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Triarylaminium salt facilitated Friedel–Crafts reaction of indoles with enamides and vinyl ethers

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ABSTRACT

Commercially available stable radical cation triarylaminium salt can be used as an efficient initiator for Friedel–Crafts reaction of indoles with enamides to regioselectively construct complex indole derivatives and for double Friedel–Crafts reaction of indoles with vinyl ethers to offer 3,3′-Bis(indolyl)alkane derivatives. The ready availability of the starting materials and the usefulness of the products make this strategy attractive.

2-Oxo-1-pyrrolidines[1] and indoles[2] are both ubiquitous structural motifs that can be found in many natural products and marketed drugs. Putting these two heterocyclic skeletons together has been discovered to exhibit good activities in the therapy of common diseases such as attention deficit hyperactivity disorder, cardiac arrhythmia, and asthmatic syndrome.[3] However, existing synthetic methods for these compounds significantly lack efficiency. Friedel–Crafts (FC) alkylation of indole was one of the most powerful routes to synthesize complex indole derivatives. Great progress has been made in FC alkylation of indole with electron-deficient olefins.[4] Nevertheless, the applications of electron-rich olefins in such a reaction still remain a challenge. In recent years, enamide has attracted considerable attention in organic synthesis as nucleophile.[5] However, the utilization of enamide as electrophile was relatively rare.[6] The development of an efficient procedure for the alkylation of indoles with electron-rich olefins such as enamides under mild conditions is highly desired. During our studies on the stable radical cation salt induced transformations, we have demonstrated that one electron oxidation can carry out polarity umpolung and provide unconventional access to various target molecules.[7] So it is expected that FC reaction between electron-rich heteroarenes such as indoles and electron-rich enamides may take place by radical cation initiation. As part of our ongoing program to expand the scope and generality of this chemistry, in this Letter, we report tris(4-bromophenyl)-aminium hexachloroantimonate ($TBPA^{+}\cdot SbCl_6^{-}$) induced regioselective FC reactions between indoles and enamides to offer complex indole derivatives. And we here also report a novel double FC reaction between indoles and vinyl ethers to generate 3,3′-Bis(indolyl)alkane (BIA) derivatives.

To begin our study, *N*-vinylpyrrolidin-2-one (**2a**) was chosen as a model substrate to react with indole (**1a**) in the presence of catalytic amount of $TBPA^{+}\cdot SbCl_6^{-}$ at room temperature. No reaction was observed in the absence of initiator. But as shown in Table 1, it was fortunately found that $TBPA^{+}\cdot SbCl_6^{-}$ was sufficient to promote the reaction; high yield of product **3aa** was isolated after a short reaction time of 0.5 h. It should be noted that the reaction was regiospecific because only C3-alkylated (from **1a**) and Markovnikov addition (from **2a**) product was observed. Solvent effects and initiator loading were screened and the results are shown in Table 1. The best yield of **3aa** was achieved with 2 mol % $TBPA^{+}\cdot SbCl_6^{-}$ in chloroform. In order to avoid the influence of the trace amount of $SbCl_5$ or any other possibly existing trace amounts of Lewis acids or Brönsted acids in $TBPA^{+}\cdot SbCl_6^{-}$, an equimolar amount of hindered non-nucleophilic base 2,6-di-tert-butylpyridine (DBP) was added as an acid scavenger.[8] No obvious inhibition was observed and the reaction performed as effectively as before but a little slower (chloroform, rt, 4 h) (Scheme 1).

With the optimal reaction conditions in hand, the scope and generality of this protocol were investigated using a variety of indoles and *N*-vinylamides (Table 2).[9] Different indoles were tested first. Indoles with electron donating groups or electron

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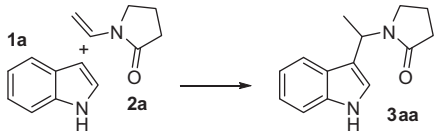
Table 1
Screening of reaction conditions[a]

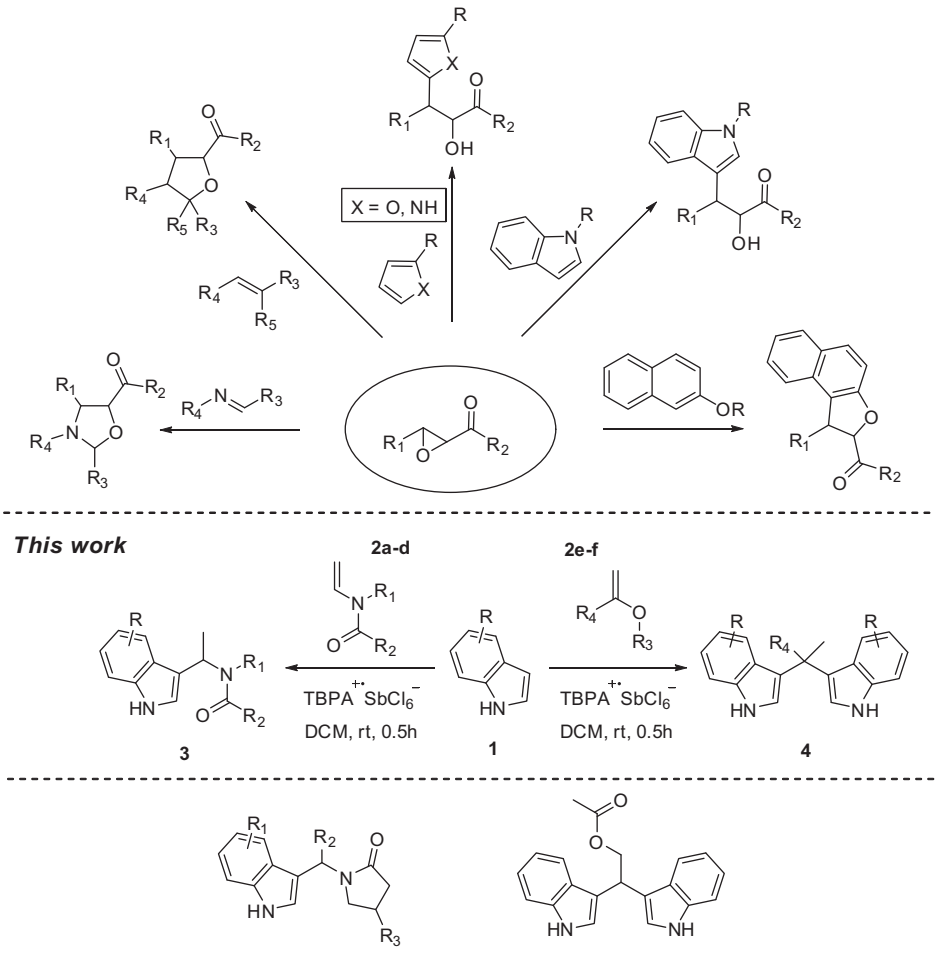


Conditions	NMR Yield[b] (%) (**3aa**)
2% TBPA$^{+\cdot}$, **DCM**, rt, 0.5 h	78
2% TBPA$^{+\cdot}$, **DEM**, rt, 0.5 h	83
2% TBPA$^{+\cdot}$, **$CHCl_3$**, rt, 0.5 h	85
2% TBPA$^{+\cdot}$, **MeCN**, rt, 0.5 h	70
2% TBPA$^{+\cdot}$, **THF**, rt, 0.5 h	ND[c]
2% TBPA$^{+\cdot}$, **MeOH**, rt, 0.5 h	ND
5% TBPA$^{+\cdot}$, $CHCl_3$, rt, 0.5 h	83
1% TBPA$^{+\cdot}$, $CHCl_3$, rt, 0.5 h	80
2% TBPA$^{+\cdot}$, 2% **DBP**, DCM, rt, 4 h	76

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), solvent (1 mL), room temperature, 0.5 h.
[b] Yields were determined by NMR spectroscopy.
[c] Not detected by NMR.

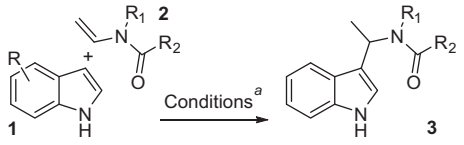
withdrawing groups on C5, C2 all worked well with *N*-vinylpyrrolidin-2-one under the present reaction conditions (Table 2, **3aa**–**3ja**). The indoles with C2 substituents delivered the corresponding alykyated indoles in high yields (Table 2, **3ga**, **3ha**), illustrating that steric hindrance played a poor role in the reaction. *N*-Me and *N*-Bn protected indoles also gave the corresponding products in high yields (Table 2, **3ia**, **3ja**). The scope of the enamide counterpart in this reaction had also been evaluated. When *N*-vinylcaprolactam (**2b**) and *N*-vinyl-acetamide (**2c**) were used, the reaction proceeded smoothly to afford the desired products in high yields (Table 2, **3ab**, **3ib**, **3ac**, **3ic**). However, when *N*-methyl-*N*-vinyl-acetamide (**2d**) was employed, to our surprise, a double FC reaction occurred and BIA product **4a** was obtained in good yield (84%, Table 3, entry 1). That is to say, *N*-vinylamides **2d** acted as an equivalent of ethanal to participate in the construction of BIA structure which had also been observed by Zhang et al. in 2011.[6c] This is an interesting result because 3,3′-Bis(indolyl)alkanes (BIAs) were widely isolated from various terrestrial and marine natural sources which exhibit a range of important biological activities.[10] To extend the scope of this finding, we next tested vinyl Ethers. To our delight, the reaction of *N*-vinyl Ethers **2e** or **2f** with indoles furnished the desired BIA products **4b**–**4i** with good yields.[11] The method was also examined on a larger scale to evaluate its practicability. The reaction between *N*-vinylpyrrolidin-2-one **2a** and indole **1a** has been performed on a 20 mmol scale (>2 g each) in a single batch and no significant yield loss was observed and the reaction was still completed within half an hour.

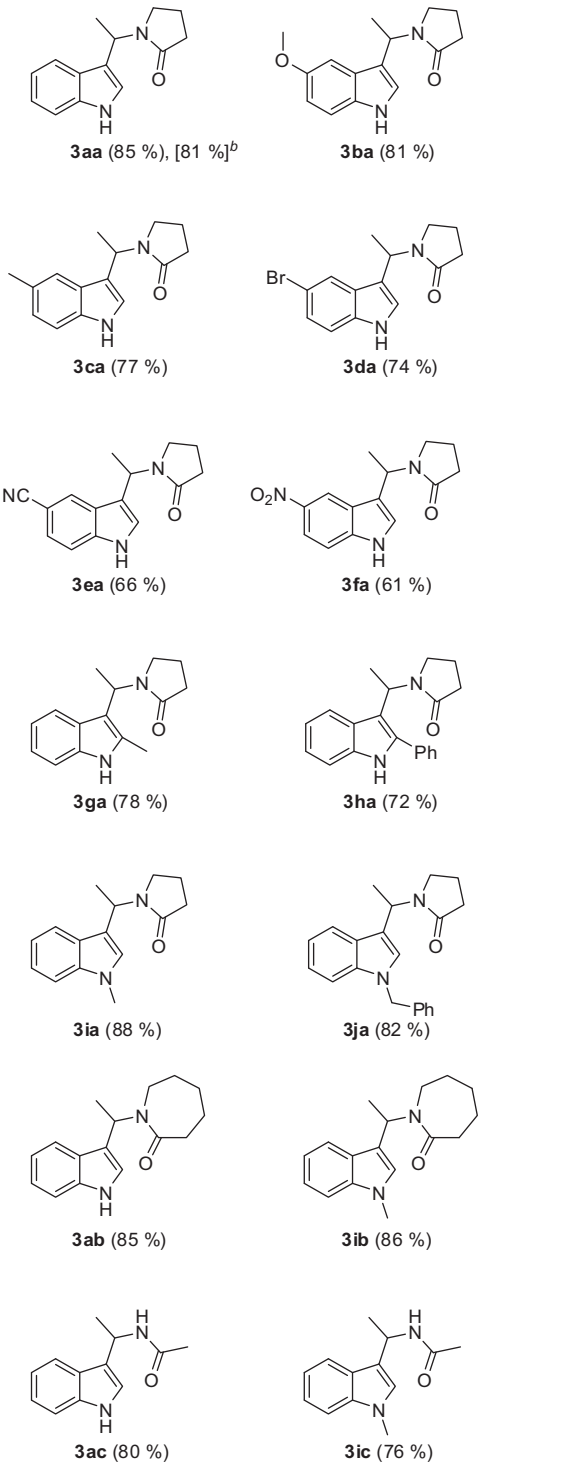
A plausible radical cation mediated chain mechanism for the reaction of *N*-vinylpyrrolidin-2-one with indole is proposed in Scheme 2. Firstly, *N*-vinylamide **2a** was oxidized by TBPA$^{+\cdot}$·$SbCl_6^-$



Scheme 1. TBPA$^{+\cdot}$·$SbCl_6^-$ induced Friedel–Crafts type reaction.

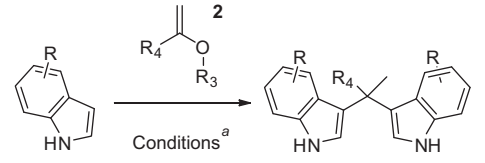
Table 2
Scope of $TBPA^{+}\cdot SbCl_6^{-}$ initiated Friedel–Crafts reaction of indoles with enamides

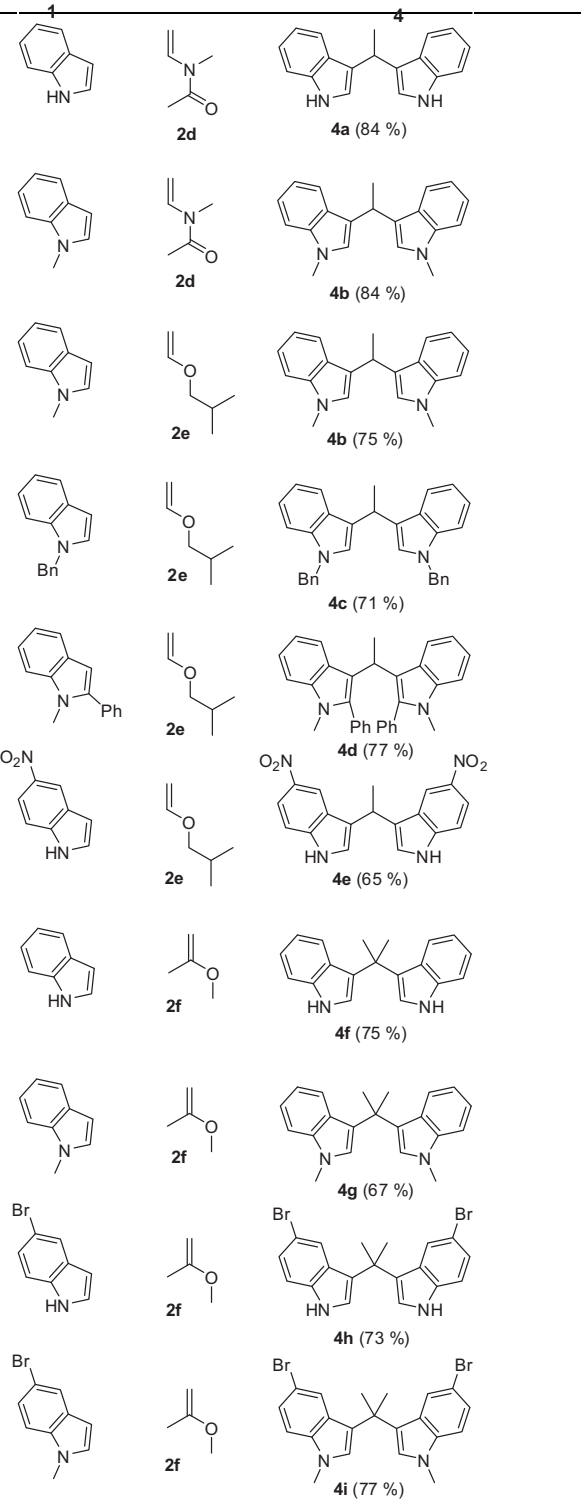




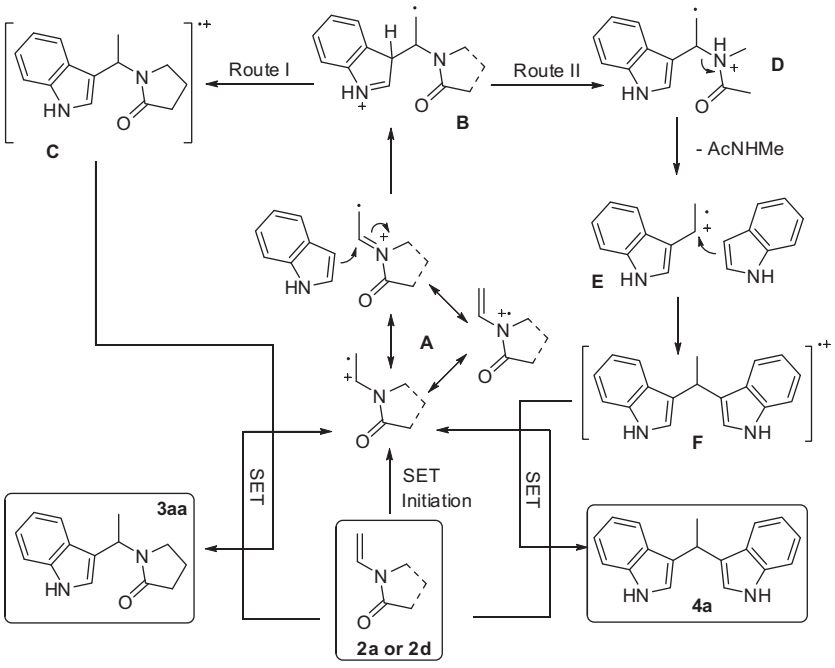
[a] Standard reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), $TBPA^{+}\cdot SbCl_6^{-}$ (0.02 mmol), $CHCl_3$ (10 mL), room temperature, 0.5 h. Isolated yields were reported in brackets under every product.
[b] 20 mol scale.

Table 3
Scope of $TBPA^{+}\cdot SbCl_6^{-}$ initiated double Friedel–Crafts reaction of indoles with vinyl ethers





[a] Standard reaction conditions: **1** (2.0 mmol), **2** (1.0 mmol), $TBPA^{+}SbCl_6^{-}$) (0.02 mmol), $ClCH_2CH_2Cl$ (10 mL), room temperature, 1 h. Isolated yields were reported in brackets under every product.



Scheme 2. Proposed mechanism.

to its radical cation intermediate **A**, which will serve as an electrophile. Indole **1a** was then attacked by the above electron deficient intermediate **A** to produce the radical cation intermediate **B**. Intermediate **B** was then transferred to intermediate **C** after a hydrogen extraction. Intermediate **C** would then undergo the second electron transfer from substrate **2a** to produce the products **3aa** and regenerate a new radical cation intermediate **A** at the same time. Chain propagation continued until all substrates were converted to the products. When **2d** was hired, Intermediate **B** would first undergo a fragmentation to generate intermediate **E.** Intermediate **E** was then attacked by another molecule of indole to produce the radical cation intermediate **F.** Intermediate **F** would then undergo the second electron transfer from substrate **2d** to produce the products **4a** and regenerate a new radical cation intermediate **A** at the same time.

In summary, we have demonstrated that enamides can be used as useful electrophiles in the stable radical cation salt initiated FC alkylation of indoles. This atom-economical and environmentally friendly procedure uses an inexpensive nonmetal catalyst with low loadings and establishes a new type of FC alkylation between indoles with enamides. And we have also developed a simple and highly efficient approach to construct pharmaceutically active BIA compounds through TBPA radical cation induced double FC reaction of indoles with vinyl ethers. Applications of this methodology to other reactions are currently under investigation in our laboratory.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.055.

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9. General procedure for $TBPA^{+}\cdot SbCl_6^{-}$ induced reaction of indoles with enamides. Indole (1, 1 mmol) and *N*-vinylpyrrolidin-2-one (2, 1 mmol) were dissolved in $CHCl_3$ (10 mL) at ambient temperature; $TBPA^{+}SbCl_6^{-}$ (0.02 mmol) was then added in one portion under stirring. The reactions were performed at room temperature and completed within 0.5 h as monitored by TLC. The products were isolated by column chromatographic separation.

Representative spectral data for the product: 1-(1-(1*H*-indol-3-yl)ethyl)pyrrolidin-2-one (**3aa**). (194 mg, 85%). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.64 (d, J = 8.0 Hz,1H), 7.39 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.15 (s, 1H), 7.11 (t, J = 7.6 Hz, 1H), 5.80 (q, J = 7.0 Hz, 1H), 3.28 (dt, J = 9.0, 5.6 Hz, 1H), 2.88 (dt, J = 9.0, 5.6 Hz, 1H), 2.45 (m, 2H), 1.93 (m, 1H), 1.80 (m, 1H), 1.61 (d, J = 7.0 Hz, 3H). HRMS (EI) Calcd for $C_{14}H_{16}N_2O$: $[M]^+$ 228.1263; Found, 228.1268.

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11. General procedure for $TBPA^{+\cdot}SbCl_6^-$ induced reaction of indoles with vinyl ethers. Indoles (1, 2 mmol) and vinyl ethers (2, 1 mmol) were dissolved in $ClCH_2CH_2Cl$ (10 mL) at ambient temperature; $TBPA^{+\cdot}SbCl_6^-$ (0.02 mmol) was then added in one portion under stirring. The reactions were performed at room temperature and completed within 1 hour as monitored by TLC. The products were isolated by column chromatographic separation. Representative spectral data for the product: 3,3′-(ethane-1,1-diyl)bis(1*H*-indole) (**4a**). (218 mg, 84%). white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.20 (t, J = 7.6 Hz, 2H), 7.08 (t, J = 7.6 Hz, 2H), 6.91 (s, 2H), 4.71 (q, J = 7.2 Hz, 1H), 1.84 (d, J = 7.2 Hz, 3H). HRMS (EI) Calcd for $C_{18}H_{16}N_2$: $[M]^+$ 260.1313; Found, 260.1320.