JOC Article

Synthesis of Fused Tetrazole Derivatives via a Tandem Cycloaddition and *N*-Allylation Reaction and Parallel Synthesis of Fused Tetrazole Amines

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A method for the synthesis of novel fused tricyclic tetrazoles from allylic bromides generated by the recently discovered DiazAll reaction has been developed. This new tandem reaction comprises a cycloaddition between a nitrile and $(TMS)N_3$ followed by an intramolecular *N*-allylation. The variation of functionalities in the benzene moiety was well-tolerated, and only a moderate difference in yield and degree of purity was noticed. An *exo*-methylene group in these new compounds permitted further derivatization. Structural resemblance with substances which possess important pharmacological properties motivated the synthesis of a series of ketones and a small library of amines.

Introduction

The tetrazole subunit is an important structural feature which has been used as a metabolically stable isosteric replacement for the carboxylic acid moiety,[1] as a *cis*-peptide bond mimetic,[2,3] as a precursor to other heterocycles,[4] in high-energy compounds,[5] and as a coordinating group in directed *ortho*-metalation.[6−8] Several biologically relevant substances incorporating a tetrazole moiety have been developed (Figure 1). Losartan (**1**), an angiotensin II antagonist, has been used to treat hypertension,[9,10] pentylenetetrazole (PTZ, **2**) has been extensively used in models for anxiety,[11,12] and tetrazole **3** has shown affinity to benzodiazepine receptors.[13]

We recently developed a method for the synthesis of allyl aromatic compounds via generation of aryl radicals by diazotization and a subsequent in situ allylation with allylic bromides (the DiazAll reaction).[14−16] Our interest to develop applications of the synthesized allyl aromatic compounds in combination with a general demand for novel substances, which could potentially interact with biological systems, made us attempt synthesizing tricyclic fused tetrazoles **8a**−**f** and **11a**−**f** (Scheme 1 and Table 1). This type of tetrazole derivative has structural similarities to 1,4-benzodiazepin-2,5-dione (**4**), representing a group of compounds which possess anxiolytic, anticonvulsant, and antitumor properties,[17] and fused tricyclic imidazoles such as flumazenil (**5**), a benzodiazepine antagonist (Figure 1).[18,19] However, our initial attempts to synthesize fused tetrazole derivatives using the DiazAll reaction did not result in the expected benzazepine **8d** (Scheme 1). Instead, the allylic bromide **9** continued to react with in situ generated bromine, in a process similar to a bromolactonization, which resulted in **10**.[16] Recently, we have developed this halocyclization methodology to access fused heterocycles, and a number of fused tetrazole and imidazole derivatives have been synthesized.[6]

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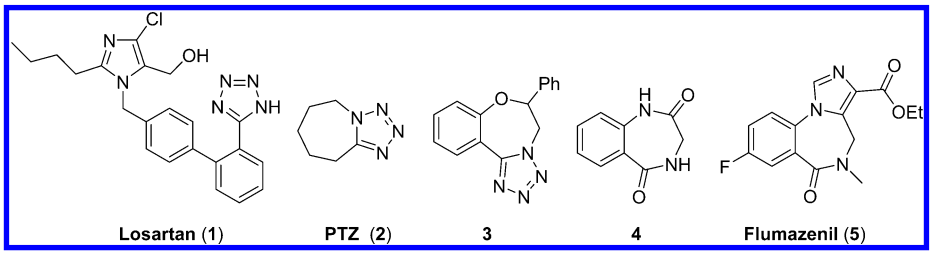


FIGURE 1. Examples of relevant pharmacologically active substances.

SCHEME 1. Allylation−Bromocyclization

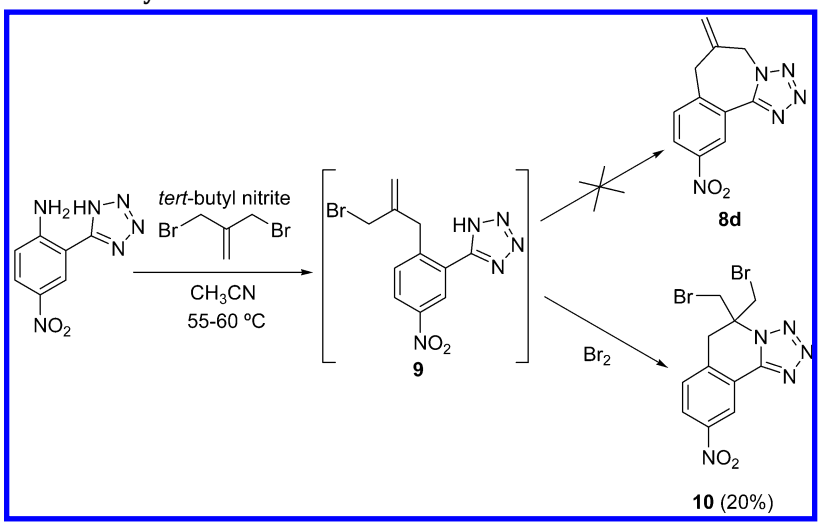
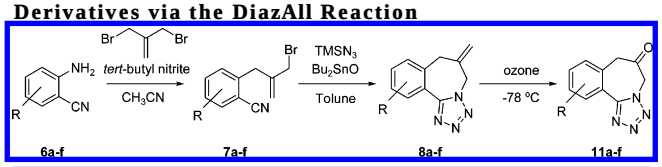


TABLE 1. Synthesis of the Tricyclic Fused Tetrazole Derivatives via the DiazAll Reaction



R	yield[a] (%)	yield[b] (%)	yield[b] (%)
5-Cl	72 (**7a**)	66 (**8a**)	63 (**11a**)
5-Br[16]	82[c] (**7b**)	67 (**8b**)	64 (**11b**)
4-NO_2	65[d] (**7c**)	63 (**8c**)	79 (**11c**)
5-NO_2	67 (**7d**)	64 (**8d**)	73 (**11d**)
4-CF_3	72 (**7e**)	60 (**8e**)	81 (**11e**)
4-Cl-5-Br	75[e] (**7f**)	68 (**8f**)	74 (**11f**)

[a] The yields of allylic bromides were determined by ^{1}H NMR spectroscopy using toluene as internal standard. [b] Isolated yields of tetrazole derivatives. [c] The isolated yield of **7b** was 62%. [d] The isolated yield of **7c** was 48%. [e] The isolated yield of **7f** was 54%.

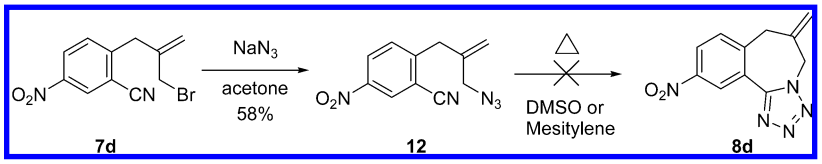
However, our objective was still to develop a method for the synthesis of the fused tetrazole derivatives and to use these compounds in the synthesis of pharmacologically relevant substances. In this paper we present a route to the synthesis of fused tetrazole derivatives. A parallel synthetic approach toward the synthesis of an amine library based on these novel tetrazole derivatives is also described.

Results and Discussion

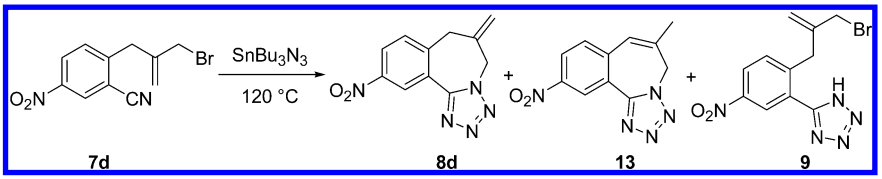
The DiazAll reaction was used in the initial step of the synthesis of the fused tetrazole derivatives (Table 1). Careful addition of the arylamine (solid) in portions to a solution containing 3-bromo-2-bromomethylpropene and *tert*-butyl nitrite in acetonitrile at 60−70 °C gave good yields of the allylic bromides. Additional *tert*-butyl nitrite was supplied during the reaction to maintain gas evolution, which indicated conversion of the arylamine. Although an excess of allylic bromide (10 equiv) was used, 5 equiv could be recovered from the reaction mixture by distillation at reduced pressure and reused. As seen in Table 1, a variety of substituents on the aromatic moiety were well-tolerated and only minor changes of the yields were observed. The purification of the crude products was troublesome due to the reactive nature of the allylic bromides. Silica gel chromatography resulted in approximately 20% lower yields as compared to the yields determined by ^{1}H NMR spectroscopy using internal standard. Also, attempts to use reversed-phase preparative HPLC gave nonreproducible results, and byproducts were difficult to remove. These were composed essentially of partly polymerized allylic bromide and 1,2,3-tribromo-2-bromomethylpropane. Thus, only allylic bromides **7b**, **7c**, and **7f** could be obtained pure by crystallization from the resulting viscous oil after column chromatography. To avoid unnecessary losses of allylic bromides **7a**−**f**, it was crucial to find a method for the synthesis of the fused tetrazole derivatives, which would allow the use of crude starting material. Furthermore, such a method must be mild enough to avoid isomerization of the *exo*-methylene group.

Both intra- and intermolecular synthetic strategies were considered as indicated in Schemes 2 and 3. The intramolecular approach was studied using allylic azide **12**, which was synthesized from the corresponding bromide (Scheme 2). However, when **12** was heated in toluene or DMSO, no product could be isolated, although

SCHEME 2. Synthesis and Attempted Intramolecular Cycloaddition of 12



SCHEME 3. Tributyltin Azide Induced Cycloaddition Followed by an Intramolecular *N*-Allylation of 7d

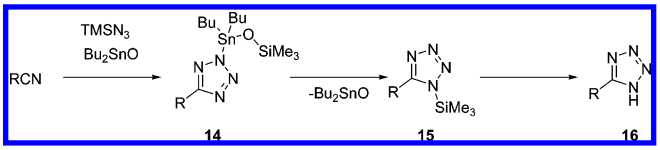


cases of successful intramolecular cycloaddition in the formation of fused tetrazoles of similar compounds have been reported.[20−22] The elevated reaction temperature (110 or 140 °C) resulted only in deterioration of **12**. Inspection of molecular models indicated that the allylic azide and the nitrile group could not easily align properly for ring closure, which may explain the negative result. In support of this, Sharpless et al. reported that a seven-membered ring system could not be obtained using an intramolecular cycloaddition procedure.[21]

Therefore, we focused on the intermolecular cycloaddition followed by an intramolecular *N*-allylation, which would result in a one-pot two-step reaction. It has been shown that a 2-tributylstannyl-substituted tetrazole derivative is formed in the cycloaddition between a nitrile and tributyltin azide.[23] Moreover, 2-stannyl tetrazole derivatives have been selectively *N*-alkylated in position 1.[24] An initial experiment that involved stirring **7d** with tributyltin azide at 120 °C resulted in a fast formation of the product as indicated by HPLC analysis. However, considerable amounts of the isomerized byproduct **13** and what was suspected to be the nonalkylated tetrazole derivative **9** were also formed, indicated by NMR and mass spectral analyses of the crude product (Scheme 3). This experiment confirmed that the tandem tetrazole formation−ring closure transformation was possible although a milder method was necessary.

A number of different methods for the synthesis of tetrazoles from nitriles have been developed[1] although only a few of them, e.g., $NaN_3/ZnCl_2$,[25] $(TMS)N_3/Me_3Al$,[26] and $(TMS)N_3$/dibutyltin oxide (DBTO),[27] were considered to be mild enough to be suitable for our application. The DBTO method, developed by Wittenberger et al., appeared to be particularly promising since this method has been reported to be useful with sterically demanding nitriles such as *ortho*-substituted benzonitriles.[27]

SCHEME 4. Mechanism of the Formation of Tetrazoles Using DBTO and $(TMS)N_3$ Suggested by Wittenberger et al.



Two of the methods ($NaN_3/ZnCl_2$ and $(TMS)N_3/Me_3Al$) resulted in deterioration of the allylic bromide or the formed product. Fortunately, using a mixture of a catalytic amount of DBTO (0.18 equiv) and $(TMS)N_3$ (2 equiv) gave **8d**, although only 50% of **7d** was consumed. In an attempt to get complete conversion of the allylic bromide, more azide reagent was added to the reaction mixture. Still, the conversion did not exceed 50%. However, full conversion was obtained using in total 0.72 mol % (four portions added over 20 h) tin reagent and 5 equiv of $(TMS)N_3$, although some isomerization of the product was noticed. Therefore, we decided to use 1 equiv of DBTO from the start of the reaction in combination with 5 equiv of $(TMS)N_3$ in toluene at 105 °C under argon. As seen in Table 1, this procedure gave the fused tetrazole derivatives in good yields with typical reaction times around 10−12 h. Furthermore, the influence of the substituents in the benzene moiety on the yield was negligible (Table 1). More importantly, no isomerization could be detected, and the use of either pure or crude allylic bromide gave similar results. Careful purification is essential due to the facile isomerization of the *exo*-methylene group. The crude products were not stable even when stored at 4−6 °C, but pure compounds were stable for at least 1.5 years at −18 °C. The stoichiometric (DBTO) procedure was also performed at elevated temperature using a sealed vessel and oil bath or microwave-assisted heating (200 °C). This resulted in reduced reaction times (from 10−12 h to 15−25 min) and almost as good yields as in the ordinary procedure. However, attempts of using crude allylic bromide **7d** at elevated reaction temperature resulted in a 1:1 mixture of the product **8d** and the isomerized byproduct **13**.

Wittenberger and co-workers have already described a plausible mechanism for the formation of tetrazoles using DBTO in combination with $(TMS)N_3$ (Scheme 4).[27] In cyclization of ordinary nitriles, the tetrazole intermediate **14** continues to form the silylated tetrazole **15**, which is hydrolyzed upon workup to give **16**.

In our case, however, an internal allylation takes place probably via intermediate **20** or **22**. This sequence results

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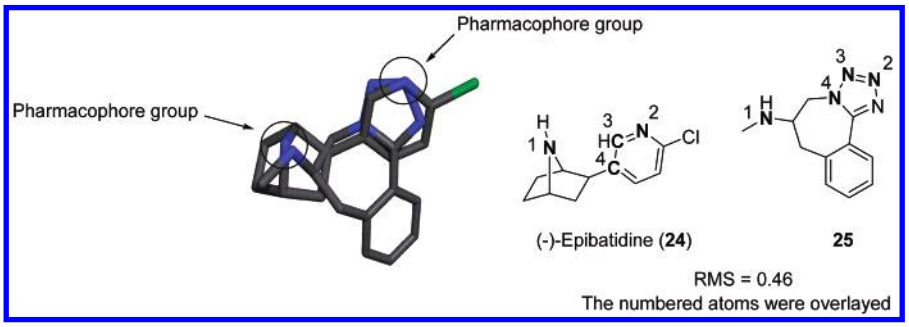
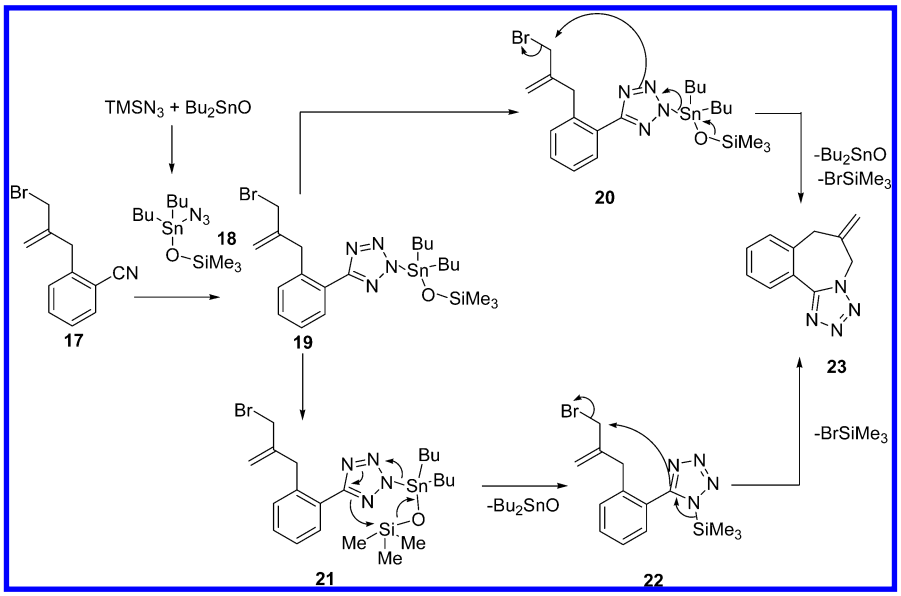


FIGURE 2. Overlay of **24** and **25**.

SCHEME 5. Mechanism of the Formation of Fused Tetrazole Derivatives via a Tandem Reaction



in the tricyclic fused tetrazole **23**, bromotrimethylsilane, and DBTO (Scheme 5). Although DBTO is regenerated according to the suggested mechanism, the tandem reaction was barely catalytic in practice.

Since our ambition was to access compounds which might possess interesting pharmacological properties, further derivatization of the *exo*-methylene compounds **8a**−**f** was desired. Ozonolysis of *exo*-methylene derivatives **8a**−**f** at −78 °C followed by addition of dimethyl sulfide gave 63−81% of the corresponding ketones (Table 1). The carbonyl group is itself a handle for further derivatizations, and our attention was drawn to reductive amination for the following reason.

It turned out that the marked atoms of a low-energy conformation of **25** (Figure 2)[28] coincided to a high degree with the pharmacophore elements of epibatidine (**24**),[29] a natural product which has shown nanomolar affinity for the nicotinic acetylcholine receptors.[30,31] The structural similarity of **25** with **24**, but also the inherent phenethylamine subunit, a common structural feature in compounds regulating several important functions in humans, motivated the synthesis of amine derivatives similar to **25**. Thus, we needed a method which would allow synthesis of a larger number of amines using a rational workup and purification procedure. Reductive amination and purification via ion exchange chromatography has been used for the parallel synthesis of amines with good results.[32,33] However, due to a fast reduction of the ketones to the corresponding alcohols, the reductive amination methodology failed, although different procedures and reagents ($NaCNBH_3$[34] or $NaHB(OAc)_3$[35]) were tested. Instead, we decided to use a stepwise procedure in which the enamine was formed prior to the addition of the reducing agent. The enamines were formed in situ using several different solvents (CH_2Cl_2, 1,2-dichloroethane, trichloroethylene, CH_3CN, and THF). In each case, a mixture of two isomeric enamines was formed due to the two directions in which conjugation could be attained. Noticeably, reactions performed in methanol, a solvent commonly used in reductive amination reac-

(28) Conformational analysis using PcSpartan Pro (AM1).
(29) The overlay was done in Chem3D using a reported low-energy conformation of **24**. See: Tønder et al. *J. Med. Chem.* **1999**, *42*, 4970−4980.
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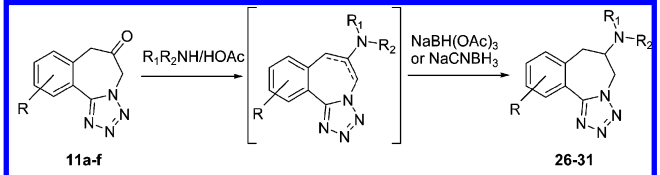
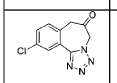
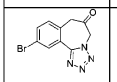
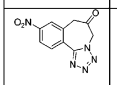
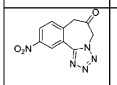
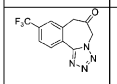
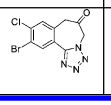
TABLE 2. Synthesis of Fused Tetrazole Amines



Starting material: Amine / Ketone	(c)	(c)	(d)
	93/93 (**26a**)	84/93 (**27a**)	93/93 (**28a**)
	98/96 (**26b**)	78/94 (**27b**)	85/93 (**28b**)
	98/88 (**26c**)	79/65 (**27c**)	91/92 (**28c**)
	96/87 (**26d**)	69/88 (**27d**)	87/89 (**28d**)
	94/93 (**26e**)	79/93 (**27e**)	93/93 (**28e**)
	99/97 (**26f**)	75/95 (**27f**)	89/94 (**28f**)

[a] Isolated yield of amine. [b] The purity of the amines was determined using HPLC (UV detection at 220 nm). The structural identification was made with ^{1}H NMR and mass spectroscopy. [c] The reaction was performed on a 0.05 mmol scale in THF and using $NaCNBH_3$ as reducing agent. [d] The reaction was performed on a 0.1 mmol scale in 1,2-dichloroethane and using $NaBH(OAc)_3$ as reducing agent.

tions, failed. Since the enamines are conjugated with the benzene ring or the tetrazole moiety, the reduction was difficult especially in those cases in which the benzene ring was substituted with a nitro group (starting from ketone **11c** or **11d**). Thus, only two different combinations of solvent and reducing agent gave the amines in good yields, namely, THF/$NaCNBH_3$ and trichloroethylene/$NaBH(OAc)_3$.[36] Due to environmental considerations, we preferred to use THF in combination with $NaCNBH_3$ in the synthesis of the small library. Using this procedure in combination with Varian Bond Elut SCX columns for purification gave good to excellent yields of the amines (average yield 88%). Most often, the products were isolated in a high degree of purity (Table 2, Figure 3, average purity 91%), but in the case of amines synthesized from the nitro-substituted ketones **11c** and **11d**, a larger amount of byproducts was formed, possibly as a result of a more problematic reduction of the enamines. We also found that 1,2-dichloroethane (solvent) in combination with benzylamine and $NaHB(OAc)_3$ gave tertiary amines in excellent yields (Table 2, row 3). The initially formed secondary benzylamine was most likely alkylated with 1,2-dichloroethane, and the resulting chloroethylamine was then reduced to give the tertiary

(36) CH_2Cl_2 and 1,2-dichloroethane reacted with the amines in the reaction mixture, which resulted in other amines than the product.

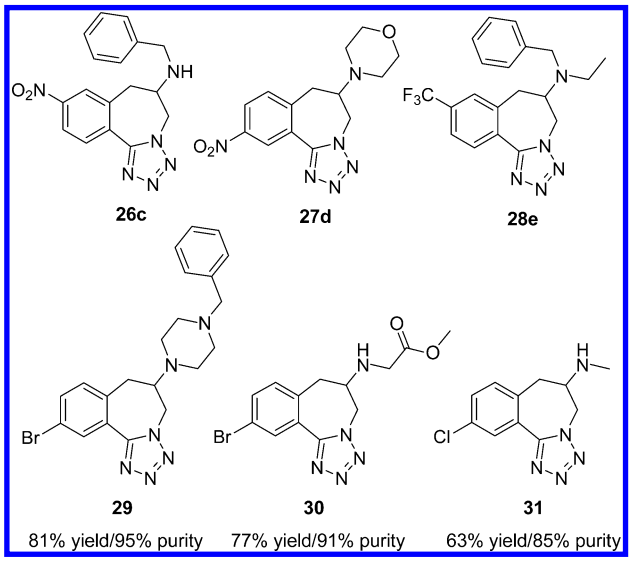


FIGURE 3. Examples of synthesized amines.

amine. Only 1 equiv of 4-benzylpiperazine could be applied in the synthesis of **29** (Figure 3), since the excess amine reagent was difficult to remove from the crude product at reduced pressure. In this case, trichlorethylene/$NaHB(OAc)_3$ was found to be a better alternative compared to the THF procedure. In addition, we have demonstrated that it is possible to access a glycine derivative of the fused tetrazoles from the corresponding hydrochloride salt of a protected amino acid (**30**; Figure 3). Also, anhydrous methylamine could be employed, although a modified procedure was applied in which the methylamine was bubbled into the reaction mixture containing the ketone and acetic acid. Reduction and purification gave the methylamine derivative **31** in moderate yield and purity (Figure 3).

In conclusion, we have developed a method for the synthesis of novel fused tricyclic tetrazoles from allylic bromides, generated by the recently discovered DiazAll reaction. This new tandem reaction comprises a cycloaddition between a nitrile and $(TMS)N_3$ induced by DBTO followed by an intramolecular *N*-allylation. An *exo*-methylene group in these compounds permitted further derivatization. By ozonolysis, a series of ketones were synthesized which were then used as starting materials in the parallel synthesis of a small library of amines. Overall, the variation of functionalities in the benzene moiety was well-tolerated, and only moderate differences in yield and degree of purity were noticed. Structural resemblance of the synthesized ketones and amines with substances possessing important pharmacological properties suggests possible bioactivity. This study is currently being performed, and the results will be presented in due course.

Experimental Section

5-Bromo-4-chloroanthranilonitrile (6f). *N*-Bromosuccinimide (2.31 g, 13.0 mmol) was added to 4-chloroanthranilonitrile (1.53 g, 10.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was then stirred at 25 °C until all 4-chloroanthranilonitrile was consumed (monitored by HPLC, usually

2−3 h).[37] Saturated aqueous Na_2SO_3 was then added to the reaction mixture, and the separated organic phase was washed with brine and then dried (Na_2SO_4). Removal of the solvent at reduced pressure and column chromatography (heptane−EtOAc, 6:1) of the residue gave 1.2 g (52%) of **6f** as white crystals: mp 176−178 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (s, 1H), 6.89 (s, 1H), 4.49 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.2, 140.8, 136.4, 116.6, 115.7, 109.6, 96.5; HRMS (EI^+) *m*/*z* calcd for $C_{11}H_9Br_2ClN$ (M) 229.9246, found 229.9244.

Typical Procedure for the Synthesis of Allyl Aromatic Bromides 7a−7f. 2-(2-Bromomethyl-2-propenyl)-5-chlorobenzonitrile (7a). Arylamine **6a** (0.30 g, 2.0 mmol) was added in small portions to a mixture of acetonitrile (4 mL), 3-bromo-2-bromomethylpropene (4.28 g, 20.0 mmol), and *tert*-butyl nitrite (0.48 mL, 4.0 mmol), keeping the temperature between 60 and 70 °C. During the 20 min of addition, more *tert*-butyl nitrite (0.24 mL, 2.0 mmol) was added in portions to maintain the evolution of gas. After complete addition of **6a**, the temperature was kept at 60 °C, and stirring was continued for 1 h before removal of the solvent at reduced pressure. The remaining 3-bromo-2-bromomethylpropene (2.15 g, 10.0 mmol) was then recovered by distillation (30 °C, 0.7 mmHg). Ether was added to the remaining oil, and the formed precipitate was filtered off and discarded. The filtrate was concentrated at reduced pressure, and the yield was determined to be 72% by ^{1}H NMR analysis using toluene as internal standard. The toluene was then removed by distillation at reduced pressure. Column chromatography (heptane−EtOAc, 23:2) of the residue gave 0.29 g (53%, 85−90% purity) of **7a** as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, 1H, J = 2.2 Hz), 7.53 (dd, 1H, J = 8.3, 2.2 Hz), 7.36 (d, 1H, J = 8.4 Hz), 5.35 (d, 1H, J = 0.7 Hz), 4.91 (d, 1H, J = 0.5 Hz), 4.01 (s, 2H), 3.80 (d, 2H, J = 0.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.7, 141.1, 134.6, 133.6, 133.0, 132.2, 118.8, 116.8, 115.1, 38.3, 36.0; HRMS (CI^+) *m*/*z* calcd for $C_{11}H_{10}NClBr$ (M + H) 269.9687, found 269.9716.

2-(2-Azidomethyl-2-propenyl)-5-nitrobenzonitrile (12). 7d (61 mg, 0.22 mmol) was added to a mixture of NaN_3 (74 mg, 1.14 mmol) in acetone (1.4 mL) under argon atmosphere. The resulting mixture was stirred for 15 min at 22 °C and then at reflux for 2 h. The mixture was cooled to ambient temperature, and water and ether were added. The aqueous phase was extracted with ether, and the combined organic phases were dried (Na_2SO_4) before removal of the solvent at reduced pressure. Column chromatography (heptane−EtOAc, 8:2) of the residue gave 31 mg (58%) of **12** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.53 (d, 1H, J = 2.4 Hz), 8.40 (dd, 1H, J = 8.6, 2.4 Hz), 7.59 (d, 1H, J = 8.6 Hz), 5.30 (s, 1H), 4.97 (s, 1H), 3.80 (s, 2H), 3.76 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.6, 147.1, 140.2, 132.0, 128.5, 127.9, 118.5, 116.0, 115.1, 56.1, 39.1; HRMS (CI^+) *m*/*z* calcd for $C_{11}H_{10}O_2N_5$ (M + H) 244.0836, found 244.0844.

Typical Procedure for the Synthesis of Compounds 8a−f. 9-Chloro-5-methylene-5,6-dihydro-4*H*-1,2,3,3a-tetraazabenzo[*e*]azulene (8a). Dibutyltin oxide (0.50 g, 2.0 mmol) was added to a mixture of crude or purified **7a** (2.0 mmol)[38] and $(TMS)N_3$ (1.3 mL, 10.0 mmol) in dry toluene (10 mL). The mixture was stirred at 105 °C under argon for 10−12 h (the reactions were monitored by HPLC). The volatile material of the reaction mixture was then removed at reduced pressure, and the residue was dissolved in methanol to methanolyze the remaining reagents. The methanol was removed at reduced pressure, and EtOAc was added to the residual oil. The resulting suspension was filtered through a pad of silica (elution with EtOAc), and the filtrate was washed with aqueous saturated $NaHCO_3$. A precipitate (possibly residues from DBTO and $(TMS)N_3$) was formed in the washing process which could not be removed from the organic phase. The resulting suspension was therefore dried (Na_2SO_4) and then filtered through a pad of silica (elution with EtOAc), and the filtrate was concentrated at reduced pressure. Column chromatography (heptane−EtOAc, 2:1) of the residue followed by recrystallization (heptane−acetone) gave 220 mg (66%) of **8a** as pale yellow crystals: mp 118−119 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, 1H, J = 2.2 Hz), 7.60−7.53 (m, 2H), 5.38 (t, 2H, J = 1.5 Hz), 5.30 (dd, 2H, J = 7.5, 0.7 Hz), 3.74 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.0, 141.5, 138.6, 133.5, 132.4, 132.3, 129.6, 126.0, 115.8, 54.2, 40.1; HRMS (EI^+) *m*/*z* calcd for $C_{11}H_9ClN_4$ (M) 232.0516, found 232.0512.

Typical Procedure for the Synthesis of Ketones 11a−f. 9-Chloro-5,6-dihydro-4*H*-1,2,3,3a-tetraazabenzo[*e*]azulene-5-one (11a). Ozone was bubbled through a solution of **8a** (220 mg, 0.95 mmol) in dichloromethane (5 mL) and methanol (5 mL) at −78 °C until a blue color of the reaction mixture persisted (10−12 min).[39] The solution was flushed with argon to remove excess ozone, and dimethyl sulfide (4 mL) was then added. The reaction mixture was slowly warmed to room temperature (3 h). EtOAc was added, the aqueous phase was extracted twice with EtOAc, and the combined organic phase was washed with H_2O and brine and then dried (Na_2SO_4). Removal of the solvent at reduced pressure followed by column chromatography (heptane−EtOAc, 1:1) and recrystallization (heptane−EtOAc) gave 140 mg (63%) of **11a** as pale yellow crystals: mp 193−195 °C dec; ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.96 (d, 1H, J = 2.2 Hz), 7.69 (dd, 1H, J = 8.3, 2.3 Hz), 7.59 (d, 1H, J = 8.3 Hz), 5.40 (s, 2H), 4.04 (s, 2H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 199.7, 153.9, 134.0, 132.8, 132.6, 131.0, 129.0, 125.5, 56.6, 48.2. Anal. Calcd for $C_{10}H_7ClN_4O$: C, 51.19; H, 3.01; N, 23.88. Found: C, 51.08; H, 3.11; N, 23.81.

Typical Examples of the Synthesis of Tetrazole Amines 26−28 via Stepwise Reductive Amination. 5-(*N*-Benzylamino)-9-bromo-5,6-dihydro-4*H*-1,2,3,3a-tetraazabenzo[*e*]azulene (26b). Benzylamine (1.0 mL, 0.045 mM in THF) and acetic acid (1.0 mL, 0.05 mM in THF) were added to ketone **11b** (14 mg, 0.05 mmol). The reaction mixture was stirred at reflux until complete consumption of the amine (monitored by HPLC). The reaction mixture was cooled, $NaCNBH_3$ (13 mg, 0.20 mmol) and acetic acid (1.0 mL, 0.1 mM in THF) were added, and stirring was continued for 48 h at 24 °C. After complete reduction of the enamines, NaOH (1 M, 1 mL), brine (1 mL), and ether (1 mL) were added to the reaction mixture, and stirring was continued for 30 min. The organic phase was then applied to a Varian Bond Elut SCX column, which had been prewashed twice with MeOH (10 mL) and once with THF (10 mL). The column was then washed twice with MeOH (10 mL) to remove neutral impurities. The product was then eluted from the column using ammonia in MeOH (3 × 2 mL). Removal of the volatile material in the eluate by passing a gentle stream of argon over the solution, maintaining the temperature at 50 °C, gave 16 mg (98%) of **26b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.23 (d, 1H, J = 2.1 Hz), 7.60 (dd, 1H, J = 8.1, 2.1 Hz), 7.38−7.25 (m, 5H), 7.21(d, 1H, J = 8.2 Hz), 4.50 (dd, 1H, J = 15.5, 5.2 Hz), 4.45 (dd, 1H, J = 15.3, 5.3 Hz), 3.92 (d, 1H, J = 13.4 Hz), 3.88 (d, 1H, J = 13.4 Hz), 3.71 (m, 1H), 2.98 (dd, 1H, J = 15.0, 4.8 Hz), 2.79 (dd, 1H, J = 14.9, 7.1 Hz); MS (ESP^+) (M + H) *m*/*z* 370.2.

9-Chloro-5-morpholino-5,6-dihydro-4*H*-1,2,3,3a-tetraazabenzo[*e*]azulene (27a). Morpholine (1 mL, 0.2 mM in THF)

(37) The starting material and product had the same R_f value in straight-phase chromatography (heptane−EtOAc). The dibrominated byproduct differed in R_f value from the other substances. To obtain a pure product, it was therefore important to consume all starting material.

(38) The allylation reactions gave approximately 2.0 mmol of nitrile-containing products and byproducts. Therefore, the amounts of DBTO and $(TMS)N_3$ used in the tandem reaction were based on the fact that the reaction mixture contained 2 mmol of crude allylic bromide. However, the final yields of the fused tetrazoles were calculated using the yields (internal standard) from the allylation reactions.

(39) Some of the starting materials, i.e., **8c** and **8f**, were difficult to dissolve in $MeOH/CH_2Cl_2$, which complicated these reactions. However, additional solvent and a change in the solvent composition remedied this problem. Also, the corresponding products **11c** and **11f** had poor solubility in common solvents, but recrystallization without prior chromatography gave the pure compounds.

and acetic acid (1 mL, 0.05 mM in THF) were added to ketone **11a** (12 mg, 0.05 mmol). The reaction mixture was stirred at reflux until complete consumption of the ketone (monitored by HPLC). The reaction mixture was cooled, $NaCNBH_3$ (13 mg, 0.20 mmol) and acetic acid (1 mL, 0.2 mM in THF) were added, and stirring was continued for 48 h at 24 °C. After complete reduction of the enamines, NaOH (1 M, 1 mL), brine (1 mL), and ether (1 mL) were added to the reaction mixture, and stirring was continued for 30 min. The organic phase, separated from the alkaline aqueous phase, was concentrated by passing a gentle stream of argon over the solution. The remaining oil was kept at reduced pressure until the excess morpholine had evaporated. The residue was dissolved in MeOH and then applied to a Varian Bond Elut SCX column which had been prewashed twice with MeOH (10 mL) and once with THF (10 mL). The column was then washed twice with MeOH (10 mL) to remove neutral impurities. The product was then eluted from the column using ammonia in MeOH (3 × 2 mL). Removal of the volatile material in the eluate by passing a gentle stream of argon over the solution, maintaining the temperature at 50 °C, gave 13 mg (84%) of **27a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03 (d, 1H, J = 2.3 Hz), 7.47 (dd, 1H, J = 8.2, 2.3 Hz), 7.34 (d, 1H, J = 8.2 Hz), 4.86 (dd, 1H, J = 14.8, 4.8 Hz), 4.33 (dd, 1H, J = 14.8, 6.1 Hz), 3.67 (t, 4H, J = 4.7 Hz), 3.50 (m, 1H), 2.96 (dd, 1H, J = 14.8, 5.2 Hz), 2.87 (dd, 1H, J = 14.7, 8.7 Hz), 2.64 (m, 4H); MS (ESP$^+$) (M + H) m/z 306.3.

5-(*N*-Benzylethylamino)-8-trifluoromethyl-5,6-dihydro-4*H*-1,2,3,3a-tetraazabenzo[*e*]azulene (28e). Benzylamine (1.0 mL, 0.09 mM in 1,2-dichloroethane) and acetic acid (1.0 mL, 0.1 mM in 1,2-dichloroethane) were added to ketone **11e** (27 mg, 0.10 mmol). The reaction mixture was stirred at reflux until complete consumption of the amine (monitored by HPLC). The reaction mixture was cooled, $NaBH(OAc)_3$ (63 mg, 0.30 mmol) was added, and stirring was continued for 48 h at reflux. After complete reduction of the enamines and *N*-alkylation of the resulting secondary amine, NaOH (1 M, 1 mL) was added to the reaction mixture, and stirring was continued for 30 min. The organic phase was then applied to a Varian Bond Elut SCX column which had been prewashed twice with MeOH (10 mL) and once with THF (10 mL). The column was then washed twice with MeOH (10 mL) to remove neutral impurities. The product was then eluted from the column using ammonia in MeOH (3 × 2 mL). Removal of the volatile material in the eluate by passing a gentle stream of argon over the solution, maintaining the temperature at 50 °C, gave 32 mg (93%) of **28e**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, 1H, J = 8.0 Hz), 7.69 (br d, 1H, J = 8.1 Hz), 7.63 (s, 1H), 7.40−7.20 (m, 5H), 4.80 (dd, 1H, J = 14.7, 5.8 Hz), 4.38 (dd, 1H, J = 14.7, 6.7 Hz), 3.81 (d, 1H, J = 14.3 Hz), 3.78 (m, 1H), 3.70 (d, 1H, J = 14.3 Hz), 3.04 (dd, 1H, J = 14.6, 5.2 Hz), 2.95 (dd, 1H, J = 14.5, 8.9 Hz), 2.64 (m, 2H), 1.12 (t, 1H, 7.1 Hz); MS (ESP$^+$) (M + H) m/z 388.4.

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Supporting Information Available: General experimental paragraph, experimental procedure and characterization data for **7b**−**7f**, **8b**−**8f**, and **11b**−**11f**, ^{1}H NMR and mass spectral data for **26a**, **26c**−**f**, **27b**−**f**, **28a**−**d**, **28f**, and **29**−**31**, and ^{1}H NMR and mass spectra and HPLC chromatograms for **6f**, **7b**, **7d**, **7f**, **8a**−**f**, and **26**−**31** (divided into four PDF files). This material is available free of charge via the Internet at http://pubs.acs.org.

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