imidazo[1,2-*a*]pyridine (**7**) and pyrazolo[1,5-*a*]pyridine (**8**) analogs displaying similar low micromolar activity (EC_{50}s of 2.2 and 1.7 μM, respectively).

Our decision to pursue the imidazopyridine (**7**) core in spite of the fact that it was less active than the corresponding pyrazolopyrimidine (**4**) and pyrazolopyridine (**8**) scaffolds was influenced by several factors. First, the key imidazopyridine intermediate **10** was easily prepared in one step from the commercially available 2-aminopyridine **9** (Figure 5.5).[33] The ability to access large quantities of **10** (>500 g) allowed the rapid development of SARs within the series and represented a significant advantage over the synthetically challenging pyrazolopyridine (**8**) scaffold. Second, compounds based on a pyrazolopyrimidine core (*i.e.* **1**) have been extensively prepared and profiled for a variety of therapeutic indications, including viral diseases.[8] In comparison, the imidazopyridine scaffold presented an opportunity to explore new chemical space and, therefore, became the primary focus of our efforts.

Compound **10** proved to be a versatile intermediate, allowing for modifications at C3, C5 and the C2-amide (Figure 5.5). For example, **10** underwent electrophilic aromatic substitution at C3 with *N*-chlorosuccinimide (NCS) and was subsequently converted to **11**. The addition of chlorine to the imidazopyridine core led to a fourfold increase in genotype 1b replicon activity compared with the C3-protio scaffold (compare the EC_{50}s of 0.5 and 2.2 μM for analogs **11** and **7**, respectively). Bromine was also well tolerated at this position and provided access to other functional groups such as methyl, cyano, and vinyl *via* Pd(0) cross-coupling reactions. Similarly, a wide variety of substituents could be selectively installed at C5 *via* Pd-catalyzed cross-coupling reactions. In this manner, the 3-furanyl moiety was introduced, thereby affording a compound with a high degree of structural similarity to the original screening hit (compare analogs **12** and **1**). Compound **12** shows a threefold improvement in genotype 1b replicon activity over analog **1** (EC_{50}s of 0.2 and 0.6 μM, respectively) with only a modest increase in MW (426 and 409, respectively).

The 3-chloro-5-furanylimidazopyridine core was combined with various amine fragments to probe the SAR at the C2-carboxamide position

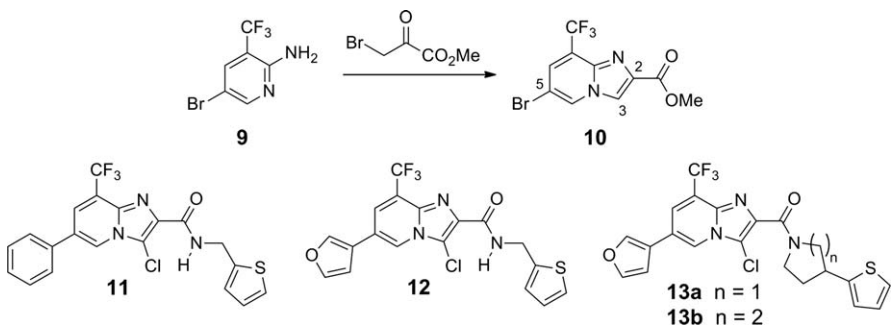

Figure 5.5 One-step synthesis of the versatile imidazopyridine analog **10** that permitted rapid modifications at C3, C5 and the C2-amide (analogs **11**, **12** and **13**, respectively).