterocyclic Chemistry*, ed. A. J. Boulton and A. McKillop, (Eds in Chief A. R. Katritzky and C. W. Rees), Elsevier, Oxford, 1984, vol. 3 (part 2B), ch. 2.19, p. 385-456; (*d*) C. W. Lindsley, M. E. Layton, 1,2,4-Triazines, in *Science of Synthesis*, Product Class 2, ed. S. M. Weinreb, Georg Thieme Verlag, Stuttgart, 2003, vol. 17, ch 17.2, p. 357-448.
8 (*a*) L. P. G. Wakelin and M. J. Waring, *Comprehensive Medicinal Chemistry*, P. G. Sammes, Ed., Pergamon Press, Oxford, U.K., 1990, Vol. 2, pp 703; (*b*) B. A. Chabner, C. J. Allegra, G. A. Curt and P. Calabresi, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th ed., J. G. Hardman, L. E. Limbird, P. B. Molinoff, R. W. Ruddon and A. G. Gilman, ed., McGraw-Hill, New York, 1996, pp 1233.
9 (*a*) S. J. Ezell, H. Li, H. Xu, X. Zhang, E. Gurpinar, X. Zhang, E. R. Rayburn, C. I. Sommers, X. Yang, S. E. Velu, W. Wang and R. Zhang, *Mar. Drugs*, 2010, **8**, 2129; (*b*) J. W. Ruan, Z. S. Huang, J. F. Huang, C. J. Du, S. L. Huang, Z. Shi, L. W. Fu and L. Q. Gu, *Chin. Chem. Lett.*, 2006, **17**, 1141; (*c*) A. Bolognese, G. Correale, M. Manfra, A. Lavecchia, O. Mazzoni, E. Novellino, V. Barone, A. Pani, E. Tramontano, P. La Colla, C. Murgioni, I. Serra, G. Setzu and R.

Loddo, *J. Med. Chem.*, 2002, **45**, 5205; (*d*) A. Bolognese, G. Correale, M. Manfra, A. Lavecchia, O. Mazzoni, E. Novellino, V. Barone, P. La Colla and R. Loddo, *J. Med. Chem.*, 2002, **45**, 5217; (*e*) S. Kamitori and F. Takusagawa, *J. Mol. Biol.*, 1992, **225**, 445; (*f*) U. Hollstein, *Chem. Rev.*, 1974, **74**, 625.
10 (*a*) T. K. Pashkevich, I. A. Postovskii, G. B. Afanaseva and L. P. Ananina, *Khim. Geterotsikl. Soedin.*, 1976, **10**, 77; (*b*) V. C. Barry, M. L. Conalty and E. E. Gaffney, *J. Pharm. Pharmacol.*, 1956, **8**, 1089.
11 (*a*) F. Wang, S. J. Ezell, Y. Zhang, W. Wang, E. R. Rayburn, D. H. Nadkarni, S. Murugesan, S. E. Velu and R. Zhang, *Invest. New Drugs*, 2010, **28**, 234; (*b*) D. H. Nadkarni, F. Wang, W. Wang, E. R. Rayburn, S. J. Ezell, S. Murugesan, S. E. Velu and R. Zhang, *Med. Chem.*, 2009, **3**, 227; (*c*) W. Wang, E. R. Rayburn, S. E. Velu, D. Chen, D. H. Nadkarni, S. Murugesan, D. Chen and R. Zhang, *Breast Cancer Res. Treat.*, 2010, **123**, 321.
12 (*a*) K. Gebhardt, J. Schimana, P. Krastel, K. Dettner, J. Rheinheimer, A. Zeeck and H.-P. Fieldler, *J. Antibiot.*, 2002, **55**, 794; (*b*) P. Krastel, A. Zeeck, K. Gebhardt, H.-P. Fiedler and J. Rheinheimer, *J. Antibiot.*, 2002, **55**, 801.
13 (*a*) A. Sugimoto, Y. Yoshino, R. Watanabe, K. Mizuno and K. Uehara, *J. Heterocycl. Chem.*, 1999, **36**, 1057; (*b*) F. Kehrmann and H. Burgin, *Ber. Dtsch. Chem. Ges.*, 1896, **29**, 1819.
14 T. Mikayama, H. Matsuoka, M. Ara, A. Sugimoto and K. Mizuno, *Sol. Energy Mater. Sol. Cells*, 2001, **65**, 133.
15 R. Huisgen and J. Wulff, *Chem. Ber.*, 1969, **102**, 1848.
16 F. A. Neugebauer and I. Umminger, *Chem. Ber.*, 1980, **113**, 1205.
17 (*a*) F. Freeman, *Chem. Rev.*, 1969, **69**, 591; (*b*) P. A. Koutentis and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2601.
18 (*a*) P. A. Koutentis and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2505; (*b*) I. C. Christoforou, P. A. Koutentis and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1236; (*c*) A. S. Kalogirou and P. A. Koutentis, *Tetrahedron*, 2009, **65**, 6850.
19 (*a*) F. Wudl, P. A. Koutentis, A. Weitz, B. Ma, T. Strassner, K. N. Houk and S. I. Khan, *Pure Appl. Chem.*, 1999, **71**, 295; (*b*) P. A. Koutentis, *Arkivoc*, 2002, **5**, 175.
20 D. Twomey, *J. Heterocycl. Chem.*, 1986, **23**, 615.
21 E. Bamberger and L. Blangey, *Justus Liebigs Ann. Chem.*, 1911, **384**, 272.