Synthetic Studies of Maleimide Derivatives for Bioconjugates Polymers by RAFT polymerization.

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Abstract: An efficient method for the synthesis of maleimides derivatives in toluene in presence of PTSA is described. The method features a broad substrate scope of utility in both simple and complex setting and provide access to valuable derivatives without any column chromatography purification is described.

KEY WORDS: maleimides, Bismaleimides, conjugates, RAFT polymerization, PTSA, Condensation.

INTRODUCTION:

Maleimide-derivatives are among the mostly used in protein chemistry, polymer chemistry and functional group transformation mainly due to its double bond is very reactive and can undergo chain extension reaction[1-2]. In protein chemistry it is used for bioconjugation[3], due to exceptionally fast reaction rates and significantly high selectivity towards cysteine[4] residues in proteins, a large variety of maleimide heterobifunctional reagents are used for the preparation of targeted therapeutics[5], PET[6]. Bradykinin

Antagonists Peptide[7], cyclic polypeptide drugs[8], Topoisomerase[9], pharmaceutical compositions[10], Highly Potent and Stable Capped siRNAs[11], nucleotide prodrugs[12], carbonic anhydrase II Activity[13], Glycosaminoglycan[14] and phospholipids[15]. Secondly, maleimides, particularly the bismaleimides are used for synthesis of self-healing polymers[16-17], self-assembled functional telechelics and modular block copolymers[18], reactive and functional polymers[19] such as click chemistry[20-22]. Maleimide derivatives are also used in chemicals applications such as dienophiles in cycloaddition reactions[23], Thia Paterno Buchi Reaction[24] C-H activation[25] and functionalized basic maleimides[26] are few of them.

Maleimide derivatives are usually synthesized from maleic anhydride and a diamine to obtain the intermediates, maleamic acids which on cyclo-dehydration to a maleimide is a general method for the preparation. Numerous reagents[11, 23, 27-31] or high pressure[32] used methods were reported for effective the dehydration of amic acids to imides. However in these methods that the synthesis leads to several by-products such as isoimides, acetanilides, maleimides, acetic acid adducts, and products with mixed functionalities which interns the yields are low[33-34]. In an Alternate route, the displacement of methoxycarbonyl group of maleimide[7] with nucleophilic group, such as amines under basic condition to get imides[4, 35-36] or N-alkylation with alkyl halides by using base in anhydrous conditions[37-38]

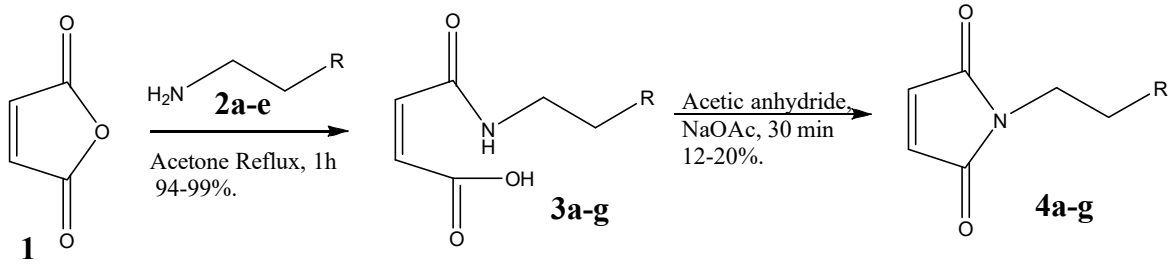
PRESENT WORK.

In our projects we need a wide range of maleimides derivatives, particularly with linkers having alkane chain **4a**, ethers, **4b, 4c**, Polyethylene Glycols (PEG), **4d** and alkyne group **4e** and ethylene glycol-OH groups compounds **4f** and **4g**. To achieve these compounds,

we employed most used method such as maleamic acid dehydration in presence AcONa[11](method-A) and N-carbonyl maleimid N-(Methoxycarbonyl) maleimide (method)[35].

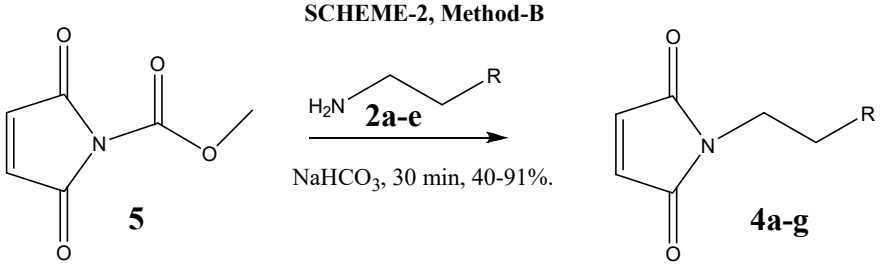
The maleamic acid (method-A) can be obtained from maleic anhydride under treatment of respective amines to get the maleamic acids derivatives (**3a-3g**). The maleamic acid derivatives (**3a-3g**) on treatment with sodium acetate[11] to get corresponding maleimide derivatives **4a-4g**, the yields after purification are low particularly for 2-Bismaleimidoethane,[29] N-Propargylmaleimide,[34] Moreover polyethylene **3d** and free hydroxyl group substrates **3f** and **3g** giving impurities.

SCHEME-1, Method-A



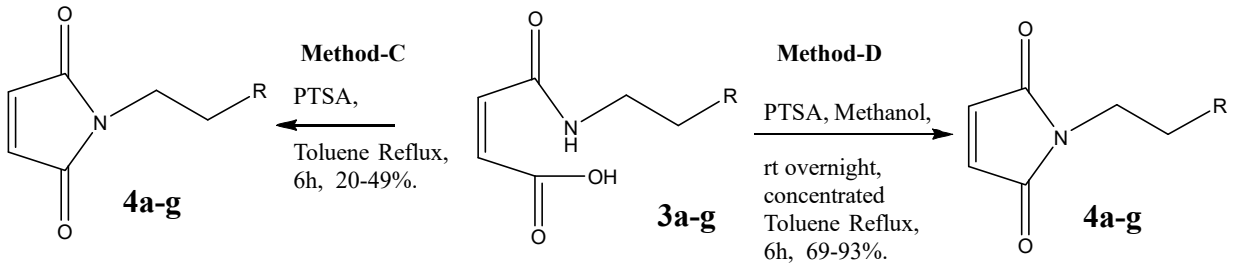
By exploring this method, (method-B) for synthesize the various maleimide derivatives by treating the free amines with N-(Methoxycarbonyl) maleimide in most of the cases we got good to excellent yields. The hydroxyl group bearing substrate gives **(4f)** N-[2-(2-Hydroxyethoxy)ethyl]-maleimide and **(4g)** N-(2-Hydroxyethyl)-maleimide[39] were obtained in good to excellent yield after purification. The maleimide-YNE and polyethylene substrate are giving complex product under this condition. The NMR data shows complex structure, the absence of acetylene moiety, it indicates that is taking part in the reaction.

SCHEME-2, Method-B



Based on the above problems, there is need to develop a general procedure where it is compatible for alkyne group and Polyethylene group along with to avoid use of column chromatography purification. A range of methods are reported[10, 40-44] for cyclic dehydration, out of that para toluene sulfonic acid in toluene reflux under condition [24, 45] is more suitable so that by acid base pH manipulation we can avoid the column chromatography purification. So, we applied this method for synthesize the maleimide derivatives ((Method-C). We took bismaleimicacid **3a** in toluene under reflux condition in presence of PTSA gives the essentially pure product but in low yield. We understood that solubility of acid bearing substrate in toluene influence the outcome (yields) of the reaction. The maleimide derivatives yields are decreasing when ether linkage is increasing in the bismaleimide because of polarity.

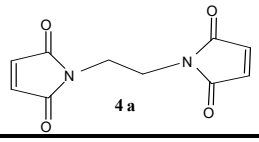
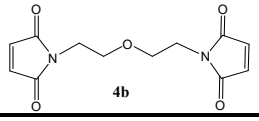
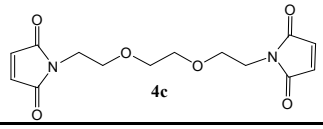
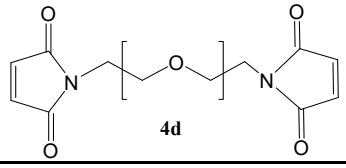
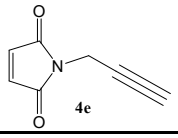
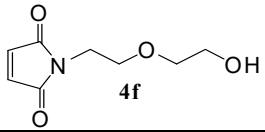
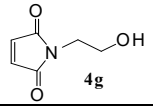
SCHEME-3,



To avoid the solubility problem of maleimide acid, we carried out one pot reaction, where the acid is first is converted into ester in methanol in presence of PTSA at room temperature. After concentration*, the crude ester in toluene under reflux condition gives required products without any column chromatography purification in good to excellent yields. (METHOD-D).

The yields are much better than from the acid directly. Under these condition Alkyl linked maleimide **4a-4c** were isolated in pure form and **4c** was characterized by single crystal data (hard copy only). PEG-Maleimide **4d** and N-Propargyl maleimide **4e** gives good yields whereas as substrate **3f**, **3g** remain unsuccessful because of free hydroxyl group, which is interfering the reaction, and giving polymeric product.

Synthesis of Maleimide derivatives from 4 Different Methods.

Product	Method-A	Method-B	Method-C	Method-D
 4a	16%	71%	21%	**70%**
 4b	13%	68%	15%	**75%**
 4c	11%	40%	11%	**80%**
 4d	impurities	No reaction		**93%**
 4e	12%	complex	49%	**74%**
 4f	impurities	91%	impurities	impurities
 4g	impurities	90%	impurities	impurities

In conclusion, we have established a operationally simple one pot cyclization method for synthesis of pure maleimide derivatives without any column chromatography purification by using PTSA in presence of methanol and toluene under reflux conditions (method-D). The notable advantage of this methodology are simple conditions, industrially applicable, tolerance to a wide range of functionalities.

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*** Note-1:** In methanol under reflux condition, aliquot NMR shows mixture of products, corresponding ester and cyclized products. To get the complete cyclized product, it is necessary to do reaction at higher temperature. To facilitate the reaction, distilled out methanol and added toluene then heated at reflux to get cyclized products in good to excellent yields.