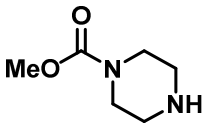
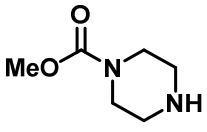
SUMMARY

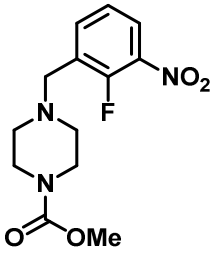
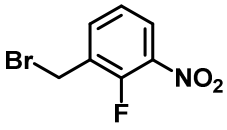
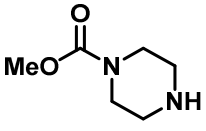
[0007] Provided herein is piperazine methyl carboxylate (PMEC) phosphate salt, e.g., a PMEC phosphate hydrate salt. PMEC is alternatively referred to as methyl piperazine-1-carboxylate.

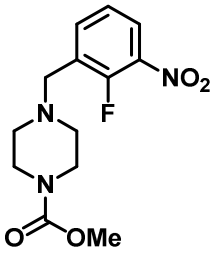
[0007a] In one aspect, the present disclosure refers to piperazine methyl carboxylate



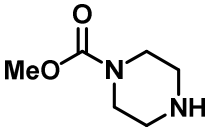
("PMEC") phosphate hydrate.

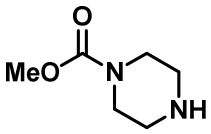
[0007b] In another aspect, the present disclosure refers to a process for synthesizing piperazine methyl carboxylate  ("PMEC") phosphate hydrate comprising (a) admixing piperazine and methyl chloroformate to form PMEC; (b) admixing the PMEC and 0.5 molar equivalents of phosphoric acid in an aqueous solution to form PMEC phosphate hydrate; and (c) optionally filtering the PMEC phosphate hydrate from the admixture of step (b).

[0007c] In yet another aspect, the present disclosure refers to a process for synthesizing methyl 4-(2-fluoro-3-nitrobenzyl)piperazine-1-carboxylate  (PIPN) comprising (a) admixing 2-fluoro-3-nitrotoluene, sodium bromate, and sodium bisulfite in isopropylacetate and water to form 1-(bromomethyl)-2-fluoro-3-nitrobenzene  (FNB); (b) optionally washing the FNB with aqueous sodium thiosulfate, with aqueous sodium chloride, or both; and (c) admixing FNB, a trialkylamine base, and piperazine methyl carboxylate  ("PMEC") phosphate hydrate to form PIPN.

[0007d] In yet another aspect, the present disclosure refers to a process for synthesizing methyl 4-(2-fluoro-3-nitrobenzyl)piperazine-1-carboxylate  (PIPN) comprising (a) admixing 2-

WHAT IS CLAIMED:

1. Piperazine methyl carboxylate  ("PMEC") phosphate hydrate.

2. A process for synthesizing piperazine methyl carboxylate  ("PMEC") phosphate hydrate comprising

(a) admixing piperazine and methyl chloroformate to form PMEC;

(b) admixing the PMEC and 0.5 molar equivalents of phosphoric acid in an aqueous solution to form PMEC phosphate hydrate; and

(c) optionally filtering the PMEC phosphate hydrate from the admixture of step (b).

3. The process of claim 2, further comprising isolating the PMEC formed from step (a) as a solution in methylene chloride, dichloroethane, 2-methyltetrahydrofuran, or mixture thereof.

4. The process of claim 3, wherein the isolating is performed by

(i) washing the resulting PMEC from step (a) with an organic solvent;

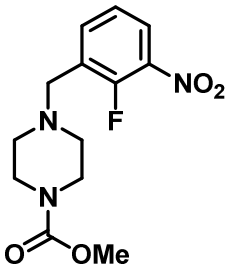
(ii) modifying the pH to 8 to 14 by adding a base to form a basic aqueous solution; and

(iii) extracting the PMEC from the basic aqueous solution of step (ii) with methylene chloride, dichloroethane, 2-methyl tetrahydrofuran, or mixture thereof.

5. The process of claim 2, wherein step (a) is performed in an aqueous solution.

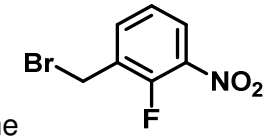
6. The process of any one of claims 2 to 5, wherein step (a) is performed at a temperature of 20 to 55°C for 1 to 12 hours.

7. A process for synthesizing methyl 4-(2-fluoro-3-nitrobenzyl)piperazine-1-carboxylate

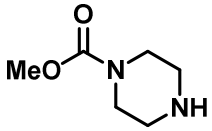


(PIPN) comprising

(a) admixing 2-fluoro-3-nitrotoluene, sodium bromate, and sodium bisulfite in isopropylacetate

and water to form 1-(bromomethyl)-2-fluoro-3-nitrobenzene  (FNB);

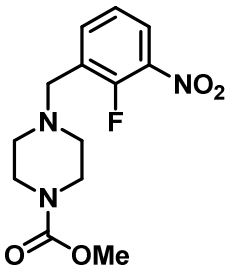
(b) optionally washing the FNB with aqueous sodium thiosulfate, with aqueous sodium chloride, or both; and

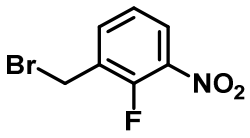


(c) admixing FNB, a trialkylamine base, and piperazine methyl carboxylate ("PMEC") phosphate hydrate to form PIPN.

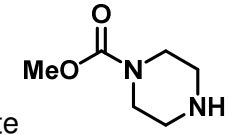
8. The process of claim 7, wherein the FNB is washed with aqueous sodium thiosulfate and aqueous sodium chloride.

9. A process for synthesizing methyl 4-(2-fluoro-3-nitrobenzyl)piperazine-1-carboxylate

 (PIPN) comprising

(a) admixing 2-fluoro-3-nitrotoluene, benzoyl peroxide, N-bromosuccinimide and acetic acid at a temperature of 70 to 95°C to form 1-(bromomethyl)-2-fluoro-3-nitrobenzene  (FNB);

(b) optionally extracting FNB with toluene, washing FNB with an aqueous basic solution, or both;



(c) admixing FNB, a trialkylamine base, and piperazine methyl carboxylate ("PMEC") phosphate hydrate to form PIPN.

10. The process of claim 9, wherein FNB is extracted with toluene and washed with aqueous sodium hydroxide.

11. The process of any one of claims 7 to 10, wherein the PIPN is formed as a hydrochloride salt.

12. The process of any one of claims 7 to 11, wherein the PMEC phosphate hydrate is prepared by a process of any one of claims 2 to 6.

13. The process of any one of claims 7 to 12, wherein the trialkylamine base comprises diisopropylethylamine or triethylamine.

14. The process of any one of claims 7 to 13, wherein prior to admixing the FNB, the trialkylamine base, and the PMEC phosphate hydrate, the process further comprises adding diethylphosphite and a trialkylamine, and admixing the resulting mixture at a temperature of 30 to 65°C.