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Peptide Coupling Reactions

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Peptide bond formation is a nucleophilic substitution reaction of an amino group (nucleophile) at a carboxyl group involving a tetrahedral intermediate. Furthermore, the peptide coupling reaction must be performed under mild conditions, and preferably at room temperature. Activation of the carboxyl component is achieved by the introduction of electron accepting moieties [1]. Carboxyl components can be activated as acyl halides, acyl azides, acylimidazoles, anhydrides, esters etc. There are different ways of coupling reactive carboxyl derivatives with an amine [2].

In recent years, peptide-coupling reactions have significantly advanced in accord with the development of new peptide-coupling reagents and their application to both solution and solid- phase synthesis [3,4]. The formerly techniques of carbodiimide is being replaced with iminium/uronium derivatives **1-5** [5-21] (Figure 1).

Later, El-Faham and Albericio [22] reported a new family of coupling reagents based on the modification of the structures of the carbocation skeleton moiety, which feature relatively high reactivity and low racemization during peptide bond formation [22]. Very recently, El-Faham and Albericio [23] extended their work taking an *N*-containing 6-membered ring structure containing O, S, and N-CH_3 for synthesis of novel coupling reagents [24] (Figure 2).

Recent reports confirmed the explosive properties of HOBt derivatives [25]. Accordingly, El-Faham and Albericio [25-26] reported the new additives as well as their uronium salts derivatives as replacement for HOBt and HOAt derivatives (Figures 3 and 4). Among these entire additives Oxyma [26] (Figure 3) and its uronium salt COMU (Figure 4) showed an excellent replacement for HOBt and its analogues [26,27].

More recently, we have reported 5-(hydroxyimino)-1,3-dimethylpyrimidine-2,4,6 (1*H*,3*H*,5*H*)-trione (Oxyma-B) as an excellent additive for the suppression of racemization during peptide synthesis [27]. Oxyma-B, has the same structure future for the carbonyl moiety in which the oxime group is flanked between the two carbonyl group as in HONM. In addition, Oxyma-B performs better as a racemization suppressor than Oxyma Pure and even better than HOAt in both stepwise and segment coupling in solid- and solution-phase peptide synthesis [28]. Lately,a new class of *O*-form uronium-type coupling reagents derived from Oxyma-B were introduced TOMBU and COMBU (Figure 5) [29].

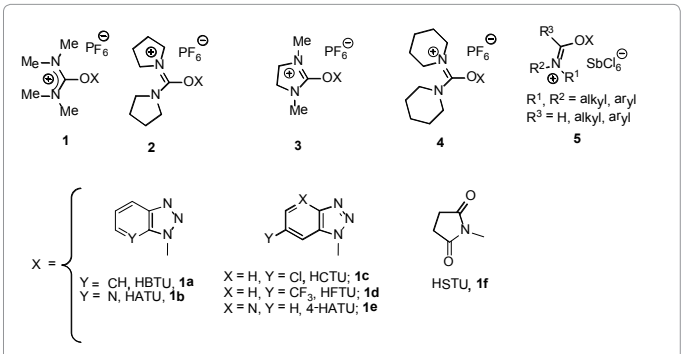

Figure 1: Structure of symmetric imininum/uronium salts coupling reagents.

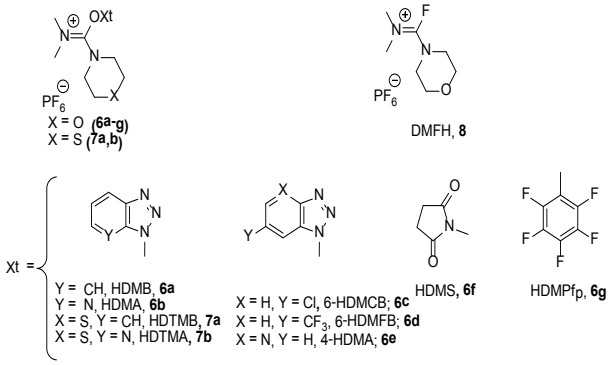

Figure 2: Structure of morpholine-based coupling reagents.

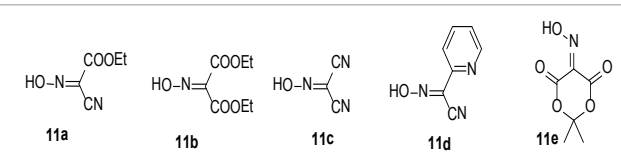

Figure 3: Structure of oximes to replace of HOBt.

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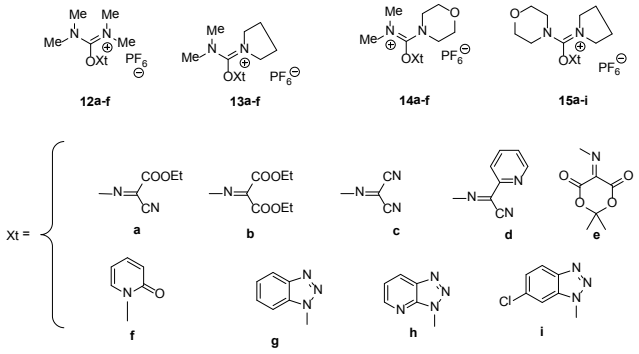

Figure 4: Structures of oximino and benzotriazolo uronium salt.

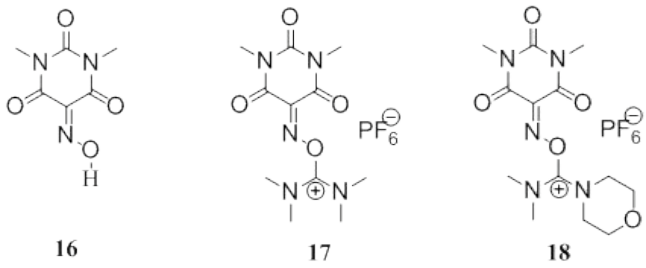

Figure 5: Structure of Oxyma-B 16 and its uronium salts TOMBU 17 and COMBU 18.

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