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Efficient synthesis of substituted 3-acyl-3,4-dihydrobenzo[*d*][1,2,3]triazines

Rüdiger Reingruber [a,b], Sylvia Vanderheiden [a,b], Thierry Muller [a,b], Martin Nieger [c], Mazen Es-Sayed [d], Stefan Bräse [a,b,*]

[a] *Institute of Organic Chemistry, University of Karlsruhe (TH), Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany*
[b] *Institute of Organic Chemistry, Karlsruhe Institute of Technology (KIT), 76131 Karlsruhe, Germany*
[c] *Laboratory of Inorganic Chemistry, University of Helsinki 00014 Helsinki, Finland*
[d] *Bayer CropScience AG, CS – R Dis I, Alfred-Nobel-Str. 50, 40789 Monheim, Germany*

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ABSTRACT

Acylated *o*-triazenylbenzylamines were cyclized to give 3-acyl-3,4-dihydrobenzo[*d*][1,2,3]triazines in good yields. Thus, a novel cyclization via a Jacobsen indazole-type reaction to aminoindazoles is observed in this context.

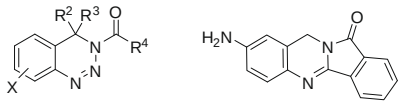
Heterocycles play a pivotal role in drug discovery and as crop protection agents.[1] Benzoannelated nitrogen heterocycles, in particular, often display highly specific biological activities, designating this class of compounds as a source of many privileged structures.[2] Over the last decade, we have shown that triazenes serve as remarkably versatile starting materials for the liquid and solid phase synthesis of numerous nitrogen heterocycles.[3] Moreover, highly functionalized benzotriazoles,[4] cinnolines,[5] benzotriazines,[6] benzothiadiazoles,[7] and various other heterocycles[8] can be formed through intramolecular cyclization of diazonium salts. The latter can easily be generated from the corresponding triazenes, which act as stable intermediates. Recently, we have shown that, above all, diisopropyltriazenes are particularly stable toward strongly basic and even Lewis acidic conditions, thus constituting extremely versatile templates for the synthesis of functionalized heterocyclic compounds.[9]

In this Letter, we describe the synthesis of 3-acylbenzotriazines[10] based on this methodology. In marked contrast to benzotriazinones, which account for a few thousand examples,[11,12] for example, Azinphos methyl (Guthion) a formerly used crop protection agent, 3,4-dihydrobenzo[*d*][1,2,3]triazines are far less abundant (fewer than 100 examples).[10] All in all, 4-alkyl-3-acylbenzotriazines have only once been reported as a byproduct whereas 4-dialkyl-3-acylbenzotriazines (R^2, R^3 = alkyl or aryl, Fig. 1) have been unmentioned in the literature up until now.[13]

We initiated that a systematic synthesis of this class of compounds can be obtained via the well-known N–C–C–C–N–N cyclization due to their potential to mimic important pharmacophores found, for example, in Batracyclin (**2**), an anticancer DNA-binding alkaloid (Fig. 1). The retrosynthetic analysis of the given 4-dialkyl-3-acylbenzotriazines is depicted in Scheme 1. The anticipated heterocycles **1** should be obtained via cyclization of acylated amines **3** bearing a triazene function as a protected diazonium group. The latter compounds can be prepared from the corresponding 2-aminobenzonitriles **4** in good yields.[9,14]

The last step of the reaction sequence, the generation of the diazonium salt followed by the in situ cyclization reaction, occurs most probably via a von Richter[5] or Widman–Stoermer reaction-type mechanism. The required acylbenzylamines **3** were prepared through acylation of benzylamines **5** and delivered, in all cases except one, good to excellent yields (Table 1).[15] The synthesis of compounds **5** has been previously described in detail.[9,13]

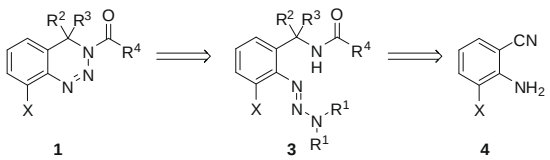
In order to broaden the applicability of the synthesis of 3-acyl-3,4-dihydrobenzo[*d*][1,2,3]triazines (**1**) to a maximum of different substrates, various parameters were investigated. Cyclizations were attempted with acetylated or benzoylated amines, the



3-Acyl-3,4-dihydrobenzo[*d*][1,2,3]triazine (**1**)

Batracylin (**2**)

Figure 1. Generic structure of benzotriazines **1**, Batracyclin (**2**).



1 **3** **4**

Scheme 1. Retrosynthesis of 3-acyl-3,4-dihydrobenzo[*d*][1,2,3]triazines (**1**).

* Corresponding author. Tel.: +49 721 608 2902; fax: +49 721 608 8581.
E-mail address: Stefan.Braese@kit.edu (S. Bräse).

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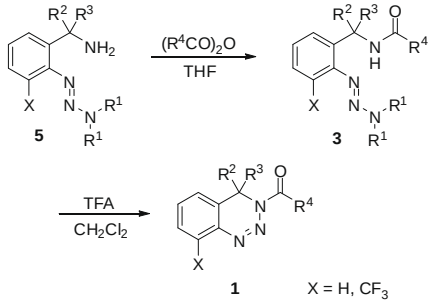
Table 1
Synthesis of acylbenzotriazines **1**



Entry	X	R^1	R^2	R^3	R^4	Acylation yield (%)	Cyclization yield (%)
a	H	*i*Pr	H	H	Me	89	— (65)[a]
b	H	*i*Pr	H	H	Ph	90	12 (44)[a]
c	H	*i*Pr	H	Me	Ph	35	49 (29)[a]
d	H	Et	CH_2–CH_2		Ph	66	80
e	CF_3	*i*Pr	H	H	Me	87	Quant
f	CF_3	*i*Pr	H	H	Ph	Quant	[b]
g	CF_3	Et	H	H	Ph	89	75
h	CF_3	*i*Pr	H	Me	Ph	88	67
i	CF_3	*i*Pr	H	Bu	Me	93	88
j	CF_3	*i*Pr	H	Ph	Me	58	99
k	CF_3	*i*Pr	CH_2–CH_2	Me	Quant	93	

[a] A phenol was formed through hydrolysis of the diazonium salt, with the yield in parentheses.
[b] An indazole **6** (Scheme 2, Fig. 4) was isolated as the main product in 93% yield.

substituents in the benzylic position were altered and the electron density of the aromatic cycle was varied (Table 1). The use of benzylamines bearing an unsubstituted benzylic position and a 3,3-diisopropyl-triazene moiety resulted in the hydrolysis of the diazonium salts, thus yielding the corresponding phenols as major products (entries a and b). The latter are frequent byproducts of these cyclization reactions. In our case, however, hydrolysis was suppressed by substitution of one benzylic hydrogen by a methyl group (entry c).

When the benzylic position bore a cyclopropane and the isopropyl groups were replaced by ethyl moieties, hydrolysis was no longer observed and the desired compound **1** was obtained in excellent yield (entry d). Modifying the electron density of the aromatic cycle by introducing a trifluoromethyl group *ortho* to the triazene led to generally better yields as hydrolysis was completely suppressed in all cases (entries e–k). The structures of **1e** and **1k** have been confirmed by X-ray crystallography (Figs. 2 and 3), which demonstrates that they are co-planar and therefore should have DNA-intercalating abilities such as those displayed by Batracyclin (**2**). Biological testing is in progress.

In the case of 3,3-diisopropyltriazene **3f**, instead of the anticipated benzotriazine **1f** (Table 1, entry f, Scheme 2), indazole derivative **6**[14] was isolated as the sole product in 93% yield. The structure of compound **6** has been proven by X-ray crystallography (Fig. 4). This transformation presumably proceeds via a Jacobsen-type indazole synthesis,[16] although the latter generally takes place in the presence of alkyl groups rather than benzylamines (Scheme 3).[15,17] This result is all the more astonishing given that reacting triazene **3g** under identical conditions leads to the desired triazine **1g** with no traces of the corresponding indazole (Table 1, entry g, Scheme 2). For the moment, we are unable to rationalize these findings. Given that in both cases the corresponding compounds were obtained as sole products in high yields, an indazole–triazine equilibrium is unlikely to exist. It seems that switching from isopropyl to ethyl groups on the triazene moiety induces a completely different reaction pathway.

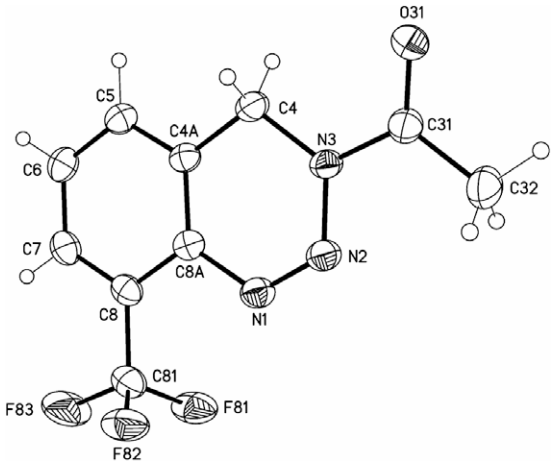


Figure 2. Molecular structure of one of the two independent molecules of **1e** in the crystal (ORTEP drawing showing 50% ellipsoids).

In contrast to acylbenzotriazines, sulfur-substituted benzotriazines are virtually unknown.[11,18] Starting from the *N-tert*-butylsulfinylamine **7**—prepared as a diastereomeric mixture (approx. 1:1) in 58% yield through 1,2-addition to the corresponding *N-tert*-butylsulfinyl-amide[9]—cyclization led to the formation of the novel heterocycle **8**, which, when the reaction time was extended, underwent complete deprotection and cleavage of the *tert*-butylsulfinyl group to form 4-methyl-4-phenyl-3,4-dihydrobenzo[*d*][1,2,3]triazine (**9**) in almost quantitative yield (Scheme 4).

In summary, we have presented an efficient synthesis of benzotriazines based on functionalized triazenes. Moreover, our group is conducting ongoing studies to further investigate the unexpected formation of an indazole during the reaction of a 3,3-diisopropyltriazene derivative.

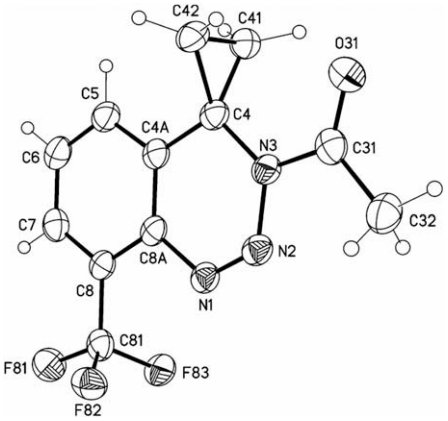
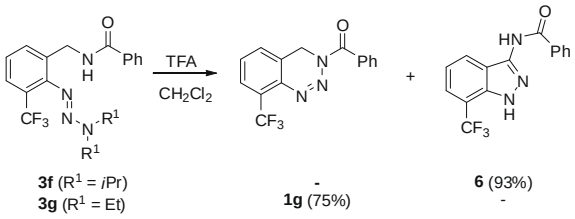


Figure 3. Molecular structure of **1k** in the crystal (ORTEP drawing showing 50% ellipsoids).



Scheme 2. Synthesis of benzotriazine **1g** and indazole **6**.

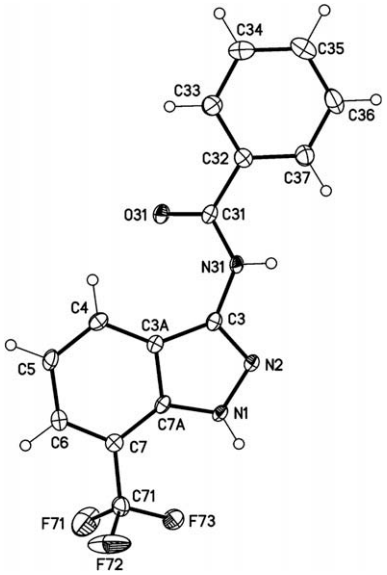
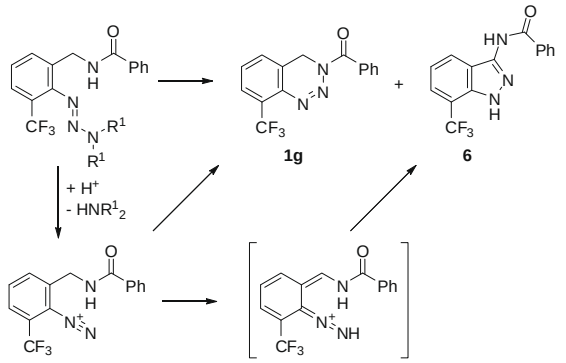
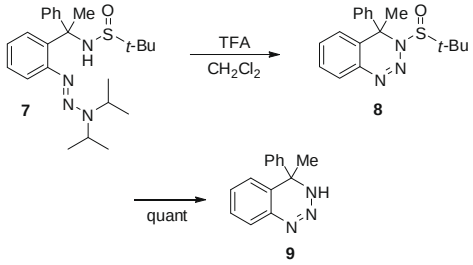


Figure 4. Molecular structure of **6** in the crystal (ORTEP drawing showing 50% ellipsoids).

Crystal structure studies of **1e**, **1k,** and **6**: Single-crystal X-ray diffraction studies were carried out on a Nonius KappaCCD diffractometer (**1k**), a Bruker–Nonius APEXII diffractometer (**1e**), and a Bruker–Nonius KappaCCD diffractometer (**6**) at 123(2) K using MoK$_\alpha$ radiation (λ = 0.71073 Å). The structures were solved by Direct Methods (SHELXS-97[19]) and refinement was carried out using SHELXL-97[19](full-matrix least-squares refinement on F^2). The hydrogen atoms were localized by difference electron density determination and were refined using a 'riding' model (in **6** H(N) free). Important data on the data collection and structure solution and refinement are listed in Table 2. Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 715560 (**1k**), 715561



Scheme 3. Proposed mechanism for the formation of the indazole **6**.[20]



Scheme 4. Formation of 4-methyl-4-phenyl-3,4-dihydrobenzo[*d*][1,2,3]-triazine (**9**).

Table 2
Crystallographic data, structure solution, and refinement of **1e**, **1k,** and **6**

	1e	**1k**	**6**
Empirical formula	$C_{10}H_8F_3N_3O$	$C_{12}H_{10}F_3N_3O$	$C_{15}H_{10}F_3N_3O$
Formula weight	243.19	269.23	305.26
Temperature (K)	123(2)	123(2)	123(2)
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)
a (Å)	14.5127(5)	7.7501(5)	4.864(1)
b (Å)	20.2533(6)	20.1213(12)	9.539(2)
c (Å)	7.3614(2)	7.9161(5)	27.379(6)
α (°)	90	90	90
β (°)	100.487(2)	111.821(3)	94.66(3)
γ (°)	90	90	90
V (Å^3)	2127.59(11)	1146.00(12))	1266.1(5))
Z	8	4	4
D_{calcd} (g cm^{-3})	1.518	1.560	1.601
Abs. coeff. (mm^{-1})	0.138	0.136	0.134
F(000)	992	552	624
Crystal size (mm)	0.45 × 0.25 × 0.15	0.30 × 0.10 × 0.05	0.40 × 0.20 × 0.10
$2\theta_{max.}$ (°)	50	50	50
Limiting indices	$-16 \le h \le 17$ $-22 \le k \le 24$ $-8 \le l \le 8$	$-9 \le h \le 8$ $-22 \le k \le 23$ $-9 \le l \le 9$	$-5 \le h \le 5$ $-11 \le k \le 11$ $-32 \le l \le 32$
Reflections collected	15,276	7640	11,325
Unique reflections	3745	2021	2205
R_{int}	0.0485	0.0674	0.0686
Data/restraints/ parameters	3745/0/309	2021/0/173	2205/2/205
GOF on F^2	1.074	1.104	1.146
R^1 [$I > 2\sigma(I)$]	0.0437	0.0626	0.0638
wR^2 (all data)	0.1064	0.1641	0.1312
Largest diff. map peak and hole (e A^{-3})	0.186/−0.239	0.387/−0.468	0.300/−0.466

(**1e**), and 715562 (**6**). Copies of the data can be obtained free of charge upon application to: The Director, CCDC, 12 Union Road, Cambridge DB2 1EZ, UK (Fax: int.code+(1223)336-033; e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgments

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