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Cyclodehydration of *N*-(Aminoalkyl)benzamides under Mild Conditions with a Hendrickson Reagent Analogue

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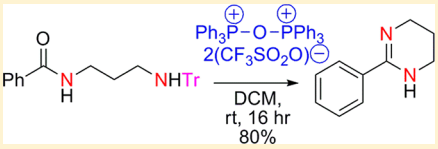
Supporting Information

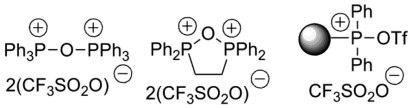
ABSTRACT: Methods for the cyclodehydration of *N*-(aminoalkyl)benzamides are few and employ harsh reaction conditions. We have found that the easily prepared phosphonium anhydrides **1** (Hendrickson reagent) or **2** can be used for cyclodehydration of *N*-(aminoalkyl)benzamides under very mild conditions (room temperature) to produce five-, six-, and seven-membered cyclic amidines. Good yields are obtained by employing a temporary trityl group protection strategy. Cyclic analogue **2** can be used when the product cyclic amidine is organic-soluble, thus producing water-soluble byproducts.



We were interested in the cyclodehydration of *N*-(aminoalkyl)benzamides to give cyclic amidines. Cyclic amidines such as tetrahydropyrimidines and imidazolines have been shown to be important pharmacophores in drug discovery because they exhibit a broad spectrum of biological and pharmacological activities including antihypertensive,[1] anti-inflammatory,[2,3] and antituberculosis[4] activity. Cyclic amidines also occur in a number of natural products such as Clathramide A[5] and Manzacidin A,[6,7] isolated from marine sponges. Cyclic amidines are also useful in organic synthesis as synthetic intermediates,[8,9] chiral auxiliaries,[10,11] chiral catalysts,[12−14] and ligands for asymmetric catalysis.[15,16]

Most of the commonly used methods for the synthesis of cyclic amidines involve treating a diamine with a carboxylic acid,[17,18] an ester,[19,20] or a nitrile,[21] and many of the synthetic protocols reported use quite forcing conditions. We were surprized to find that the most obvious method of synthesis, the cyclodehydration of *N*-(aminoalkyl)benzamides to produce products such as **13** or **16**, has only rarely been used. For example, a simple SciFinder substructure reaction search from amino amide to **13** as the product gave no hits. Of the four references[22−25] found in the seach from amino amide to **16** as the product, one method[22] employed xylene at 200 °C, while another patent method[23] employed $POCl_3$ at 80−90 °C for 4−8 h. The remaining two patents used silylating agents:[24,25] hexamethyldisilazane/TMSCl at 100 °C for 16−48 h or TMSI/dimethylaminomethyl polystyrene for 2−18 d. In contrast, cyclodehydration of the corresponding hydroxy amides is much more common (15 references for the oxazine analogue of **13** and 370 references for the oxazoline analogue of **16**).

As noted by Chouiery et al.,[24] most of the literature procedures for the cyclodehydration of amino amides suffer from disadvantages such as harsh reaction conditions, potentially hazardous reagents, prolonged reaction times, low yields, difficulty in preparation of starting materials, and tedious workups. We considered that the Hendrickson reagent (triphenylphosphonium anhydride trifluoromethane sulfonate, **1**)[26−29] might overcome these difficulties. It is one of the mildest reagents known for cyclization/cyclodehydration[29,30] and being highly "oxophilic" was expected to react preferentially with the carbonyl oxygen of the amide rather than the amino group. In this paper we explore the use and generality of the Hendrickson reagent (**1**), the cyclic analogue 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoro methanesulfonate) **2**,[31] and polymer-supported triphenylphosphine ditriflate **3**[32,33] for the cyclodehydration of *N*-(aminoalkyl)-benzamides to give cyclic amidines such as tetrahydropyrimidines and imidazolines.



1 **2** **3**

Initially, activated polymer-supported oxyphosphonium intermediates **4** or **5** were generated by stirring a mixture of reagent **3** (2 equiv) and benzoic or 4-nitrobenzoic acid (1 equiv), respectively, for 1 h in dry DCM, followed by addition of propane-1,3-diamine (1 equiv) and DIPEA. The major product formed in each case was the bis-amide **8**[34] (66% yield based on benzoic acid) or **9**[34] (86% yield based on 4-nitrobenzoic acid) rather than the corresponding tetrahydropyrimidine (Scheme 1). These results confirmed that the first intermolecular dehydration, via the oxyphosphonium intermediate **4** or **5**, had occurred to give amides **6** and **7**, respectively. However, instead of activation of amide **6** or **7** with the polymer-supported triphenylphosphine ditriflate **3** and subsequent intramolecular dehydration, a second intermolecular reaction had occurred between the amine groups of **6** or **7** and a second equivalent of **4** or **5**, respectively, to give the corresponding bis-amides **8** or **9**.

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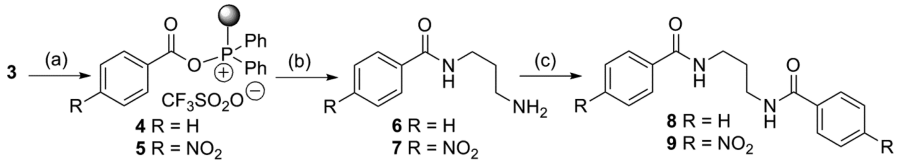
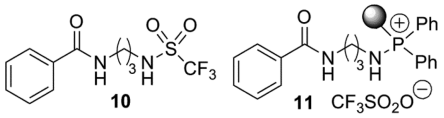
Scheme 1. Attempted Cyclodehydration of Amides 6 and 7 with Polymer-Supported Reagent 3[a]



[a]Reagents and conditions: (a) benzoic acid or nitrobenzoic acid, DCM; (b) 1,3-propanediamine, DIPEA, DCM; (c) **4** or **5**.

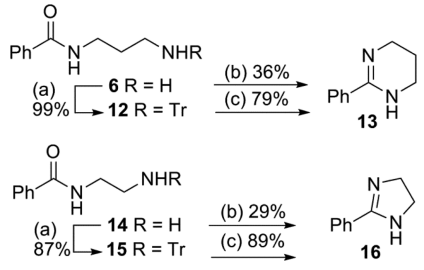
Treatment of amide **6** with acetyl chloride (2.0 equiv) and triethylamine (2.0 equiv) gave *N*-[3-(acetylamino)propyl]-benzamide[35] (52%). Addition of *N*-[3-(acetylamino)propyl]-benzamide and DIPEA to a mixture of reagent **3** (1.0 equiv) in dry DCM gave recovered *N*-[3-(acetylamino)propyl]-benzamide. Direct treatment of amide **6**[36,37] with reagent **3** in the presence of DIPEA in dry DCM also failed to give the desired cyclic amidine. The only product isolated (apart from starting material) was the sulfonamide **10** (25%), which was characterized additionally as the stable acetyl derivative.



It is possible that the amino group of **6** reacts competitively with reagent **3** to give the aminophosphonium salt **11**. The formation of **11** would block the cyclodehydration reaction, as activation of the amide would be rendered most unlikely given that the substrate is already bound to the polymer bead. Upon aqueous workup, **11** would be hydrolyzed to give back the amide **6**.

Much more promising results were obtained with the solution phase reagent **1**. Thus, when the amide **6** was treated with 1 equiv of reagent **1** and DIPEA in dry DCM (Scheme 2),

Scheme 2. Synthesis of Tetrahydropyrimidine 13 and Imidazoline 16 with Reagent 1[a]

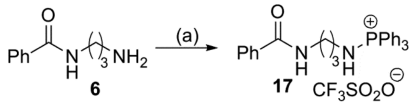


[a]Reagents and conditions: (a) TrCl, TEA, DCM; (b) reagent **1**, DIPEA, DCM; (c) reagent **1**, DCM.

the desired cyclic amidine **13**[38,39] was isolated in 36% yield following an aqueous workup (the triphenylphosphine oxide byproduct remains in the organic layer) and chromatography on basic alumina.

Similar results were obtained when the amide **14**[40] was treated with **1** and DIPEA in dry DCM. The desired imidazoline **16**[18,41] was again isolated but only in modest yield (29%, Scheme 2). We considered that the low yields of tetrahydropyrimidine **13** (36%) and imidazoline **16** (29%) and the recovery of amides **6** and **14**, respectively, could be the result of competitive formation of an aminophosphonium salt of the type **17** (Scheme 3), which upon workup and

Scheme 3. Formation of Aminophosphonium Salt 17[a]



[a]Reagents and conditions: (a) reagent **1**, DIPEA, DCM.

chromatography is hydrolyzed to give the starting amide **6** (*n* = 3) or **14** (*n* = 2). Presumably, despite the oxophilicity of **1**, the primary amino group of **6** is so reactive that it can compete with the amide carbonyl group for the phosphorus atom of **1**. If the reactivity of the amino group in amides **6** and **14** toward reagent **1** could be reduced, so that activation of the amide functionality became kinetically favored, this problem might be avoided.

What was required was a "temporary" protecting group that increased the steric hindrance of the amino group sufficiently to prevent or slow its reaction with **1** but would ideally drop off once activation of the amide (by **1**) had occurred. Two possibilities were considered, the trityl group and the Boc group.

Accordingly, amide **6** was converted to the trityl amide **12**, which was then treated with reagent **1** (1.5 equiv) in the absence of base in dry DCM. The cyclic amidine **13** was isolated in good yield (79%) after chromatography on basic alumina (Scheme 2). Similar results were obtained with the trityl amide **15**, which upon treatment with **1** was converted to the desired imidazoline **16** (Scheme 2) in high yield (89%). The trityl group strategy was clearly successful. Interestingly, when the reaction of **12** with **1** was carried out in the presence of DIPEA (2.0 equiv), the cyclic amidine **13** was not formed. Only the starting material **12** and triphenylphosphine oxide were recovered. This suggests that the tritylamino group is too sterically crowded to undergo the cyclization reaction and must be detritylated prior to this step (triflic acid is formed during activation of the amide functionality by **1**).

It is also interesting to note in this regard that the isopropylamino benzamide **18**[42] (formed in 94% yield from *N*-isopropyl-1,3-propanediamine by treatment with benzoic anhydride) undergoes cyclization to the corresponding cyclic amidine **19** with reagent **1** in high yield (86%) without recourse to trityl group protection (Scheme 4). Presumably the isopropyl group provides sufficient steric hindrance to slow down the (bimolecular) reaction of the amino group with the phosphonium reagent but is small enough to allow the (intramolecular) cyclization reaction. Extension of the trityl group strategy to the synthesis of tetrahydropyrimidine **22**[43,44] and hexahydro-1*H*-benzimidazole **25**[45] is illustrated in Scheme 4.

A mechanism, involving a (favored) 5- or 6-*endo-dig* cyclization, for the formation of the five- or six-membered cyclic amidines is suggested in Scheme 5 (illustrated for the conversion of **6** to **13**).

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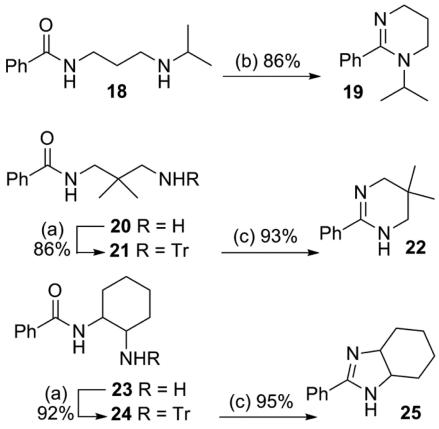
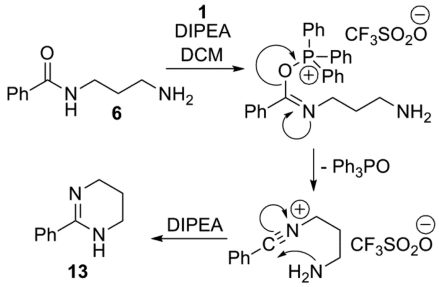
Scheme 4. Synthesis of Tetrahydropyrimidines 19 and 22 and Hexahydro-1*H*-benzimidazole 25 with Reagent 1[a]



[a]Reagents and conditions: (a) TrCl, TEA, DCM; (b) reagent **1**, DIPEA, DCM; (c) reagent **1**, DCM.

Scheme 5. Proposed Mechanism for Formation of Tetrahydropyrimidine 13[a]

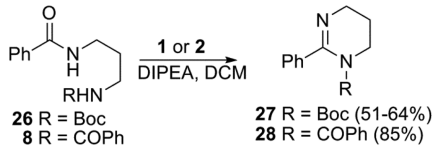


[a]Reagents and conditions: (a) reagent **1**, DIPEA, DCM; (b) DIPEA.

Use of the benzyl or Boc protecting group was also investigated. Thus treatment of *N*-[3-(benzylamino)propyl]-benzamide[46] with **1** (1.0 equiv) and DIPEA (2.2 equiv) in dry DCM for 2 h at room temperature resulted in the recovery of *N*-[3-(benzylamino)propyl]benzamide, after silica chromatography. ^{1}H NMR spectroscopy of the crude product suggested the presence of a cyclic amidine product; however, none was isolated. Instead, treatment of Boc-amide **26**[47] with **1** (1 equiv) and DIPEA (2.2 equiv) in dry DCM for 2 h at room temperature resulted in the formation of the cyclic amidine **27**. Analysis of the crude mixture by ^{1}H NMR spectroscopy showed that Boc-amide **26** and cyclic amidine **27** were present in a ratio of approximately 40:60. There was no change in this ratio after 24 h. Use of >1.5 equiv of **1** led to a decrease in the yield of cyclic amidine **27**. Due to the difficulty of separating **27** from triphenylphosphine oxide, the reaction was repeated but with reagent **2** instead of **1**.

Reagent **2** has the advantage over reagent **1** in that the bis-phosphine oxide byproduct, 1,2-bis(diphenylphosphinyl)ethane is water-soluble and readily removed by a water wash. Treatment of Boc-amide **26** with reagent **2** (1.0 or 1.5 equiv) and DIPEA in dry DCM gave the cyclic amidine **27** in moderate (51% or 64%, respectively) isolated yield (Scheme 6). Surprisingly, when the reaction was repeated but in the absence of DIPEA (i.e., trityl amide conditions), only traces of **27** were observed. The major product formed was the amide **6**. This suggests that under these reaction conditions, Boc-deprotection is faster than detritylation.

Scheme 6. Cyclodehydration of Bis-amides with 1 or 2[a]

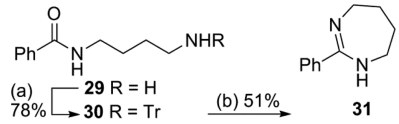


[a]Reagents and conditions: (a) reagent **2**, DIPEA, DCM.

As the reagents **1** and **2** could be used to convert Boc-amide **26** into the cyclic amidine **27** without loss of the Boc group, we examined the reaction of the (symmetrical) bis-amide **8** with reagent **2** in the presence of DIPEA in dry DCM. Analysis by ^{1}H NMR spectroscopy showed the clean formation of the cyclic amidine **28** (ratio **28**:**8** = 92:8) (Scheme 6). After chromatography on silica gel, cyclic amidine **28** was isolated in good yield (85%).

The success of the temporary trityl protecting group strategy prompted us to extend the cyclization reaction to the synthesis of the seven-membered tetrahydrodiazepine **31**. The amide **29**[48] was readily prepared by treatment of a dilute solution of butane-1,4-diamine (5 equiv) with benzoic anhydride. After conversion to the trityl derivative **30**, treatment with reagent **1** (1.5 equiv) in the absence of base gave the tetrahydrodiazepine **31**[38] in modest yield (51%) (Scheme 7).

Scheme 7. Synthesis of Tetrahydrodiazepine 31[a]



[a]Reagents and conditions: (a) TrCl, TEA, DCM; (b) reagent **1**, DCM.

In conclusion, a convenient synthesis of five-, six-, and seven-membered cyclic amidines from *N*-(aminoalkyl)benzamides under mild conditions is reported. Good yields are obtained by employing a temporary trityl group protection strategy and the easily prepared phosphonium anhydrides **1** or **2** as cyclodehydrating agents. When the product cyclic amidine is water-soluble, **1** is the preferred reagent; however, when the amidine is organic-soluble, the preferred reagent is **2**. Several examples of tetrahydropyrimidines and imidazolines are reported as well as a hexahydro-1*H*-benzimidazole and a tetrahydrodiazepine. The method is much milder than the hexamethyldisilazane procedure of Chouiery et al.[24] and gives as good or better yields (their yield for the seven-membered ring **31** was only 5%, whereas our procedure gives 57%).

EXPERIMENTAL SECTION

General Methods. Air-sensitive reactions were carried out in flame-dried or oven-dried glassware under an inert atmosphere. CH_2Cl_2 and THF were freshly distilled. Triflic anhydride was distilled from phosphorus pentoxide before use. 1,2-Bis(diphenylphosphinyl)-ethane, triphenylphosphine oxide, benzoic acid, and all synthesized amides were dried under high vacuum for 48 h prior to use. All other reagents were purchased from commercial suppliers and used without further purification. Column chromatography was performed using silica gel 60 Å (0.040−0.063 mm). Analytical thin layer chromatography (TLC) was performed using aluminum plates coated with silica gel 69 F254 (0.2 mm) and visualized by means of ultraviolet light. Melting points were measured on a variable temperature apparatus by the capillary method and are uncorrected. Infrared (IR) spectra were recorded on a FTIR apparatus. High resolution mass spectroscopy

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(HRMS) was performed on a Fourier transform mass spectrometer equipped with an electrospray source (ESI-FTMS). Mass spectra were recorded using electrospray as the ionization technique. ^{1}H NMR spectra were obtained at 300 or 400 MHz and chemical shifts are reported in parts per million, using the appropriate signal for solvent protons as a reference. The following are abbreviations were used for signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, quin = quintet, sept = septet, dt = doublet of triplets. Compound structures were assigned and confirmed using gCOSY, gHMBC, and gHSQC NMR spectroscopy.

Typical Procedure for the Preparation of Amides. Benzoic anhydride (1.0 g, 4.42 mmol) in dry CH_2Cl_2 (100 mL) was added dropwise (over 2 h) to a vigorously stirred solution of 2,2-dimethylpropane-1,3-diamine (2.65 mL, 22.1 mmol) in dry CH_2Cl_2 (300 mL) at −78 °C under a nitrogen atmosphere. The reaction mixture was warmed slowly (over 2 h) to room temperature and stirred for 16 h. The mixture was extracted with hydrochloric acid (5% in aqueous solution, 3 × 100 mL). The acidic water layer was neutralized by addition of sodium hydroxide (2 M, aqueous solution), then extracted with CH_2Cl_2 (4 × 100 mL), dried (anhydrous Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. Purification of the residue by aluminum oxide (basic) chromatography (methanol/CH_2Cl_2/hexane,1:3:6) gave *N*-(3-amino-2,2-dimethylpropyl)benzamide (**20**) as a colorless oil (866 mg, 95%); IR (neat) ν 3298, 3061, 2958, 1643, 1577, 1546, 1311 cm^{-1}; ^{1}H NMR (400 MHz; acetone-d_6) δ 8.75 (1H, br s), 7.84−7.87 (2H, m), 7.43−7.52 (3H, m), 3.39 (2H, d, J = 4.8 Hz), 3.17 (2H, s), 0.99 (6H, s), NH_2 not observed); ^{13}C NMR (100 MHz; acetone-d_6) δ 166.3, 135.9, 131.0, 128.5, 127.1, 62.5, 50.5, 34.7, 24.1; MS (ESI$^+$) m/z 206.9 (M + Na$^+$, 58%), 243.0 [C(C$_6$H$_5$)$_3^+$, 100%]; HRMS (ESI-FTMS, MH$^+$) m/z calcd for $C_{12}H_{20}N_2O$ requires 207.1492, found 207.1490.

***N,N′*-Propane-1,3-diylbis(4-nitrobenzamide) (9).** Amorphous white solid (79 mg, 86%); crystallized from CH_2Cl_2; mp 226−229 °C; IR (KBr disc) ν 3448, 3333, 1640, 1598, 1518, 1353 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (2H, br t, J = 5.7 Hz), 8.31 (4H, d, J = 9.0 Hz), 8.07 (4H, d, J = 9.0 Hz), 3.37 (4H, dt, J = 5.7, 6.9 Hz), 1.83 (2H, quin, J = 6.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 149.4, 140.7, 129.1, 124.0, 37.9, 29.3; MS (ESI$^+$) m/z 373.1 (M + H$^+$, 53%), 395.2 (M + Na$^+$, 46%); HRMS (ESI-FTMS, MH$^+$) m/z calcd for $C_{17}H_{17}N_4O_6$ 373.1143, found 373.1147.

***N*-[3-(Isopropylamino)propyl]benzamide (18).**[42] Colorless oil (919 mg, 94%) using alumina (basic) chromatography (methanol/CH_2Cl_2, 0:100 to 3:97); ^{1}H NMR (400 MHz; CD_3OD) δ 7.80−7.82 (2H, m), 7.51−7.55 (1H, m), 7.44−7.47 (2H, m), 3.45 (2H, t, J = 7.0 Hz), 2.80 (1H, sept, J = 6.3 Hz), 2.65 (2H, t, J = 7.0 Hz), 1.81 (2H, quin, J = 7.0 Hz), 1.08 (6H, d, J = 6.3 Hz), NH and C(O)NH not observed); ^{13}C NMR (100 MHz; CD_3OD) δ 170.4, 135.9, 132.6, 129.8, 128.1, 49.8, 45.5, 38.8, 30.6, 22.3; MS (ESI$^+$) m/z 221.0 ([M + H]$^+$, 71%); HRMS (ESI-FTMS, MH$^+$) m/z calcd for $C_{13}H_{21}N_2O$ 221.1648, found 221.1647.

***N*-(2-Aminocyclohexyl)benzamide (23).**[45] Amorphous pale yellow solid (752 mg, 97%) crystallized from CH_2Cl_2; mp 110−112 °C; IR (KBr disc) ν 3307, 3055, 2931, 2857, 1638, 1578, 1532, 1488 cm^{-1}; ^{1}H NMR (400 MHz; CD_3OD) δ 7.83−7.86 (2H, m), 7.51−7.56 (1H, m), 7.44−7.48 (2H, m), 4.12−4.16 (1H, m), 3.16 (1H, m), 1.44−1.82 (8H, m), NH and C(O)NH not observed); ^{13}C NMR (100 MHz; CD_3OD) δ 170.3, 136.0, 132.6, 129.5, 128.5, 53.0, 51.0, 32.1, 28.0, 24.4, 21.7; MS (ESI$^+$) m/z 219.0 (M + H$^+$, 100%), 241.0 (M + Na$^+$, 28%), 225.0 (M + Li $^+$, 66%); HRMS (ESI-FTMS, MH$^+$) m/z calcd for $C_{13}H_{19}N_2O$ 219.1492, found 219.1498.

***N*-(4-Aminobutyl)benzamide (29).**[48] Colorless oil (802 mg, 94%) isolated from CH_2Cl_2; IR (neat) ν 3300, 3065, 2933, 2866, 1637, 1544, 1310 cm^{-1}; ^{1}H NMR (400 MHz; CD_3OD) δ 7.80−7.83 (2H, m), 7.50−7.54 (1H, m), 7.42−7.47 (2H, m), 3.39 (2H, t, J = 7.0 Hz), 2.68 (2H, t, J = 7.0 Hz), 2.64 (2H, br s), 1.47−1.69 (4H, m), NH not observed); ^{13}C NMR (100 MHz; CD_3OD) δ 170.3, 135.8, 132.6, 129.6, 128.2, 41.6, 40.5, 29.5, 27.8; MS (ESI$^+$) m/z 193.0 (M + H$^+$, 95%); HRMS (ESI-FTMS, MH$^+$) m/z calcd for $C_{11}H_{17}N_2O$ 193.1335, found 193.1337.

Typical Procedure for the Preparation of Trityl Amides. Tritylchloride (626 mg, 2.24 mmol) was added to *N*-(3-aminopropyl)-benzamide (**8**) (200 mg, 1.12 mmol) and TEA (390 μL, 2.81 mmol) in dry CH_2Cl_2 (10 mL), and the mixture stirred at room temperature under a nitrogen atmosphere for 16 h. The solvent was removed under reduced pressure, and the residue purified by silica column chromatography (ethyl acetate/hexane, gradient from 10:90 to 50:50). *N*-[3-(Tritylamino)propyl]benzamide (**12**) was obtained as an amorphous white solid (678 mg, 94%); R_f 0.33 (ethyl acetate/hexane, 1:3); mp 167−169 °C; IR (KBr disc) ν 3422, 3291, 3056, 3023, 2835, 1646, 1519, 1487, 1475 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.63−7.66 (2H, m), 7.29−7.41 (9H, m), 7.09−7.21 (9H, m), 6.83 (1H, br s), 3.56 (2H, dt, J = 6.2, 6.2 Hz), 2.25 (2H, t, J = 6.2 Hz), 1.69 (2H, quin, J = 6.2 Hz), NH not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 145.7, 134.9, 131.3, 128.6, 128.5, 127.9, 126.9, 126.4, 71.2, 42.1, 39.0, 30.0; MS (ESI$^+$) m/z 443.3 (M + Na$^+$, 63%), 243.0 ([C(C$_6$H$_5$)$_3$]$^+$, 100%), 427.3 (M + Li$^+$, 100%); HRMS (ESI-FTMS, MNa$^+$) m/z calcd for $C_{29}H_{28}N_2ONa$ 443.2094, found 443.2106. Anal. Calcd for C, 82.82; H, 6.71; N, 6.66. Found: C, 82.96; H, 6.64; N, 6.70.

***N*-[2-(Tritylamino)ethyl]benzamide (15).** Amorphous white solid (366 mg, 87%); R_f 0.47 (ethyl acetate/hexane, 1:3); mp 149−151 °C; IR (KBr disc) ν 3263, 3052, 2917, 2840, 1639, 1545, 1488, 1311 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.81 (2H, m); 7.42−7.53 (9H, m), 7.24−7.28 (6H, m), 7.17−7.21 (3H, m), 6.70 (1H, br s), 3.54 (2H, dt, J = 6.0, 6.0 Hz), 2.43 (2H, t, J = 6.0 Hz), 1.81 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 145.4, 134.5, 131.5, 128.61, 128.56, 128.0, 127.0, 126.7, 77.3, 43.8, 40.3; MS (ESI$^+$) m/z 429.2 ([M + Na]$^+$, 3%), 243.0 ([C(C$_6$H$_5$)$_3$]$^+$, 100%); HRMS (ESI-FTMS, MH$^+$) m/z calcd for $C_{28}H_{27}N_2O$ 407.2118, found 407.2114. Anal. Calcd for $C_{28}H_{26}N_2O$: C, 82.73; H, 6.45; N, 6.89. Found: C, 82.61; H, 6.43; N, 6.78.

***N*-[3-(Tritylamino)-2,2-dimethylpropyl]benzamide (21).** Amorphous white solid (1.03 g, 86%); R_f 0.61 (ethyl acetate/hexane, 1:3); mp 143−145 °C; IR (KBr disc) ν 3322, 3052, 2958, 2917, 1644, 1538, 1487, 1448 cm^{-1}; ^{1}H NMR (400 MHz; CD_3OD) δ 7.58−7.60 (2H, m), 7.44−7.52 (7H, m), 7.37−7.41 (2H, m), 7.15−7.19 (6H, m), 7.07−7.11 (3H, m), 3.34 (2H, s), 1.91 (2H, s), 1.01 (6H, s), NH and C(O)NH not observed); ^{13}C NMR (100 MHz; CD_3OD) δ 170.6, 147.6, 135.9, 132.5, 130.0, 129.4, 128.6, 128.4, 127.1, 72.0, 52.5, 48.6, 37.7, 25.3; MS (ESI$^+$) m/z 243.0 (C(C$_6$H$_5$)$_3^+$, 100%); HRMS (ESI-FTMS, MH$^+$) m/z calcd for $C_{31}H_{33}N_2O$ 449.2587, found 449.2607. Anal. Calcd for $C_{31}H_{32}N_2O$ C, 83.00; H, 7.19; N, 6.24. Found: C, 83.12; H, 7.00; N, 6.40.

***N*-[2-(Tritylamino)cyclohexyl]benzamide (24).** Amorphous white solid (936 mg, 92%); R_f 0.5 (ethyl acetate/hexane, 1:3); mp 163−164 °C; IR (KBr disc) ν 3422, 3300, 3052, 2932, 1624, 1535, 1488 cm^{-1}; ^{1}H NMR (400 MHz; DMSO-d_6) δ 7.91−7.95 (3H, m), 7.49−7.58 (9H, m), 7.23 (6H, t, J = 7.4 Hz), 7.15 (3H, t, J = 7.4 Hz), 4.13 (1H, br s), 2.58 (2H, br s, H2), 1.91−1.94 (1H, m), 1.18−1.41 (4H, m), 0.91−0.99 (1H, m), 0.75−0.81 (1H, m), 0.26 (1H, br d, J = 12.8 Hz); ^{13}C NMR (100 MHz; DMSO-d_6) δ 166.9, 147.1, 135.4, 130.9, 128.4, 128.1, 127.6, 127.5, 126.1, 70.7, 52.5, 51.6, 29.1, 27.9, 23.7, 20.8; MS (ESI$^+$) m/z 243.0 (C(C$_6$H$_5$)$_3^+$, 100%); HRMS (ESI-FTMS, MH$^+$) m/z calcd for $C_{32}H_{32}N_2ONa$ 483.2387, found 483.2387. Anal. Calcd for $C_{30}H_{30}N_2O$ C, 83.44; H, 7.00; N, 6.08. Found: C, 83.27; H, 6.90; N, 5.88.

***N*-[4-(Tritylamino)butyl]benzamide (30).** Amorphous white solid (883 mg, 78%); R_f 0.29 (ethyl acetate/hexane, 1:3); mp 140−143 °C; IR (KBr disc) ν 3299, 3056, 2950, 2860, 2815, 1630, 1534, 1489, 1449 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.72−7.74 (2H, m), 7.40−7.50 (9H, m), 7.24−7.28 (6H, m), 7.15−7.19 (3H, m), 6.11 (1H, br s), 3.42 (2H, dt, J = 6.0, 6.8 Hz), 2.18 (2H, t, J = 6.8 Hz), 1.53−1.69 (5H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.5, 146.1, 134.8, 131.3, 128.6, 128.5, 127.8, 126.8, 126.2, 70.9, 43.3, 40.1, 28.3, 27.6; MS (ESI$^+$) m/z 435.3 (M + H$^+$, 16%), 457.3 (M + Na$^+$, 100%; HRMS (ESI-FTMS, MH$^+$) m/z calcd for $C_{30}H_{30}N_2ONa$ 457.2250, found 457.2250. Anal. Calcd for $C_{30}H_{30}N_2O$ requires C, 82.91; H, 6.96; N, 6.45. Found: C, 83.06; H, 6.82; N, 6.32.

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Reaction of *N*-(3-Aminopropyl)benzamide (6) with Polymer-Supported Triphenylphosphine Ditriflate 3. Prior to use, polymer-supported triphenylphosphine oxide[32] beads (250 mg, 0.76 mmol, 3 mmol/g) were dried under high vacuum for 48 h. The polymer was swollen in dry CH_2Cl_2 (8 mL) under an atmosphere of nitrogen. Triflic anhydride (94 μL, 0.56 mmol) was added, and the mixture stirred for 1 h. *N*-(3-Aminopropyl)benzamide (**6**) (100 mg, 0.56 mmol) and DIPEA (341 μL, 1.97 mmol) were added consecutively, and the slurry was stirred at room temperature for 16 h. The polymer beads were removed by filtration and washed with CH_2Cl_2 (35 mL), and the filtrate was washed with sodium hydrogen carbonate (5% aqueous solution, 3 × 20 mL). The solvent was removed under reduced pressure, and the residue was purified by silica column chromatography (CH_2Cl_2/CH_3OH, gradient from 100:0 to 90:10). *N*-(3-{[(Trifluoromethyl)sulfonyl]amino}propyl) benzamide (**10**) was obtained as an amorphous white solid (43 mg, 25%) recrystallized from ethyl acatate; mp 114−116 °C; IR (KBr disc) ν 3436, 3060, 2864, 1640, 1368, 1183 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.76−7.78 (2H, m), 7.54−7.58 (1H, m), 7.45−7.49 (2H, m), 7.22 (1H, br t), 6.46 (1H, br s), 3.65 (2H, dt, *J* = 5.2, 6.6 Hz), 3.34 (2H, dt, *J* = 5.2, 6.6 Hz), 1.81−1.87 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.4, 133.4, 132.1, 128.8, 126.9, 119.8 (1C, q, *J* = 320 Hz), 40.7, 36.1, 30.6; MS (ESI$^+$) *m*/*z* 311.1 (M + H^+, 95%), 333.0 (M + Na^+, 100%), 317.1 (M + Li^+, 100%); HRMS (ESI-FTMS, MH^+) *m*/*z* calcd for $C_{11}H_{14}F_3N_2O_3S$ 311.0672, found 311.0679.

***N*-(3-{Acetyl[(trifluoromethyl)sulfonyl]amino}propyl)-benzamide.** Acetyl chloride (7.6 μL, 0.11 mmol) was added dropwise to **10** (18 mg, 0.058 mmol) and TEA (15 μL, 0.11 mmol) in dry CH_2Cl_2 (3 mL), and the mixture was stirred at room temperature under a nitrogen atmosphere for 16 h. The mixture was washed with sodium hydroxide (2 M aqueous solution, 5 mL) and brine (5 mL), dried (anhydrous Na_2SO_4), and filtered. The solvent was removed under reduced pressure, and the residue was purified by silica column chromatography (ethyl acetate/hexane, gradient from 5:95 to 50:50). *N*-(3-{Acetyl[(trifluoromethyl)sulfonyl]amino}propyl)benzamide was obtained (in approximately 95% purity) as a pale yellow oil (20 mg, 98%); IR ν_{max} 3444, 3321, 2929, 1732, 1638, 1405, 1209, 1194 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.79−7.82 (2H, m), 7.41−7.53 (3H, m), 6.62 (1H, br s), 3.94 (2H, t, *J* = 7.0 Hz), 3.49 (2H, dt, *J* = 5.9, 7.0 Hz), 2.55 (3H, s), 2.01 (2H, quin, *J* = 5.9 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.0, 167.8, 134.5, 131.8, 128.8, 127.1, 119.8 (1C, q, *J* = 321 Hz), 46.3, 36.7, 29.6, 25.3; MS (ESI$^+$) *m*/*z* 353.1 (M + H^+, 66%), 359.1 (M + Li^+, 100%); HRMS (ESI-FTMS, MH^+) *m*/*z* calcd for $C_{13}H_{16}F_3N_2O_4S$ 353.0777, found 353.0767.

Typical Procedure Using Hendrickson Reagent 1. Triflic anhydride (180 μL, 1.07 mmol) was added slowly to a solution of triphenylphosphine oxide (715 mg, 2.57 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C under a nitrogen atmosphere. A thick white precipitate was formed, and the mixture was stirred at 0 °C for 30 min. *N*-[3-(Tritylamino)propyl]benzamide (**12**) (300 mg, 0.71 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise (over 5 min), and the reaction mixture was warmed to room temperature. After 16 h of stirring, water (10 mL) was added, and the layers separated. The organic layer (containing the triphenylphosphine oxide) was discarded. The aqueous layer was concentrated and redissolved in a 1:1 CH_2Cl_2/sodium hydroxide (2 M aqueous solution) mixture (20 mL), and the two layers separated. The organic layer was concentrated, and the residue was purified by aluminum oxide (basic) chromatography (methanol/CH_2Cl_2/hexane, gradient from 0:4:6 to 1:3:6). 2-Phenyl-1,4,5,6-tetrahydropyrimidine (**13**): compound **13**[38,39] was obtained as a white solid (90 mg, 79%) recrystallized from ethyl acetate. The ^1H NMR was identical to that in the literature;[39] mp 98−99 °C (lit.[38] mp 88−91 °C).

Triflic anhydride ((94 μL, 0.56 mmol), triphenylphosphine oxide (375 mg, 1.35 mmol), *N*-(3-aminopropyl)benzamide (**6**) (100 mg, 0.56 mmol), and DIPEA (214 μL, 1.23 mmol) were reacted in dry CH_2Cl_2 (5 mL) and worked up as above gave compound **13** (32 mg, 36%).

2-Phenyl-4,5-dihydro-1*H*-imidazole (16).[18,41] Amorphous white solid (65 mg, 89%) recrystallized from CH_2Cl_2; mp 147−150 °C (lit.[18,49] mp 149−151 and 147−149 °C).

Triflic anhydride (41 μL, 0.24 mmol), triphenylphosphine oxide (163 mg, 0.58 mmol), *N*-(2-aminoethyl)benzamide (**14**) (40 mg, 0.24 mmol), and DIPEA (91 μL, 0.53 mmol) were reacted in dry CH_2Cl_2 (3 mL) and worked up as above gave compound **16** (10 mg, 29%).

1-Isopropyl-2-phenyl-1,4,5,6-tetrahydropyrimidine (19). Colorless oil (159 mg, 86%); IR (neat) ν 3425, 3245, 3121, 1621, 1280, 1251, 1154, 1030 cm^{-1}; ^1H NMR (400 MHz; CD_3OD) δ 7.59−7.69 (3H, m), 7.54−7.57 (2H, m), 3.89 (1H, sept, *J* = 6.7 Hz), 3.61 (2H, t, *J* = 5.6 Hz), 3.51 (2H, t, *J* = 5.6 Hz), 2.17 (2H, quin, *J* = 5.6 Hz), 1.23 (6H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz; CD_3OD) δ 163.0, 133.0, 131.2, 130.6, 128.4, 54.4, 40.7, 40.0, 20.2, 19.5; MS (ESI$^+$) *m*/*z* 203.1543 (M + H^+, 100%); HRMS (ESI-FTMS, MH^+) *m*/*z* calcd for $C_{13}H_{19}N_2$ 203.1543, found 203.1549.

5,5-Dimethyl-2-phenyl-1,4,5,6-tetrahydropyrimidine (22).[43,44] Colorless oil that solidified upon standing (109 mg, 93%), crystallized from CH_2Cl_2/methanol; mp 113−116 °C (lit.[43] mp 116−118 °C).

2-Phenyl-3a,4,5,6,7,7a-hexahydro-1*H*-benzimidazole (25).[45] From alumina oxide (basic) (methanol/CH_2Cl_2, gradient from 0:100 to 5:95) and characterized as the CF_3SO_2OH salt; mp 140−142 °C; IR (KBr disc) ν 3223, 2946, 2868, 1616, 1587, 1557, 1237, 1167, 1032 cm^{-1}; ^1H NMR (400 MHz; CD_3OD) δ 7.87−7.90 (2H, m), 7.78−7.82 (1H, m), 7.64−7.68 (2H, m), 4.36−4.42 (2H, m), 1.96−2.02 (2H, m), 1.76−1.81 (2H, m), 1.51−1.68 (4H, m), NH not observed; ^{13}C NMR (100 MHz; CD_3OD) δ 167.4, 136.1, 130.8, 129.2, 123.9, 121.8 (1C, q, *J* = 316.7 Hz), 57.8, 26.8, 19.9; MS (ESI$^+$) *m*/*z* 200.9 (M + H^+, 100%); HRMS (ESI-FTMS, MH^+) *m*/*z* calcd for $C_{13}H_{17}N_2$ 201.1386, found 201.1393.

2-Phenyl-4,5,6,7-tetrahydro-1*H*-1,3-diazepine (31).[38] Amorphous white solid (52 mg, 51%), crystallized from CH_2Cl_2; mp 96−99 °C (lit.[38] mp 99−102 °C).

Typical Procedure Using Reagent 2. Triflic anhydride (25 μL, 0.15 mmol) was added slowly to a solution of 1,2-bis-(diphenylphosphinyl)ethane (78 mg, 0.18 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C under a nitrogen atmosphere. A thick white precipitate was formed, and the mixture was stirred at 0 °C for 30 min. *tert*-Butyl [3-(benzoylamino)propyl]carbamate (**26**) (42 mg, 0.15 mmol) and DIPEA (57 μL, 0.33 mmol) in dry CH_2Cl_2 (3 mL) were added dropwise over 5 min to the reaction mixture. The pale yellow mixture was warmed to room temperature. After 16 h, the reaction mixture was quenched with sodium hydrogen carbonate (5% aqueous solution, 2 × 8 mL), dried (anhydrous Na_2SO_4), and filtered. The solvent was removed under reduced pressure, and the residue was purified by silica column chromatography (ethyl acetate/hexane, gradient from 25:75 to 100:0), followed by aluminum oxide (basic) chromatography (methanol/CH_2Cl_2/hexane, gradient from 0:50:50 to 1:99:0). *tert*-Butyl 2-phenyl-5,6-dihydropyrimidine-1(4*H*)-carboxylate (**27**) was obtained as a colorless oil (20 mg, 51%); IR (neat) ν 3395, 2969, 2931, 1711, 1624, 1366, 1336, 1158 cm^{-1}; ^1H NMR (400 MHz; CD_3OD) δ 7.83−7.85 (2H, m), 7.51−7.56 (1H, m), 7.43−7.49 (2H, m), 3.92 (2H, t, *J* = 6.9 Hz), 3.49 (2H, t, *J* = 6.9 Hz), 1.99 (2H, quin, *J* = 6.9 Hz), 1.14 (9H, s); ^{13}C NMR (100 MHz; acetone-d_6) δ 159.0, 154.5, 140.5, 130.6, 129.2, 128.0, 83.3, 46.7, 44.4, 27.8, 24.9; MS (ESI$^+$) *m*/*z* 261.1598 (M + H^+, 4%), 204.9 (M-OC$(CH_3)_3^+$, 64%); MS (ESI$^+$) *m*/*z* 261.1598 (M + H^+, 4%), 204.9 (M-OC$(CH_3)_3^+$, 64%); HRMS (ESI-FTMS, MH^+) *m*/*z* calcd for $C_{15}H_{21}N_2O_2$ 261.1598, found 261.1588.

1-Benzoyl-2-phenyl-1,4,5,6-tetrahydropyrimidine (28). The compound was unstable, and repeated aluminum oxide (basic) chromatography (ethyl acetate/CH_2Cl_2/hexane, gradient from 0:75:25 to 80:20:0) continued to give a mixture of **28** (∼90%) and **8** (∼10%); ^1H NMR (400 MHz; $CDCl_3$) δ 7.29−7.32 (4H, m), 7.18−7.22 (1H, m), 7.06−7.15 (5H, m), 3.92 (2H, t, *J* = 7.0 Hz), 3.76 (2H, t, *J* = 6.4 Hz), 2.05 (2H, tt, *J* = 6.4, 7.0 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.7, 157.9, 137.8, 136.3, 131.0, 129.5, 128.1, 127.90, 127.89, 127.3, 46.4, 43.2, 24.5; MS (ESI$^+$) *m*/*z* 265.1 (M + H^+, 100%).

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■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data for compounds **9**, **10**, **12**, **13**, **15**, **16**, **18**−**25**, and **27**−**31**]. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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