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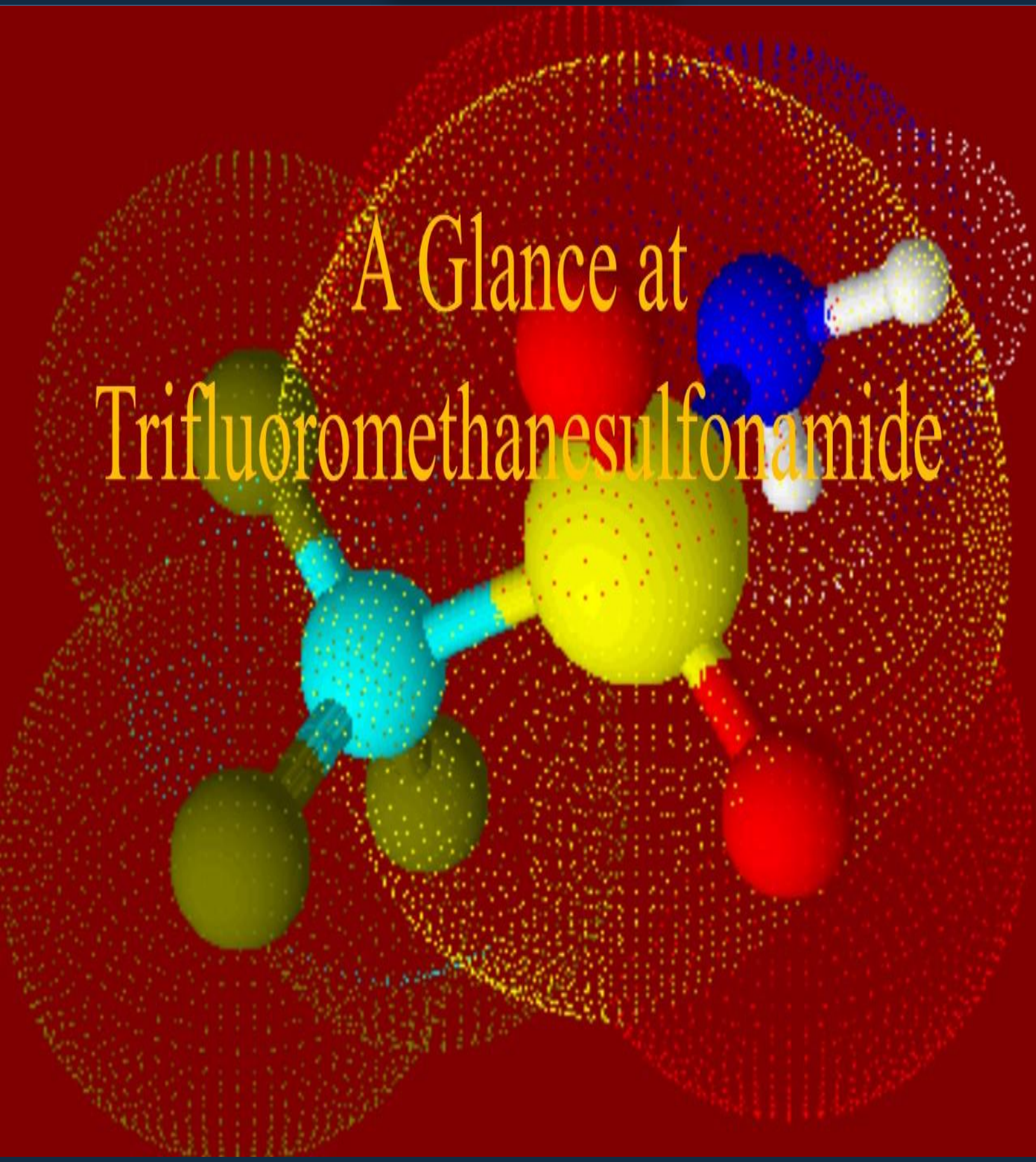
A Glance at Trifluoromethanesulfonamide



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A Glance at Trifluoromethanesulfonamide

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Triflamide has been widely employed as efficient electrophiles, as an exceptional catalyst, or as additive in numerous reactions. The motive for such wide utility is related to its high acidity, lipophilicity, catalytic activity, and its outstanding chemical properties. Furthermore, the low nucleophilicity of its conjugate anion constitutes one of the significant blots on the landscape of triflamide chemistry. This article focuses briefly on the chemistry of triflamide and its derivatives; their synthesis and reactions; as well as a cursory look at some of their applications.

Keywords: Triflamides, perfluoroalkylsulfonamides, triflimides, applications of triflamide derivatives.

1. Introduction

Trifluoromethanesulfonamides (triflamides), in all their various guises, have arguably influenced the landscape of synthetic organic chemistry over the last 15 years. The outstanding physical and chemical properties of these classes of compounds attracted many fields, especially medicinal and pharmaceutical fields, to develop and construct many drugs and prodrugs containing triflamide group as a key structural motif. Furthermore, there has been a burgeoning interest in recent years in their use as powerful electrophiles in a wide range of reactions; as a relatively hydrophobic solvent in lithium-sulfur batteries; and as water-tolerant Lewis acid catalysts, etc. This article presents briefly the chemistry of triflamide's family, its synthesis, reactions, and a cursory look at some of the applications of triflamides and their derivatives.

2. The chemistry of triflamides

Triflamide and its N–monosubstituted as well as polyfluorinated analogues are strong NH-acids. As shown in Table 1 & Table 2, the pK_a values reflect that the acidity is influenced by both of the electronegativity of substituent R, and the processes of their homo- and heteroassociation[1-3]. The letter factor is exemplified by the low pK_a value of $(CF_3SO_2NH)_2CH_2$ compared to $CF_3SO_2NHCH_2NHCO$-CH_3, in spite of a stronger electron-acceptor character of CF_3SO_2 group as compared to CH_3CO group.

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Among this class of compounds, bis(trifluromethanesulfonyl)imide $(CF_3SO_2)_2NH$, the most distinctive feature of which is its extremely high acidity and extraordinary properties of its metal salts used in batteries.[4] It shows very similar pK_a values in H_2O, MeOH, and DMSO (2.8, 2.7, and 2.1 respectively), which contrasted with the pK_a values of conventional protic acids (HCl and HBr) in different media, *i.e.* their acidity in DMSO is much lower than in H_2O, with the difference reaching 10 pK units.[5] This is related to the fact that in the conjugate anion $(CF_3SO_2)_2N^-$, the negative charge is strongly delocalized over the nitrogen atom, four oxygen atoms, and two trifluoromethyl groups, which drastically decreases the needs in external solvation and levels out the acidic properties in different solvents.

Another feature of triflamide and its analogues is that they are strong hydrogen-bond donors.[1] They have two centers of basicity, the nitrogen and oxygen atoms. Owing to the planarization of the nitrogen atom in triflamide, it has shown a decrease of its basicity with respect to that of methanesulfonamide.

Table 1. Acidity of triflamides CF_3SO_2NHR.

No.	R	p*K*a/in MeOH
1	H	11.06
2	CH_3	12.70
3	CH_2SiMe_3	12.84
4	$CH_2NHCOCH_3$	10.11
5	$CH_2NHCOCF_3$	10.76
6	$COCH_2Ph$	5.45
7	SO_2CF_3	2.7

Table 2. pK_a Values for some fluoroalkylsulfonamide $R_FSO_2NH_2$ in MeOH.

No.	R	p*K*a/in MeOH
1	$Cl(CF_2)_2$	6.17
2	$I(CF_2)_2O(CF_2)_2$	6.22
3	$H(CF_2)_2O(CF_2)_2$	5.83
4	$I(CF_2)_4O(CF_2)_2$	5.70
5	$I(CF_2)_6O(CF_2)_2$	4.22
6	$Cl(CF_2)_6O(CF_2)_2$	5.74
7	$H_2NO_2S(CF_2)_2O(CF_2)_2$	5.67
8	$H_2NO_2S(CF_2)_2O(CF_2)_4O(CF_2)_2$	5.90

3. Preparation of triflamides

The synthesis of triflamides and other perfluoroalkylsulfonamides $R_FSO_2NH_2$ can be accomplished via the reaction of the corresponding fluoroalkylsulfonyl fluorides with ammonia or amines (**1**) (Scheme 1). Another approach can also be employed for amination using trifluoromethanesulfonyl chloride or trific anhydride in the presence of trimethylamine (**2**) (Scheme 1).

$$R_FSO_2F + NH_3 \text{ or } RNH_2 \longrightarrow R_FSO_2NH_2 \quad (1)$$

$$CF_3SO_2Cl \text{ or } (CF_3SO_2)_2O \xrightarrow{Et_3N} CF_3SO_2NH_2 \quad (2)$$

$$R_FSO_2NH_2 + RX \xrightarrow[THF]{K_2CO_3} R_FSO_2NHR \quad (3)$$

Scheme 1. Synthesis of triflamides.

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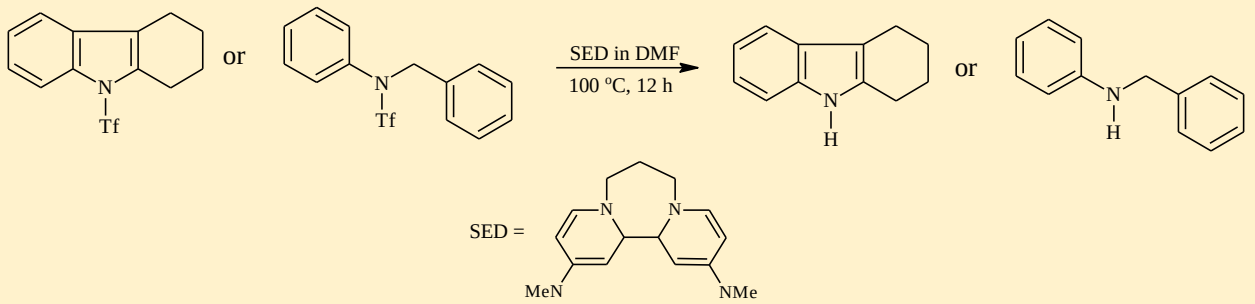
A wide variety of mono- and disubstituted perfluoroalkanesulfonamides are prepared by alkylation of the primary parent compounds with alkyl halogenides or tosylates in the presence of potassium carbonate in aprotic medium (**3**) (Scheme 1).[1]

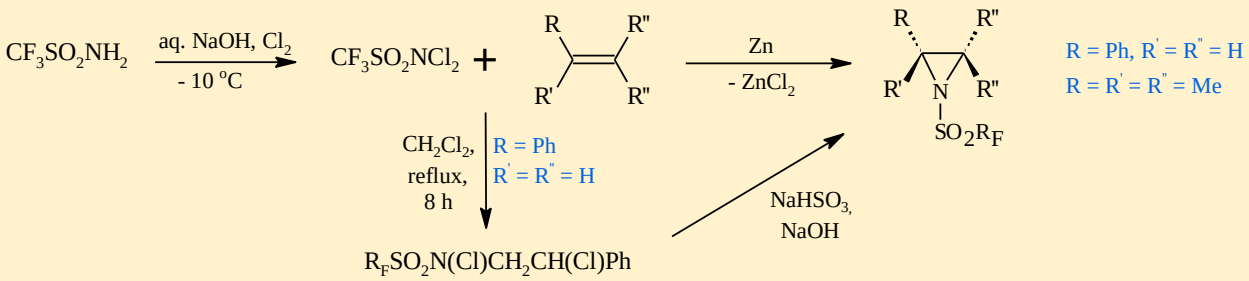
4. Reactions of triflamides

In this part of the article, I highlight a number of reactions as illustrative examples that feature one or more of the performance of triflamides. The N-substituted triflamides in reaction with nucleophiles show quite different reactivity patterns depending on the attached groups to nitrogen, the reaction condition, and the nature of the reagents. For example, the reaction with a super-electron-donor bis-piridinylidene (SED) leads to the S-N bond cleavage to give the amines (Scheme 2).[6]



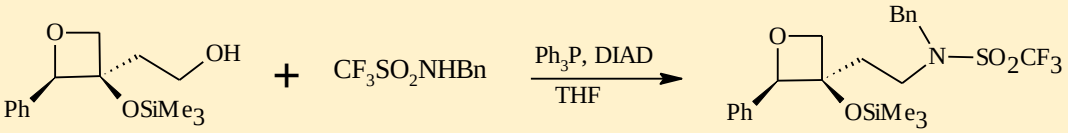
Sheme 2. Reaction of super-electron-donor (SED) with N-substituted triflamides.

Various N-substituted derivatives can be obtained by the addition to multiple bonds or by the displacement of hydrogen atom. In the presence of zinc dust, *N*,*N*-dichloroperfluoroalkanesulfonamides afford the corresponding nitrenes, which add to styrene or 2,3-dimethylbut-2-ene to yield perfluoro-alkanesulfonylaziridiens.[7] Whereas in the absence of zinc dust, the reaction with styrene produces 1:1 adduct followed by reduction with $NaHSO_3$ and elimination of the produced HCl yields the same aziridine product[8] (scheme 3).



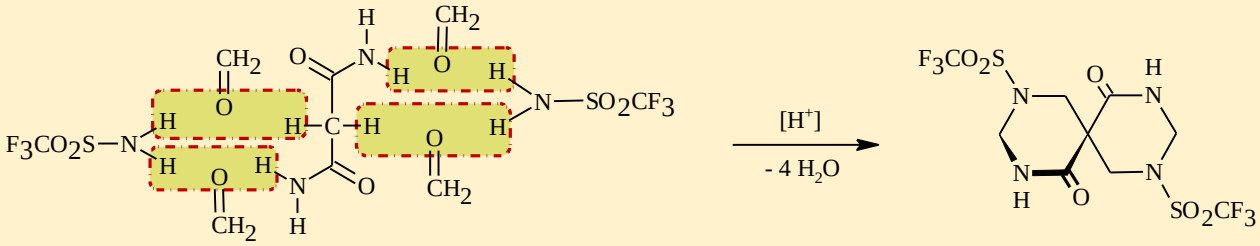
Scheme 3. The synthesis of *N*-perfluoroalkanesulfonylaziridiens.

Alkylation of triflamides with alcohols can be achieved by the Mitsunobu reaction to give numerous N-alkylated triflamides, which are featured by their high acidity and lipophilicity (Scheme 4).[9]



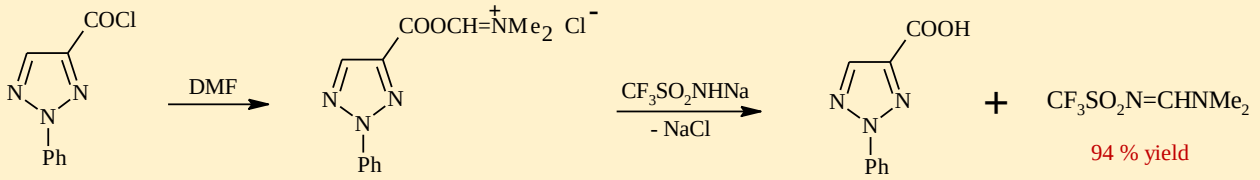
Schem 4. The alkylation of triflamides with alcohols.

Another interesting reaction, the three-component condensation of malonamide and triflamide with paraformaldehyde affords 4,10-bis(trifluoromethylsulfonyl)-2,4,8,10-tetraazaspiro[5.5]-undecane-1,7-dione (Scheme 5).[10] The three-component heterocyclization is formed through the participation of both amide groups of malonamide and its active methylene group.



Scheme 5. The tree-component condensation of malonamide, triflamide, and paraformaldehyde.

An elegant synthetic pathway of *N*-[(dimethylamino)-methylidene]triflamide $CF_3SO_2N{=}CHNMe_2$, was accomplished via the reaction of 2-phenyl-2*H*-1,2,3-triazol-4-ylcarbonyl chloride with the sodium salt of triflamide in DMF (Scheme 6).[11] In an insightful piece of mechanistically analysis, they proposed that the formation of the intermediate "Vilsmeier-type" adduct arises from the reaction of acyl chloride with DMF, which it, in turn, reacts with the triflamide salt to produce the desired product and 2-phenyl-2*H*-1,2,3-triazol-4-yl carboxylic acid as byproduct. Indeed, they found that a substituted chloroimminium ion was initially formed in order to react further with the triflamide salt.



Scheme 6. The synthesis of $CF_3SO_2N{=}CHNMe_2$.

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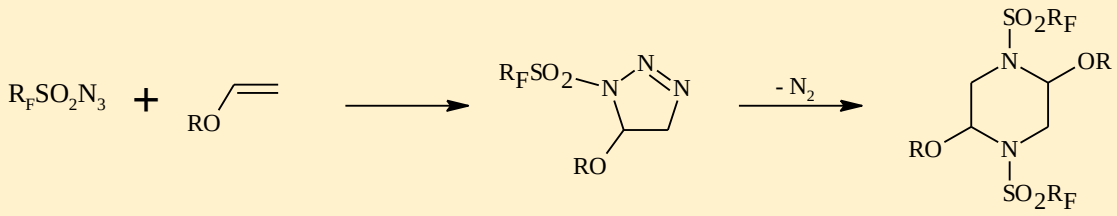
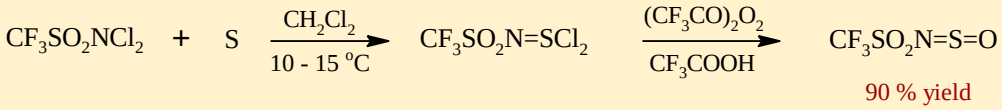
In solvent-free reaction, vinyl ethers react with perfluoroalkanesulfonylazides to give substituted 1,2,3-triazolines, which undergo slow dimerization with elimination of nitrogen producing the symmetrically substituted piperazines (Scheme 7).[12]



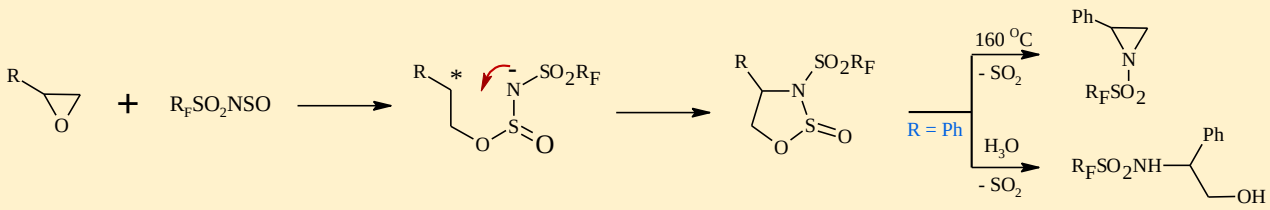
Scheme 7. The reaction of vinyl ethers with perfluoroalkanesulfonylazides.

N-sulfinyltriflamide $CF_3SO_2N{=}S{=}O$ is an alternative for triflamide, which reacts more actively than its progenitor in different reactions. This heterocumulene is versatile reagent for introduction of the R_FSO_2N moiety in different organic molecules. It was readily synthesized by the reaction of *N*,*N*-dichlorotriflamide with sulfur followed by heating of the formed product with trifluoroacetic anhydride (Scheme 8).[13]



Scheme 8. The synthesis of N-sulfinyltriamide $CF_3SO_2N{=}S{=}O$.

N-sulfinyltriflamide reacts with oxiranes via a ring-opening/ring-closure sequence of reactions to give 2-oxa-3-fluoroalkanesulfonyl-1,2,3-oxathiazolidines. The product with R=Ph decomposes above 160 °C with elimination of SO_2 to afford aziridine, whereas the acidic hydrolysis gives *N*-(1-phenyl-2-hydroxy-ethyl)perfluoroalkanesulfonamide (Scheme 9).[14]



Sheme 9. The preparation of different products from the reaction of N-sulfinyltriflamide with oxiranes.

Remarkably, the reactions of oxidative triflamidation of unsaturated triflamide derivatives lead to a series of new linear, cyclic and bicyclic products, whose structure depends on the reaction conditions and the nature of the reagents. The reaction of *N*-allyltriflamide with triflamide under oxidative conditions in

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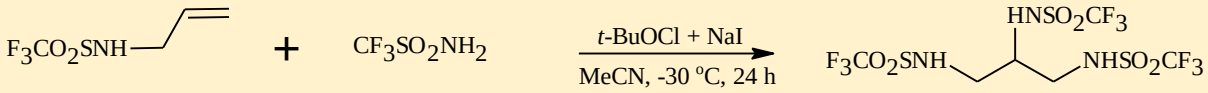
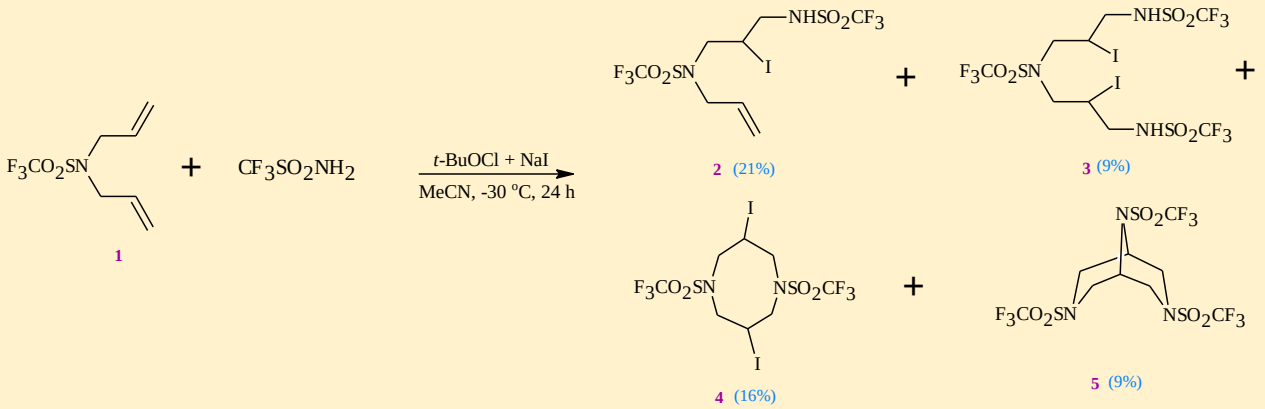
the system (*t*-BuOCl + NaI) at -30 °C proceeds in quantitative yield and affords a single product, *N*,*N*',*N*''-propane-1,2,3-triyltris(triflamide) (Scheme 10).[15]



Scheme 10. Oxidative addition of triflamide to *N*-allyltriflamide.

Whereas under the same conditions, *N*,*N*-diallyltriflamide gives a mixture of linear and cyclic products in a moderate total yield and in comparable amounts depending on the reaction conditions (Scheme 11).[15] With equimolar ratio of the reagents at -10 °C, the reaction mixture contains monoadduct **2**; 3,7-diiodo-1,5-bis(trifluoromethylsulfonyl)-1,5-diazocane **4**; and 3,7,9-tris(trifluoromethylsulfonyl)-3,7,9-triazabicyclo[3.3.1]nonane **5**, as well as a small amount of unreacted substrate **1**. Increasing the ratio and carrying out the reaction at -30 °C results in full conversion of the reagents and formation of diadduct **3**, apart from products **2**, **4**, **5**.



Scheme 11. Oxidative addition/cycloaddition of triflamide to *N*,*N*-diallytriflamide.

5. Applications of triflamides

It could be argued that some of the most spectacular applications of triflamides have been in effecting electrochemical energy storage systems. Indeed, one of the reported uses of triflamides in Lithium-sulfur batteries was the developing of a new electrolyte which based on a unique combination of a relatively non-polar triflamide solvent and a low ion-pairing salt (a fluorinated lithium aluminate salt) in order to overcome the problem associated with the formation of highly soluble intermediate polysulfides during the redox cycle, which migrate to and from the negative electrode (Figure 1).[16] Such problem creates the well-known shuttle phenomenon, which leads to poor coulombic efficiency and loss of active material

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from the positive electrode on cycling. Interestingly, the new electrolyte behaves as a sparingly solvating electrolyte at slightly elevated temperatures, where it sustains high reversible capacities over a wide range of current density when paired with lithium metal anode, with a coulombic efficiency of > 99.7 % in the absence of $LiNO_3$ additive.

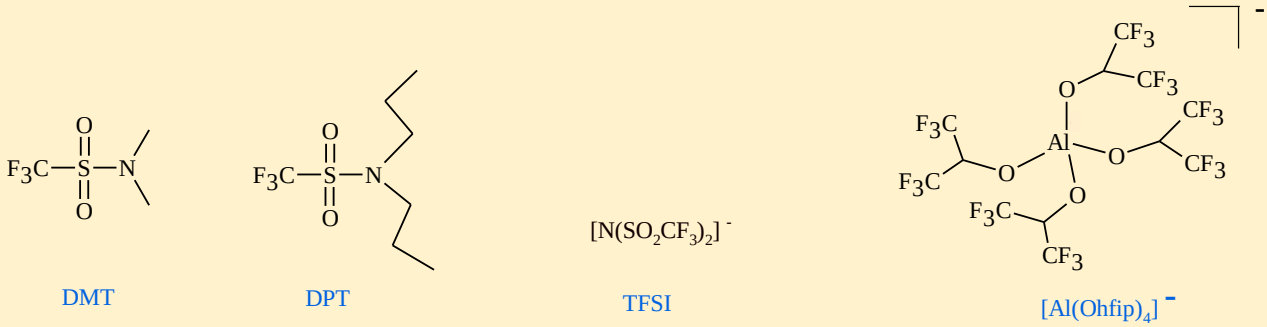
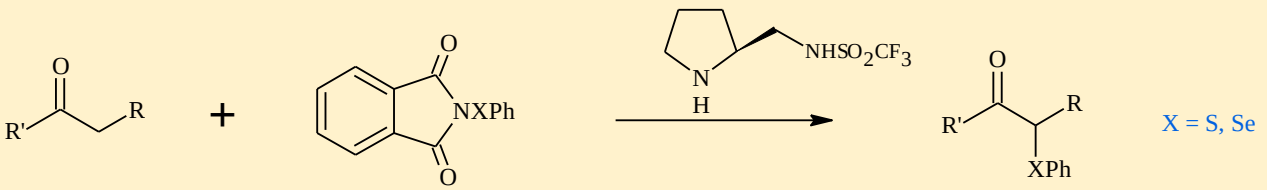


Figure 1. The employed triflamide solvents, and fluorinated lithium aluminate salt.

Triflimide ionic liquids, which most of them or related anions are alkylimidazolium-based, have been known as being low viscous, being highly conductive, and having the lowest melting points. In addition, the most significant features of triflimide anion are the high degree of fluorination; a highly diffuse negative charge; and prevention of hydrolysis of the lithium anode in lithium-air batteries. For example, the cell using ionic liquids consisting of 1-ethyl-3-methyl imidazolium cation and triflimide anion showed the best electrolyte performance.[17]

Catalysis containing the triflamide or triflimide moiety are widely employed in many reactions, including the Michael addition, Friedel-Crafts reaction, Diels-Alder reaction, Mannish reaction, different coupling reactions, etc. For example, *N*-(pyrrolidin-2-ylmethyl)triflamide catalyzes α-sulfenylation[18] and α-selenenylation[19] of a wide series of aldehydes and ketones. As a source of phenylsulfenyl and phenylselenenyl substituents, N-(phenylthio)- and N-(phenylseleno)phthalimide, respectively, were used (Scheme 12).



Scheme 12. *N*-(pyrrolidin-2-ylmethyl)triflamide catalyzes α-sulfenylation and α-selenenylation of ketones.

The most significant features of biological activity of triflamide derivatives are their lipophilicity, imparted by the presence of the CF_3SO_2NH moiety, and their acidity. Lipophilicity of triflamides makes

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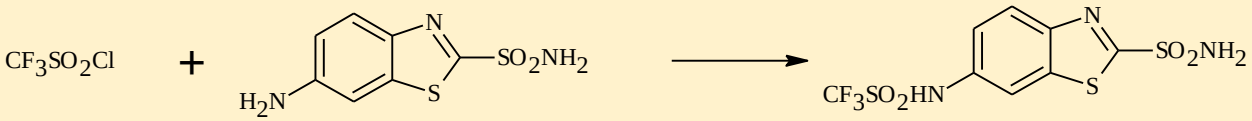
them good uncouplers, that is, compounds that facilitate the transfer of protons from the mitochondrial inner-membrane space into the mitochondrial matrix. Another distinction of the triflamides derivatives of aromatic and heteroaromatic with the sulfonamide moiety in the chain is that a number of them has shown good inhibitory properties against isozymes I, II, and IV of carbonic anhydrase such as the triflamide derivative of 6-aminobenzo[*d*]thiazole-2-sulfonamide. (Scheme 13).[20]



Scheme 13. Synthesis of triflamide derivative of 6-aminobenzo[*d*]thiazole-2-sulfonamide.

6. Conclusion

The outcome of these illustrative examples is plausible in light of the fact that such triflamides and related compounds may strongly affect the reactivity of the chemical reactions as compared to the alkyl- and arylsulfonamides. Indeed, there are many differences between both of these domains, including the structure, the planarity of the nitrogen atom in the N-substituted triflamides versus tetrahedral configuration of $Me_2SO_2NH_2$, the inversion of the site of protonation from nitrogen in alky- or arylsulfonamides to oxygen in triflamide, the condensation reactions, as well as the inertness of triflamide to strong electrophiles that easily react with other sulfonamides.

Such a different behavior is related to the fact that the CF_3 group possess a unique specificity as such strong electron-withdrawing effect. In addition, the acting role of the CF_3 group is described as a modifier of the electronic properties of the RSO_2 group, which is a strong electron acceptor. In hindsight, such strong acceptor effect of the sulfonyl group brings the sulfonamides to such a threshold of reactivity after which even a moderate modifying effect of the CF_3 group lead to switch the focus from quantity to quality.

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Snapshots of some topics of interest of recent notable advances in chemistry

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Managing Director / Founder

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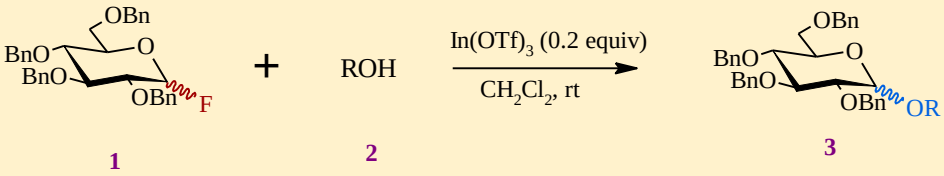
A Mild Catalytic Glycosylation of Glycosyl Fluoride

Indium(III) triflate-mediated glycosylation through an ambient activation of glycosyl fluoride is described. The procedure is compatible with a broad range of alcohol acceptors including the stereoselective C-glycosylation.

A wide range of glycosyl donors have been developed in order to achieve an efficient and simple glycosylation procedure. Among the developed donors, glycosyl fluoride is widely used owing to its thermal and chemical stability. In this context, an efficient catalytic procedure for glycosylation under ambient conditions was reported, which took advantage of the commercially available, mild, and non-toxic indium(III) triflate ($In(OTf)_3$) to employ it as a catalytic activator for glycosyl fluoride.

O-glycosylation

The activation of glycosyl fluoride **1** (α/β isomer) and alcohol acceptors **2** was accomplished in the presence of $In(OTf)_3$ as a catalyst at ambient temperature to afford *O*-glycoside **3** (Scheme 1).



Scheme 1. Catalytic *O*-glycosylation of glycosyl fluoride with alcohol or phenol acceptors.

It was observed that the $In(OTf)_3$-mediated activation of **1β** was much faster than that of **1α** due to the stereoelectronic stabilization of **1α**-isomer via anomeric effect, which resulted in the production of **3α** as the major product. Furthermore, the activation of the relative reactive **β**-glycosyl fluoride proceeded more readily than that of **α**-isomer to form glycosyl bond with alcohol acceptor.

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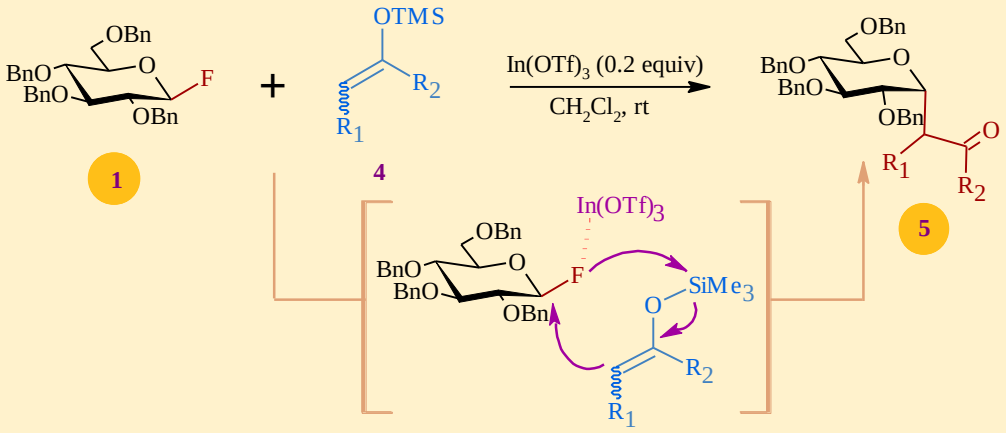
The secondary, tertiary, and benzyl alcohol substrates including acid sensitive alcohols as well as the electron-rich phenols smoothly underwent glycosylation to produce the corresponding glycosides as anomeric mixture (in favor of the α-anomer) in excellent yield.

C-alkyl glycosides

Glycosylation of silyl enol ethers under the same conditions also selectively provided α-C-glycosides in moderate yields (Scheme 2).



Scheme 2. Catalytic C-glycosylation of glycosyl fluoride with silyl enol ether acceptors.

The procedure does not require special precautions or cumbersome work-up process and occurs in the absence of additives.

Review

J. Sim, S.-H. Kim, J. Hur, C. Lim, H. S. Kim, Y.-G. Suh, *Asian J. Org. Chem.*, **2019**, *8*, 107-110.

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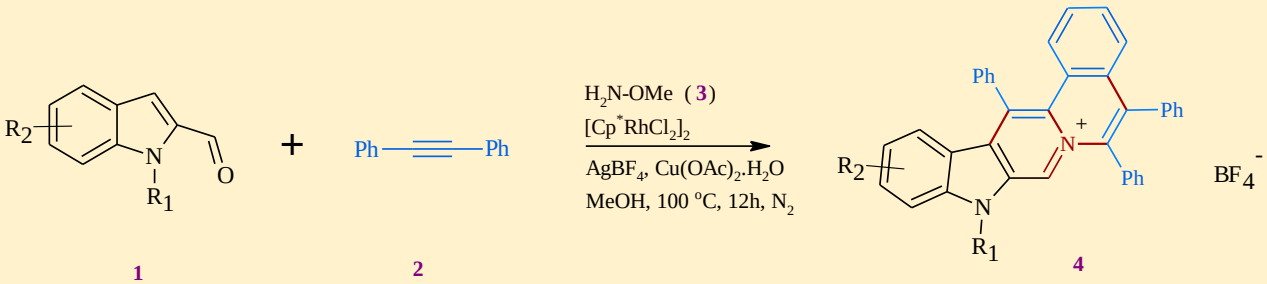
Construction of Pentacyclic Carboline-Containing Salts

A $[Cp^*RhCl_2]_2$-mediated tandem reaction of indolyl aldehydes, amines, and alkynes is highlighted. This one-step multicomponent reaction resulted in the formation of two C-C bonds, two C-N bonds, and one C=N bond to furnish a series of pentacyclic carboline-containing salts in good yield under mild conditions.

Carbolines constitute an important class of structural motifs in medicinal chemistry. Owing to the application potential of polycyclic carboline-containing compounds for bioactive evolution in drug discovery, Wang and co-workers developed an efficient synthetic strategy based on tandem reactions initiated by C-H activation. The strategy involves double C-H activation and double insertion of alkynes.

The tandem reaction of indole-2-carboxaldehyde **1** with alkyne **2** and amine **3** in MeOH at 100 °C in the presence of $AgBF_4$ and $Cu(OAc)_2.H_2O$ as additives using $[Cp^*RhCl_2]_2$ as the catalyst under N_2 atmosphere provided the desired product **4** (Scheme).



1 2 4

Scheme Tandem reactions initiated by C-H activation.

It was found that electron-donating aldehydes provided tandem products in better yields than electron-accepting aldehydes.

The strategy features high bonding efficiency, simple operation, mild reaction conditions, and good yield.

Review

Z. Wang, T. Li, S. Xing, B. Zhu, *Asian J. Org. Chem.*, **2019**, *8*, 191-195.

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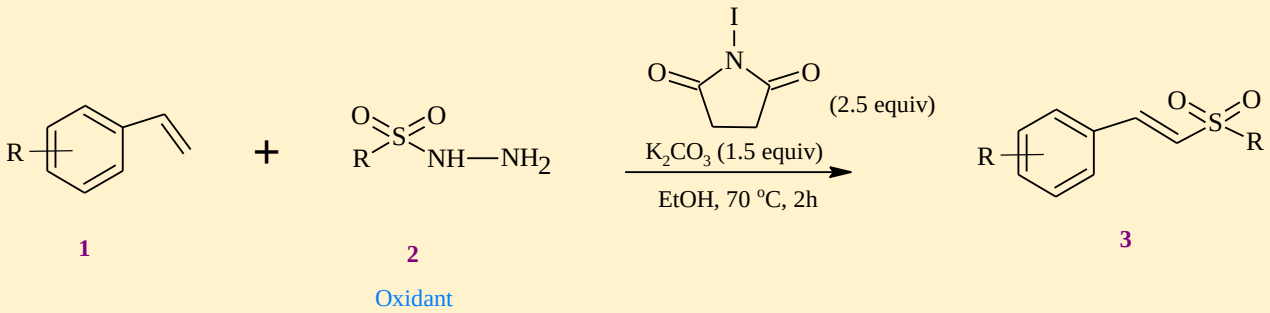
(*E*)-Selective C(sp^2)-H Sulfonylation of Styrenes

A one-pot sustainable method for the synthesis of (*E*)-vinyl sulfones from styrenes is highlighted. The method employed *N*-iodosuccinimide as a bifunctional reagent for a regio- and (*E*)-selective C(sp^2)-H sulfonylation of styrenes.

Vinyl sulfones (Michael acceptors) have many medicinal applications, and are used as dienophiles in cycloaddition, cycloproponation, and epoxidation reactions. Toward a sustainable synthetic method of vinyl sulfones, Pramanik and co-workers reported a convenient one-pot procedure, in which styrenes **1** and sulfonyl hydrazides **2** treated with *N*-iodosuccinimide (NIS) and potassium carbonate in ethanol at 70 ^oC to afford (*E*)-vinyl sulfones **3** in moderate to excellent yield (Scheme 1).



Scheme 1. Synthesis of vinyl sulfones.

In this reaction, NIS plays a dual role, firstly, generation of sulfonyl radical from sulfonyl hydrazides, then formation of *β*-iodosulfone intermediate followed by conversion to (*E*)-vinyl sulfones (Scheme 2). In order to generate sulfonyl radical, sulfonyl hydrazide is employed as an excellent synthon owing to its stability, inexpensive, and easy handling.

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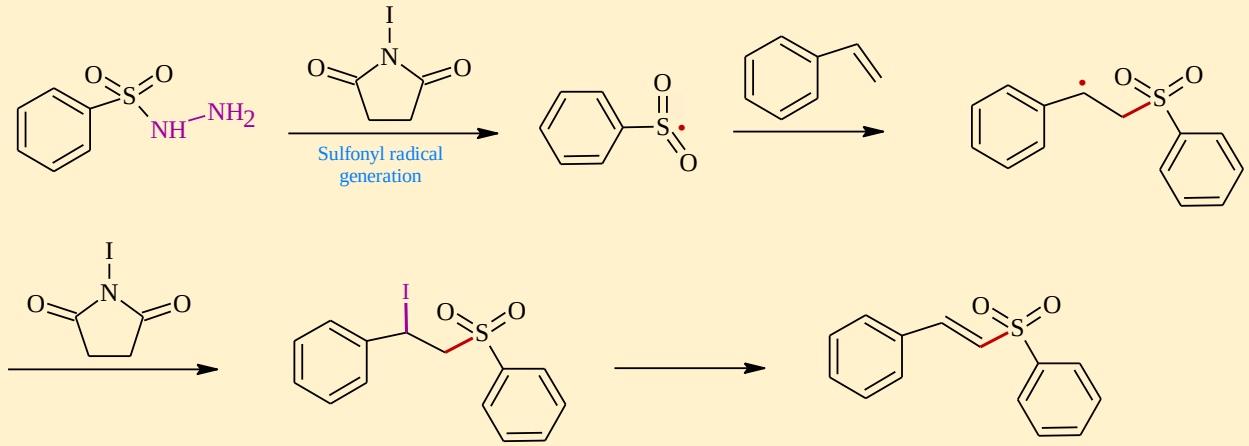

Scheme 2 NIS acting as a bifunctional reagent.

This transition metal free methodology was found to be highly regioselective and mild for the C-S coupling reactions.

Review

M. Pramanik, K. Choudhuri, P. Mal, *Asian J. Org. Chem.*, **2019**, *8*, 144-150.

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Treatment of Rheumatoid Arthritis Using Gold Multifunctional Nanoparticles

This snapshot highlights a multifunctional gold (Au) half-shell nanoparticles delivery system that can deliver both heat, upon near-infrared (NIR) irradiation, and drug simultaneously to the selected region for the treatment of rheumatoid arthritis (RA).

Gold nanoparticles strongly absorb NIR light, and produce localized cytotoxic heat upon NIR irradiation. As a delivery system for the treatment of RA, it was reported that methotrexate (MTX), a disease-modifying anti-rheumatic drug, loaded poly(DL-lactic-*co*-glycolic acid) Au half-shell nanoparticles (MTX-PLGA-Au), and conjugated arginine-glycine-aspartic acid (RGD) peptides to the surface of the Au half-shell, where the RGD peptide is a targeting moiety for inflammation. After the injection, then, upon NIR exposure, heat was generated as a result of Au half-shell, which led to the release of drug from PLGA nanoparticles, allowing photothermally controlled drug delivery. The application of such multifunctional nanoparticles in CIA mice had shown superior therapeutic efficacy with a much smaller dosage of MTX compared to conventional treatment.

Procedure

MTX-loaded PLGA (MTX-PLGA) nanoparticles were firstly prepared, then, Au film (15 nm) was deposited onto the MTX-PLGA nanoparticle monolayer prepared on a Si substrate using a thermal evaporator, which formed a half-shell structure (MTX-PLGA-Au). Next, Au-deposited MTX-PLGA nanoparticles were released into 1 wt % SH-PEG-COOH solution from substrate by sonication and collected by centrifugation.

For targeted delivery, cyclic RGD peptide, which binds $\alpha_v\beta_3$ integrins expressed on angiogenic vascular endothelial cells at sites of inflammation, was conjugated on the Au surface to afford (RGD-MTX-PLGA-Au) nanoparticles in 100-115 nm diameter (Figure).

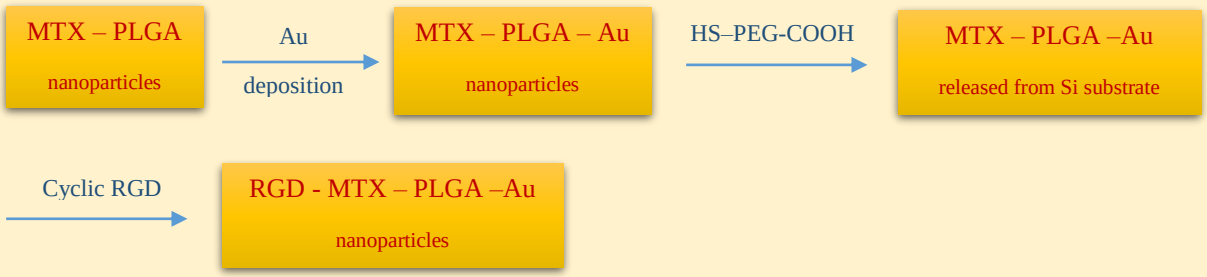

Figure Schematic illustration of the process of RGD-MTX-PLGA-Au nanoparticles.

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These results revealed that the targeted Chemo-photothermal treatments using multifunctional nanoparticles are a mature and effective option for maximizing the therapeutic efficacy and minimizing dosage-related side effects in the treatment of RA.

Review

S. –M. Lee, H. J. Kim, Y. –J. Ha, Y. N. Park, S. –K. Lee. Y. –B. Park, K. –H. Yoo, *ACS Nano*, **2013**, *7*, 50-57.