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N-Bromosuccinimide mediated synthesis of triazatruxenes from indoles ☆

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ABSTRACT

A new synthetic method for triazatruxenes from indoles is developed using *N*-bromosuccinimide (NBS) as a user-friendly reagent. Major reaction parameters including the amount of NBS, substrate concentration, temperature, addition rate and addition method are investigated. Additional experiments are also conducted in order to gain access toward the reaction mechanism. Compared to the use of Br_2 in the conventional method, this reaction requires less reaction time, provides better yields, and displays excellent reproducibility. The reaction can be conveniently performed at 10 g scale and it is also applicable to several substituted indoles, benzoindole, and *N*-alkyl indoles.

Triazatruxenes (TAT) are cyclic trimers of indole which are known for their excellent thermal stability and outstanding photophysical behavior.[1] They have been frequently used as key building blocks in the synthesis of optoelectronic materials for various applications such as organic light-emitting diodes,[2] solar cells,[3] batteries and capacitors.[4] According to the literature survey, there are two conventional synthetic methods for TAT which involve the cyclotrimerization of either indoles or oxindoles (Scheme 1). The treatment of indole with liquid Br_2 followed by debromination using Pd/C and triethylammonium formate has been reported by Robertson[5] and Franceschin.[6] The reaction usually provided poor yields of TAT ranging between 13 and 18%, and there has never been any example of such reaction on *N*-alkylated indole reported in the literature. Meanwhile, there have been reports on the reaction of oxindoles with phosphorus oxychloride ($POCl_3$) which provided triazatruxene in varying yields between 6 and 48% yield.[3b–6] However, the higher price of oxindoles as compared to indole derivatives along with the high toxicity of reactive liquid reagents (both Br_2 and $POCl_3$) led us to investigate the cyclotrimerization of indoles using a safer and more manageable reagent. Since *N*-bromosuccinimide (NBS) has been a successful replacement for Br_2 in a number of reactions,[7] we herein report our development of NBS-catalyzed cyclotrimerization of indoles. The key reaction parameters such as the amount of NBS, the type of solvent, the substrate concentration, reaction time and temperature were investigated on the 0.1-g reaction using the unsubstituted indole as a model substrate. The scope and generality of this process were explored using substituted indoles as reactants. The reproducibility and scalability were also demonstrated on several 1 and 10-g batches.

We began this work by re-examining the synthesis of TAT from indole using liquid Br_2 in CH_3CN as reported by Franceschin.[6] It should be noted that in this procedure, the crude product mixture became insoluble in most organic solvents since it was composed of various poly-brominated TAT. Without isolation, this insoluble mixture was converted to the unsubstituted TAT by a reductive debromination using triethylammonium formate and Pd/C. We next directly replaced liquid Br_2 with NBS under the same reaction conditions to obtain an insoluble crude mixture which was supposed to be a mixture of compounds including brominated TAT. The crude product mixture was then subjected to the reductive debromination procedure mentioned previously. As for this initial viability assessment, we found that the use of NBS could poorly afford both symmetrical TAT (**2**) and asymmetrical TAT (**3**) in 6 and 8% yields, respectively, after flash chromatography. When NBS was replaced by its chloro and iodo analogs (NCS and NIS), only starting indole was detected by TLC. These results indicated a feasibility of this project and prompted us to further investigate other reaction parameters.

☆ In remembrance of His Majesty King Bhumibol Adulyadej (1927–2016), for his life-time dedication to Thailand.

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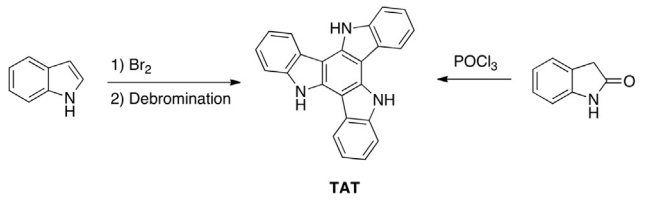


Scheme 1. Typical synthesis of triazatruxenes (TAT).

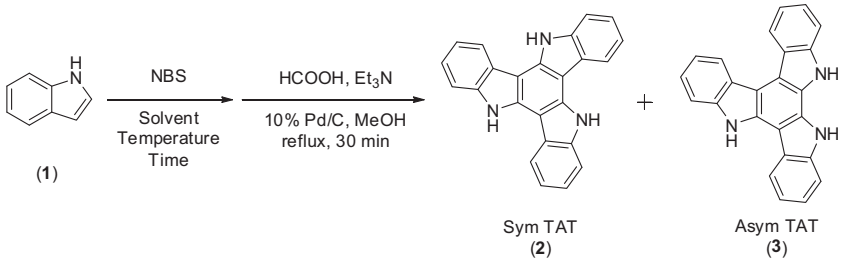
The reaction optimization was conducted on 0.1 g of indole using a 2-step procedure as mentioned above. We first examined the effect of the solvent by using nonpolar ($CHCl_3$), aprotic polar (EtOAc, acetone, CH_3CN, DMF, DMSO) and protic solvent (CH_3OH) (Table 1, entry 1–7). Reactions in $CHCl_3$ and EtOAc were very sluggish and a lot of unreacted indole was detected after 16 h. This might probably be due to the low solubility of NBS. The treatment of indole with NBS in DMF or DMSO, which has been a conventional method for preparation of 3-bromoindole, gave raise to very poor yields of the trimerized products. On the other hands, reactions in acetone and CH_3OH resulted in a number of unidentified products. Acetonitrile (CH_3CN) was then chosen as the best solvent for further experiments. Next, we varied the amount of NBS from 1 to 5 M equivalents compared to indole (Table 1, entry 4, 8–11) and noticed that the ratios between **2** and **3** decreased as the amount of NBS increased. The results implied that the amount of NBS can affect the mechanism by which the two products are formed.

Since this reaction involves a combination of three indole molecules, the reactant concentration can affect the product yields. We then varied the amount of CH_3CN from 1 to 8 mL in order to obtain solutions of starting indole at 0.85–0.11 M (Table 1, entry 9, 12–14). Significantly lower yields were obtained at the indole concentration of 0.11 M (0.1 g in 8 mL), but a strongly exothermic reaction with unaffected product yields was observed at 0.85 M of indole (0.1 g in 1 mL). Therefore, the concentration of indole at 0.43 M (0.1 g in 2 mL) was selected as the most practical condition. Even though this reaction is exothermic, it poorly produced the expected products in 4–5% yields when conducted at 0 °C (Table 1 entry 15). The reactions at ambient temperature (28 °C) and 50 °C (Table 1, entry 9 and 16) were quite similar in term of product yields and ratios. Therefore, we chose to perform this reaction at 28 °C which is convenient for further studies.

According to Franceschin procedure, the reaction time between indole and liquid bromine required an overnight stirring at room temperature. From our investigation, the overall yields of the NBS-catalyzed trimerization reached about 40% after 3 h of stirring at room temperature. Prolong stirring of the reaction mixture did not improve the yields (Table 1, entry 9 and 17–20). The optimal conditions, therefore, involve a treatment of indole with 2 equivalents of NBS in CH_3CN at room temperature for 3 h (Table 1, entry 19), followed by a reductive debromination. This condition provides symmetrical TAT (**2**) and asymmetrical TAT (**3**) in a total yield of 39%.

During the addition of NBS into a solution of indole, we usually observed generation of heat that could cause evaporation of volatile solvent if the NBS addition was too fast. Therefore, we studied the effect of addition rate and addition method on the reaction efficiency. For every reaction in the optimization studies

Table 1
Optimization studies on the cyclotrimerization reaction.[a]



Entry	Solvent	NBS (eq.)	[indole] (M)	Temp. (°C)	Time (h)	Yield (%)[b]	
						2	**3**
1	$CHCl_3$	3	0.43	28	16	2	12
2	EtOAc	3	0.43	28	16	1	1
3	Acetone	3	0.43	28	16	–	–
4	MeCN	3	0.43	28	16	15	18
5	DMF	3	0.43	28	16	1	1
6	DMSO	3	0.43	28	16	2	1
7	MeOH	3	0.43	28	16	–	–
8	MeCN	1	0.43	28	16	10	1
9	MeCN	2	0.43	28	16	23	12
10	MeCN	4	0.43	28	16	13	24
11	MeCN	5	0.43	28	16	9	18
12	MeCN	2	0.11	28	16	8	6
13	MeCN	2	0.21	28	16	21	11
14	MeCN	2	0.85	28	16	21	12
15	MeCN	2	0.43	0	16	5	4
16	MeCN	2	0.43	50	16	21	8
17	MeCN	2	0.43	28	1	15	16
18	MeCN	2	0.43	28	2	16	15
19	MeCN	2	0.43	28	3	23	16
20	MeCN	2	0.43	28	6	23	17

[a] Conditions: Indole (0.1 g, 0.85 mmol), HCOOH (3.02 mmol), Et_3N (3.02 mmol), 10% Pd/C (0.018 mmol), in MeOH (3 mL).
[b] HPLC yields were estimated from the calibration curves.

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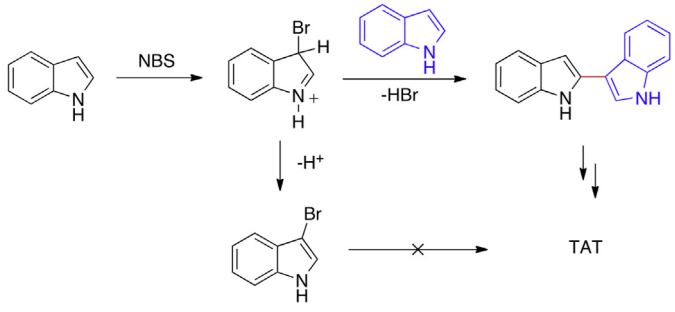
(Table 1), NBS was added portionwise into indole solutions over a 10-min period. When the addition rate was slowed down to 90 min, the yields of both **2** and **3** were slightly decreased to 14 and 12%, respectively. A reversed addition of indole to a solution of NBS in CH_3CN caused much poorer yields of **2** and **3** (6 and 2%, respectively). These results clearly suggested that the addition rate and method of addition greatly influenced the course of this reaction.

With respect to the reaction mechanism, it is possible that the 3-bromoindolium ion is formed in the first step (Scheme 2). This reactive intermediate can react with another molecule of indole to form a 2,3-indole dimer upon elimination of HBr. A sequential bromination and nucleophilic substitution could lead to the TAT structures. However, deprotonation of the 3-bromoindolium ion can lead to a stable 3-bromoindole, which could not react further. This was proven by a complete recovery of starting material when 3-bromoindole was treated with NBS under the optimal conditions. In addition, we looked at the possibility for a free radical pathway by performing this reaction in the presence of 0.2 and 1 equivalent of BHT. Regardless to the amount of BHT, the yields of **2** and **3** were slightly decreased to 19 and 11%, respectively. This result suggested that this reaction should not involve radical intermediates. We postulate that the slightly lower yields may cause by a side reaction between NBS and BHT; for example, benzylic bromination.[8]

With the optimal reaction conditions in hands, we tested the scalability of reaction by scaling up the batch size to 1 and 10 g. Data from three repeated experiments in each batch size is summarized in Table 2. The overall isolated yields of TATs were in a range of 25 and 30% after column chromatography.

To investigate the scope and limitation of this reaction, a number of substituted indoles were reacted with NBS under the optimal conditions and the outcomes are depicted in Fig. 1. It is apparent that this reaction is influenced by both electron-donating and withdrawing groups. With a methyl or methoxy group at the 5-position, the reactions provided two isomeric products (**4a**,**b** and **5a**,**b**) with the overall yields and isomeric ratios similar to those from the reaction of unsubstituted indole. Interestingly, reactions of 5-chloro and 5-acetoxyindole produced only the symmetrical TAT **6** and **7** in 12 and 10% yields, respectively. To our delight, this procedure is also applicable to benzoindole derivative such as



Scheme 2. Plausible reaction mechanism.

Table 2
Reaction scaling-up studies.

Entry	Batch size (g)	Yield [%][a]	
		2	**3**
1	1.0	15 ± 2	10 ± 1
2	10.0	19 ± 3	11 ± 1

[a] Isolated yield after column chromatography.

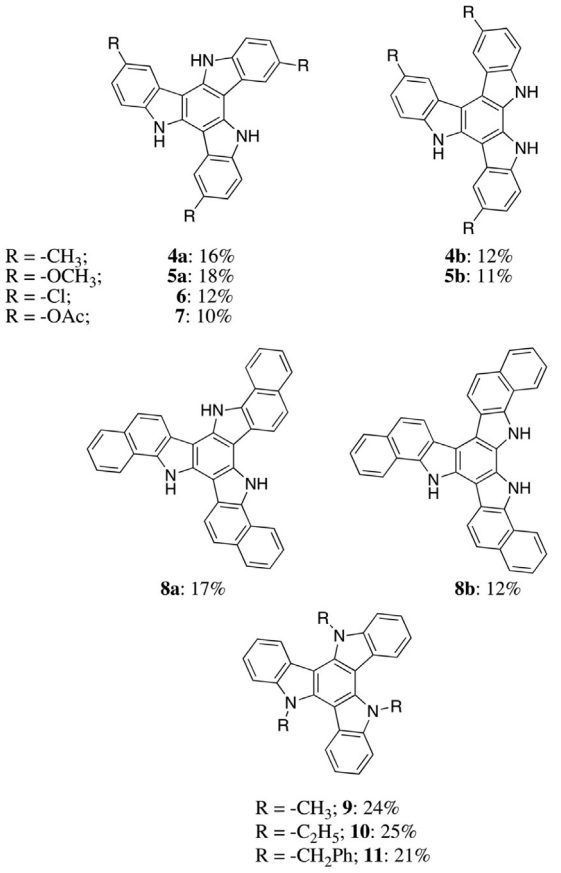


Fig. 1. Structures and isolated yields of triazatruxenes derived from substituted indoles.

1*H*-benzo[*g*]indole from which the corresponding products **8a** and **8b** were obtained in 17 and 12% yields, respectively. The usefulness of this procedure could be further recognized as the reaction of *N*-alkylindoles proceeded smoothly to afford only the symmetrical TAT **9**–**11** in 21–25% yields. This new synthetic method allows a straightforward access to these compounds from commercially available *N*-alkylindoles, which is more convenient than the typical method relying on the trialkylation of **2**.

In conclusion, we have demonstrated that *N*-bromosuccinimide (NBS) can be a safe and practical reagent for cyclotrimerization of indole to triazatruxenes under mild conditions. The optimal conditions include a slow addition of 2 equivalent of NBS (over 10 min) into indole solution in CH_3CN (0.1 g/2 mL or 0.43 M) at room temperature. After 3 h of stirring and subsequent reductive dehalogenation, the overall yield of 39% after two consecutive steps was determined by HPLC. The reaction exhibited some robustness and reproducibility as the synthesis on 1 and 10-g scale could afford the expected products in slightly lower yield of 25–30% after purification by column chromatography. The reaction displayed a compatibility with 5-alkyl, 5-alkoxy, and *N*-alkyl and benzoindoles.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.09.061.

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