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PyBroP: a convenient activator for the synthesis of formamidines

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Abstract

PyBroP was used as a convenient coupling reagent in the synthesis of formamidines from aliphatic and aromatic primary amines and *N,N*-dimethylformamide.

Formamidines, derivatives of the unstable imidic acid, have been extensively studied as intermediates in organic synthesis[1] and are of increasing interest in medicinal chemistry.[2–12] The reaction of an amine with a suitable formamide derivative is widely used for the synthesis of formamidines. The activation of the formamide is a necessary prerequisite since the formamide carbon atom is not available for nucleophilic attack by an amine. Imidoyl chlorides[13–16] resulting from the action of P_2O_5, PCl_5, PCl_3, $SOCl_2$ or alkoxy derivatives[17] generated by the action of triethyloxonium fluoroborate have been utilized as activated forms in formamidine synthesis. The reaction of (diaminomethyl)di-*tert*-butylphosphine with primary amines to give formamidines has also been reported.[18] All these intermediates are rather unstable and only provide the desired compounds in moderate to poor yields and purity, owing to some side-reactions. Recently, a more efficient synthesis of formamidines, employing a set of sulfonyl chlorides was described. Although yields were reasonable, the procedure utilized reagents that were not easy to handle and was unsuitable for aliphatic amines.[19]

In this paper, we report a convenient and versatile synthesis of formamidines based upon the use of PyBroP, the well-known coupling agent in peptide synthesis. This reaction has already been reported in solid phase peptide synthesis.[20] In our study, a variety of anilines differing in their steric hindrance, a 4-aminoquinoline, the 1,3-phenylenediamine and its pyridyl analogue, benzylamine and the corresponding saturated cyclohexanemethylamine as a non-aromatic amine control, were used.

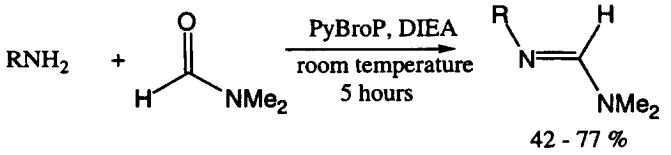

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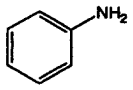
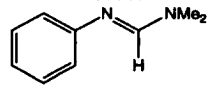
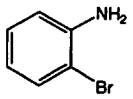
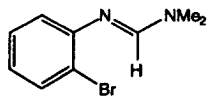
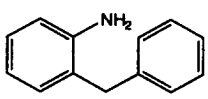
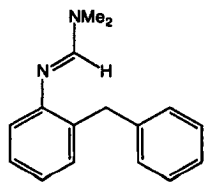
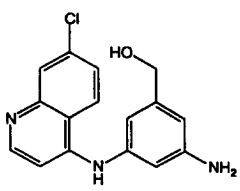
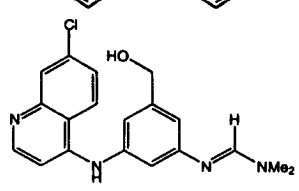
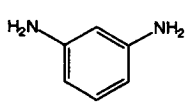
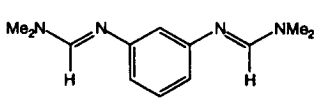
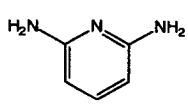
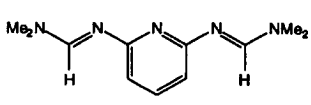
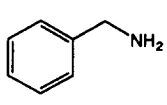
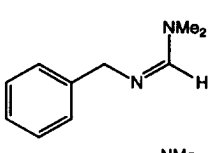
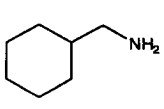
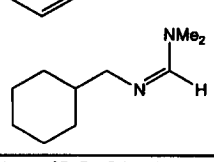
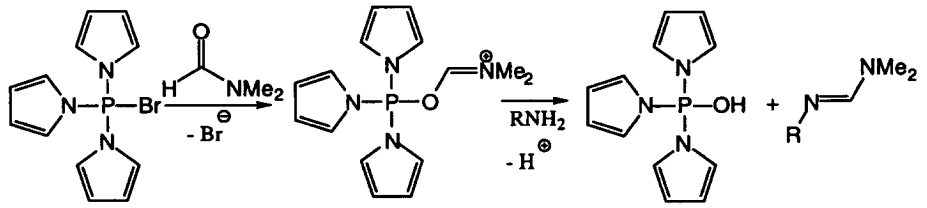
Table 1
Synthesis of formamidines by coupling primary amines with DMF[a]

Entry	Amine		Product		Yield
1		1A		1B	56[c]
2		2A		2B	57[c]
3		3A		3B	63[d]
4		4A		4B	42[d]
5		5A		5B	53[d]
6		6A		6B	48[d]
7		7A		7B	77[d]
8		8A		8B	52[d]

(a) The reaction is performed with 1 eq. of amine, 1 eq. of DIEA and 1 eq. of PyBroP in DMF at room temperature except for entries 5 and 6 (1 eq. of amine, 2 eq. of PyBroP and 2 eq. of DIEA). (b) Yields based on amines. (c) After purification by HPLC. (d) After purification by thick-layer chromatography.

The common procedure is as follows (Eq. 1): a mixture of amine (1 equiv.), PyBroP (1 equiv.), and *N,N*-diisopropylethylamine (1 equiv.) in DMF was stirred for 5 hours at room temperature. Removal of the solvent yielded a residue which was purified either by thick-layer chromatography or by HPLC. All formamidines were characterized by ^{1}H NMR and mass spectrometry. Spectral data for compound **3B** are given as a representative example in the references.[21] Experimental conditions and yields following purification are summarized in Table 1. Amine conversion rates were quantitative, yet loss of yield occurred owing to strong interactions between products and silica phase during chromatography purifications.

The mechanism suggested for the formation of formamidines resembles that suggested for the synthesis using arylsulfonyl chlorides as coupling agents and is shown on Scheme 1.



Scheme 1.

It is important to note that, under the same conditions, no formation of formamidines was observed with BOP, another popular activation reagent used in peptide synthesis and also less effective than PyBroP for coupling hindered amino acids such as the *N*-methyl variants.

The evaluation of the synthesis of formamidines as a side-reaction in DMF, when a carboxylic acid is used to generate an amide linkage in the presence of PyBroP as a coupling reagent, seemed worthy of interest. In the case of amine **4A** chosen as a reference, we observed an obvious influence of the steric hindrance with a 56% yield of amide and 17% yield of formamidine in the case of chloroacetic acid compared with the 27% and 50% yield, respectively, for the most hindered bromoacetic acid. Therefore, formation of formamidines becomes preponderant and can be correlated to the steric hindrance of the carboxylic acid.

In conclusion, we have described a convenient and efficient preparation of formamidines from primary amines and *N,N*-dimethylformamide in the presence of PyBroP. Its advantages are: (i) the mildness of the reaction conditions (room temperature) and a rather short reaction time; (ii) moderate to good yields; (iii) the use of a commercial coupling reagent which is easy to handle; (iv) the suitability for both aliphatic and aromatic amines. Work is now in progress to determine the optimum conditions for the replacement of the dimethylamino moiety which will permit the obtention of analogues for each family of compounds.

Acknowledgements

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21. Compound **3B**: yellow oil. *m/z*=238,6 (M=238.3 g/mol). ^{1}H NMR (DMSO, 300 MHz): 3.04 (s, 3H), 4.00 (s, 2H), 7.10–7.23 (m, 9H), 7.93 (s, 1H).