经典化学合成反应标准操作

脲与硫脲的合成

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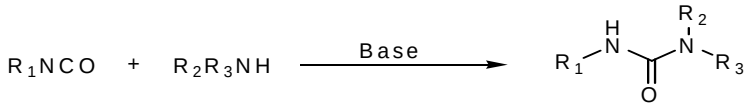
1.前言

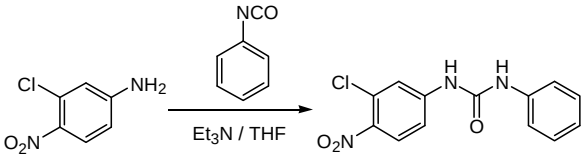
脲 Urea 在石油化工、医药化工有着广泛的应用前景，很多医药分子中都还有脲的结构片断。通常含脲的分子可以分为对称性脲和非对称性脲两大类，对称性脲的合成相对简单，而非对称性脲的合成相对难一些。由于非对称性脲的合成大多适用于对称性脲的合成，所以我们着重介绍非对称脲合成的一些常用方法。

2. 异氰酸酯与胺反应生成脲

异氰酸酯与胺反应成脲是最为方便的一种方法，特别对于那些可以直接在市场上买到的异氰酸酯，一般这类反应收率也很高。但本方法最重要的一点是：反应物的用量是取决于底物的活性。通常是等量的底物在非质子性溶剂反应，加入适量的碱有利于反应的进行。如果其中一个底物的活性较差的话，可以适当增加用量。常用的溶剂有：二氯甲烷、四氢呋喃等。



2.1 异氰酸酯与胺反应生成脲示例 [1]

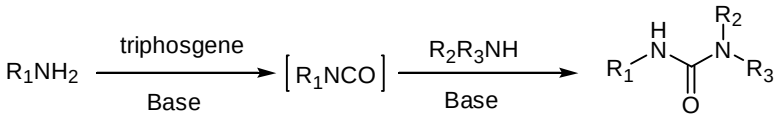


To a solution of 3-chloro-4-nitro-phenylamine (1.72 g, 10 mmoL) and triethylamine (3 mL, 20 mmol) in 100 mL of THF was added isocyanato-benzene (1.19 g, 10 mmol) in 10 mL of THF at 0 ^{o}C dropwise. After the addition was completed, the resulting mixture was allowed to raise room temperature and stirred overnight before being poured into water (150 mL). The mixture was extracted with DCM (3 x 100 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to give

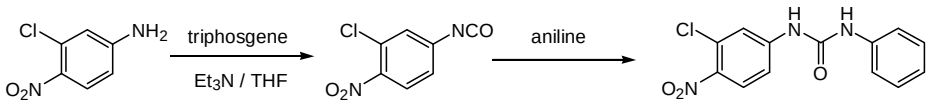
the crude product, which was purified by column to afford 2.4 g of 1-(3-chloro-4-nitro-phenyl)-3- phenyl-urea (80 %)

3. 三光气（或光气、双光气）与胺反应生成脲

除了一些常用的伯胺的异氰酸酯可以购买到以外，在药物化学中决大多数异氰酸酯是无法购得的，因此需要自己合成异氰酸酯。 常用异氰酸酯的合成方法是伯胺与三光气反在碱性条件下生成异氰酸酯，而后异氰酸酯与另一分子胺反应生成脲，第二步反应其实同前。对于低沸点的异氰酸酯，第一步反应完后最好将其蒸馏出来，再投第二步反应，这样下一步产物相对干净。如果异氰酸酯沸点很高，一般生成异氰酸酯后，直接一锅用到下一部，但必须严格控制三光气的用量 （注意三光气用底物胺的 1/3 的量）。光气与双光气也适用本方法，但考虑到使用的方便性和安全问题，一般使用三光气。



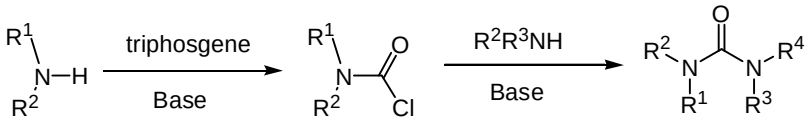
3.1 三光气与胺反应生成脲示例 [2]



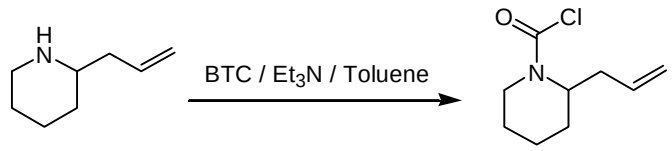
To a stirred solution of 3-chloro-4-nitro-phenylamine (1.72 g, 10 mmoL) and diisopropyl ethylamine (2.1 g, 20 mmol) in 100 mL of dry DCM was added a solution of triphosgene (0.99 g, 3.3 mmol) in 10 mL of DCM. The resulting mixture was stirred at 0 ^{o}C for 3 hours and then treated with aniline (930 mg, 10 mmol). The reaction mixture was allowed to warm to room temperature overnight. After removal of the solvent, the residue partitioned between ethyl acetate and saturated bicarbonate solution. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to the residue, which was purified by column chromatography on silica to afford 1.9 g of the 1-(3-chloro-4-nitro-phenyl)-3- phenyl-urea (65 %).

4. 使用氯甲酰胺与胺反应生成脲

对于仲胺由于无法形成异氰酸酯，我们可以通过其与三光气反应得到氯甲酰胺然后再与另一个胺反应。 一般仲胺的氯甲酰胺中间体对水是稳定的，可以分离纯化出来。

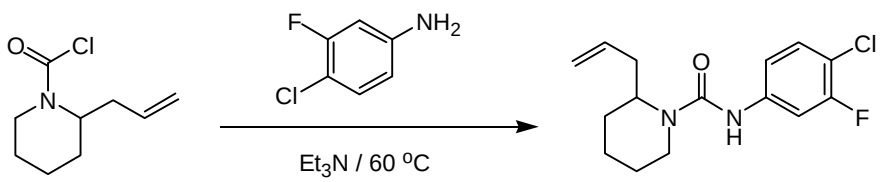


4.1 三光气与仲胺反应氯甲酰胺 [3]



To a solution of 2-allyl-piperidine (0.63 g, 5 mmol) and pyridine (0.52 g, 6.6 mmol) in 50 mL of dichloromethane was added a solution of triphosgene (0.66 g, 2.2 mmol) in 10 mL of dichloromethane at 0 ^{o}C dropwise over 40 min. The resulting mixture was then warmed to room temperature and stirred overnight. The reaction mixture was added 50 mL of 1 N of aqueous HCl solution dropwise. After separation, the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic phases were washed with a saturated $NaHCO_3$ solution and brine (3 x 50 mL), then dried over $MgSO_4$. After removal of the solvent, the crude product was taken into Et_2O and the solids were filtered. The filtrate was concentrated to 860 mg of carbamoyl chloride as yellow oil (92 %).

4.2 氯甲酰胺与胺反应脲

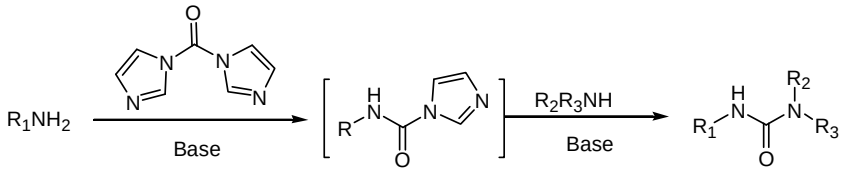


A solution of 2-allyl-piperidine-1-carbonyl chloride (1.87 g, 10 mmol), triethylamine (5 mL),

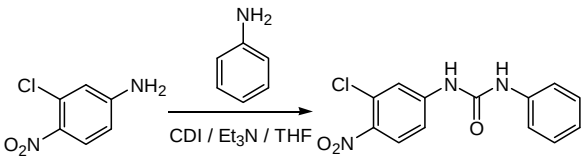
and 4-chloro-3-fluoro-phenylamine (1.7 g, 12 mmol) in 100 mL of anhydrous dioxane was stirred at room temperature under nitrogen for 26 h and then concentrated to dry under vacuum. The residue was dissolved in 100 mL of dichloromethane, and washed with 0.5 N of aqueous HCl solution and brine, After dried over anhydrous Na_2SO_4 and filtered, the filtrate was concentrated to the crude product, which was purified by flash column chromatography to afford 2-Allyl-piperidine-1-carboxylic acid (4-chloro-3-fluoro-phenyl)-amide (2.3g, 77 %)

5. 羰基二咪唑（CDI）与胺反应生成脲

胺也可以先与羰基二咪唑（CDI)反应，形成一个中间体，然后与另一分子胺反应生成脲。本方法适用范围也很广，对那些底物很昂贵、或较难得到的，本方法也很适用。但由于 CDI 不稳定，放置时间长，遇水会分解，造成加料不准确，容易生成较难分离的二聚体。因此反应前确定 CDI 的质量尤为关键。



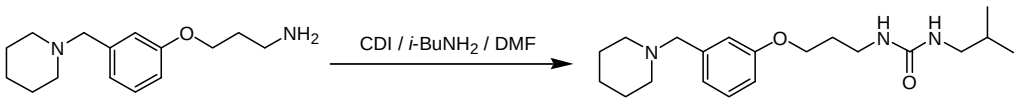
5.1 羰基二咪唑与芳香伯胺反应生成脲示例一 [4]



To a solution of 3-chloro-4-nitro-phenylamine (1.72 g, 10 mmoL) and triethylamine (1.0 g, 10 mmol) in 50 mL of DMF was added CDI (1.61 g, 10 mmol) at room temperature under N_2 atmosphere. The mixture was stirred at that temperature for 1 h and then added a solution of aniline (1.0 g, 11 mmol) in 5 mL of DMF. After stirred for another 10 h, the reaction mixture was poured into water (100 mL) and extracted with DCM (3 x 50 mL). The combined organic phases were washed with brine (5 x 100 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to give the crude product, which was purified by

column to afford 2.0 g of 1-(3-chloro-4-nitro-phenyl)-3- phenyl-urea (68 % yield)

5.2 羰基二咪唑与胺反应生成脲示例二 [5]



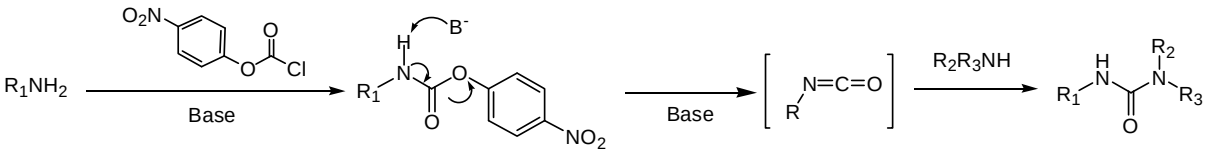
To a solution of 3-(3-piperidin-1-ylmethyl-phenoxy)-propylamine (2.48 g, 10 mmoL) and diisopropylethylamine (1. 4 mL, 10 mmol) in DMF (50 mL) was added CDI (1.61 g, 10 mmol) at room temperature under N_2 atmosphere. The mixture was stirred at that temperature for 1 h and then a solution of *i*-$BuNH_2$ (146 mg, 20 mmol) in 5 mL of DMF was added to the mixture. The reaction mixture was stirred at room temperature overnight before poured into water (100 mL). The mixture was extracted with DCM (3 x 50 mL). The combined organic phases were washed with brine (5 x 100 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to give the crude product, which was purified by column to afford 2.75 g of 1-isobutyl-3-[3-(3-piperidin-1-ylmethyl-phenoxy)-propyl]-urea (80 %).

6. 氯甲酸酯与胺反应生成脲

胺先与氯甲酸酯反应得到相应的烷氧基碳酰胺，然后再与另一分子胺反应生成脲。本方法适用范围也很广，对那些底物很昂贵、或较难得到的，本方法尤为适用。一般来说比较常用的为氯甲酸对硝基苯酯和氯甲酸苯酯。

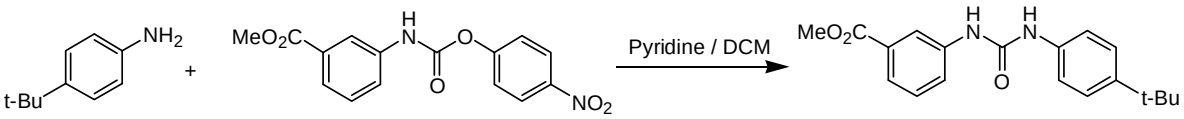
6.1 利用氯甲酸对硝基苯酯合成脲

氯甲酸对硝基苯酯主要用于伯胺的反应，其反应机理是中间体对硝基苯氧基碳酰胺在碱性条件下，脱去对硝基苯酚得到相应的异氰酸酯，然后再与另一分子胺反应得到脲。使用本方法一个主要的注意点是第一步对硝基苯氧基碳酰胺的制备，一定要选择好相应的碱，用好当量。()另外也有文献在第一步用过量的碱生成异氰酸酯的溶液，马上再与另一分子胺反应。该法的一个缺点就是有时产生的黄色的副产物对硝基苯酚，不易除干净（一般用强碱洗）。



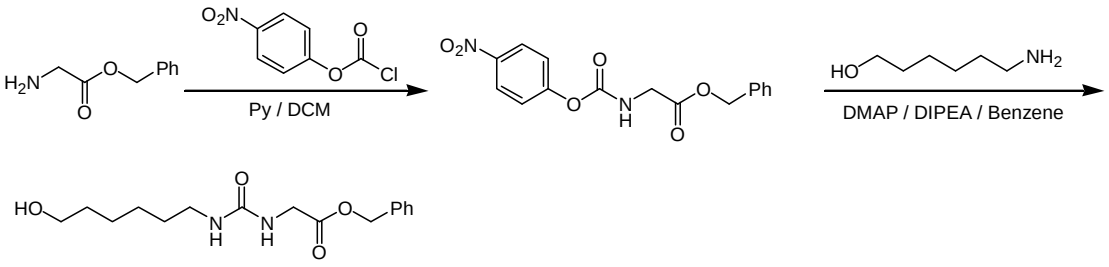
氯甲酸对硝基苯酯也可以与仲胺反应生成脲，一般在 DMAP-CH_3CN，加热体系进行胺交换。

6.1.1 芳香伯胺的对硝基苯氧基碳酰胺和脲的合成示例 [6]



To a solution of methyl 3-aminobenzoate (1.0 g, 6.5 mmol) and pyridine (1.0 mL) in 100 mL of dichloromethane was added a solution of 4- nitrophenylchloroformate (1.4 g, 6.7 mmol) in 10 mL of dichloromethane dropwise at 0 ^oC under N_2 atmosphere. The resulting mixture was stirred at r.t. for 20 h before poured into ice-water. The mixture was extracted with DCM (3 x 100 mL). The combined organic phases were washed with 0.5 N aq. HC1 and brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to give the crude product, which was purified by column to afford 2.1 g of 3-[3-(4-tert-Butyl-phenyl)-ureido]-benzoic acid methyl ester (94 %)

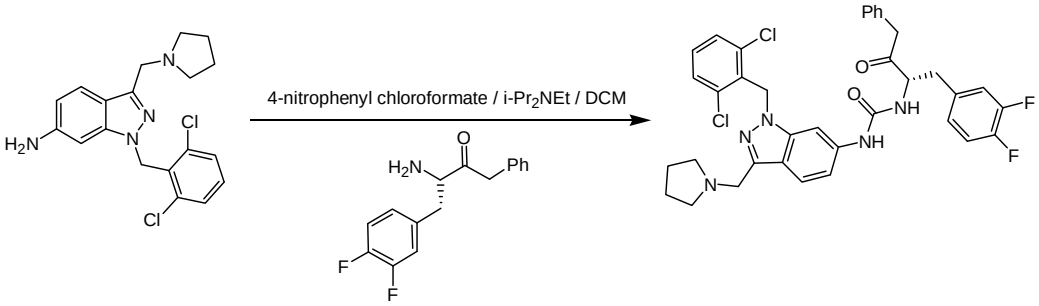
6.1.2 脂肪伯胺的对硝基苯氧基碳酰胺和脲的合成示例 [7]



To a solution of 4-nitrophenyl chloroformate (2.3 g, 11 mmol) in 20 mL of CH_2Cl_2 was added

a solution of benzyl glycinate (0.62 g, 3.8 mmol) in 4 mL of 1:1 CH_2Cl_2/ pyridine at 0 °C dropwise. The solution was stirred for 30 min and then diluted with 100 mL of CH_2Cl_2. The reaction mixture was washed with 1 M $NaHSO_4$ (3 x 50 mL) and brine (3 x 50 mL). The organic phase was concentrated to the crude product, which was purified by column chromatography to afford 0.81 g of *N*-(4-nitrophenyloxycarbonyl)benzyl glycinate (65%) as white solid. To the solution of *N*-(4-nitrophenyloxycarbonyl)benzyl glycinate (0.79 g, 2.4 mmol) in 10 mL of benzene were added 1,6-aminohexanol (0.34 g, 2.9 mmol), DMAP (88 mg, 0.72 mmol) and diisopropylethylamine (0.46 g, 3.6 mmol) at room temperature. The reaction mixture was stirred at for 30 min before diluted with 50 mL of CH_2Cl_2. The mixture was washed with 1 M $NaHSO_4$ (3 x 50 mL), 2% Na_2CO_3 (3 x 50 mL) and brine (3 x 50 mL). The organic phase was dried and concentrated to the crude product, which was purified by column chromatography to afford 0.61 g of [3-(6-hydroxyhexyl)ureido]acetic acid benzyl Ester (86%) as white solid..

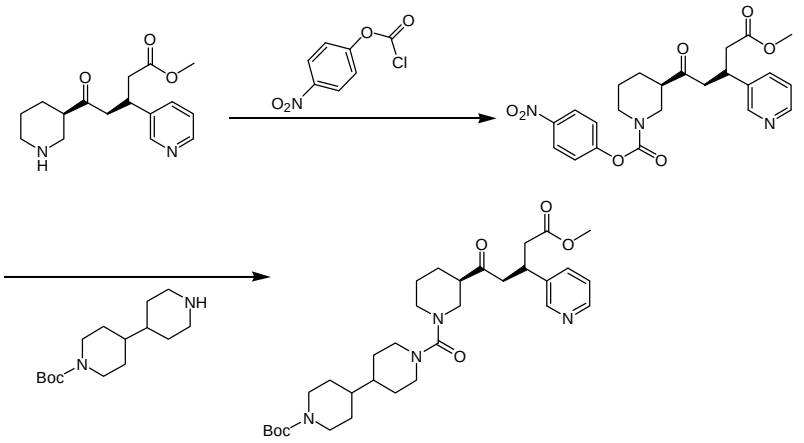
6.1.3 利用氯甲酸对硝基苯酯一锅法合成脲示例 [8]



To a solution of 1-(2,6-dichloro-benzyl)-3-pyrrolidin-1-ylmethyl-1H-indazol-6-ylamine (374 mg, 1.0 mmol) and diisopropylethylamine (640 mg, 5.0 mmol) in 100 mL of DCM was added a solution of 4-nitrophenyl chloroformate (220 mg, 1.1 mmol) in 10 mL of DCM at –20 ^oC under N_2 atmosphere. The resulting mixture was stirred for 30 min and then added 3-amino-4-(3,4-difluoro-phenyl)-1-phenyl-butan-2-one (275 mg, 1.0 mmol). After stirred at –20 ^oC for 30 min, the mixture was warmed to room temperature and then stirred for another 6 h before poured into water. The reaction mixture was extracted with DCM (3 x 100 mL). The combined organic phases were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to the crude product, which was purified by column

chromatography to afford 175 mg of 1-[1-(2,6-dichloro-benzyl)-3-pyrrolidin-1-ylmethyl-1H-indazol-6-yl]-3-[1-(3,4-difluoro-benzyl)-2-oxo-3-phenyl-propyl]-urea (26 %)

6.1.4 氯甲酸对硝基苯酯用于仲胺的脲合成示例 [9]



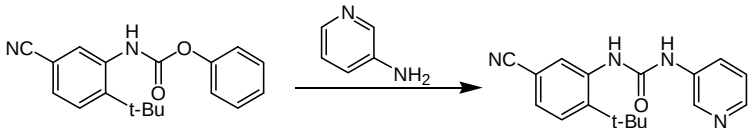
To a solution of 5-oxo-5-piperidin-3-yl-3-pyridin-3-yl-pentanoic acid methyl ester (2.9 g, 10 mmol) in DCM (200 mL) was added 4-nitrophenylchloroformate (2.0 g, 10 mmol) and NMM (6.0 mL, 30 mmol) at 0 ^{o}C. The resulting mixture was stirred for 2 h before poured into water (15 mL). After separated, the organic layer was dried over anhydrous Na_2SO_4 and evaporated to oil, which was dissolved in 100 mL of MeCN. The solution was then treated by [4,4']bipiperidinyl-1-carboxylic acid tert-butyl ester (4.3 g, 15 mmol) and DMAP (1.2 g, 10 mmol), and heated to reflux for 24 h. After removal of the solvent, the residue was dissolved in EtOAc (200 mL). The organic phase was washed with 1 N NaOH (3 x 100 mL), brine (3 x 100 mL) and dried over anhydrous Na_2SO_4. After filtered, the filtrate was concentrated to the crude product, which was purified by silica gel chromatography to afford 4.1 g of 1'-[3-(4-methoxycarbonyl-3-pyridin-3-yl-butyryl)-piperidine-1-carbonyl]-[4,4']bipiperidinyl-1-carboxylic acid tert-butyl ester (69 %)

6.2 利用氯甲酸苯酯合成脲

氯甲酸苯酯也是一般用于伯胺脲的合成，其首先与胺的反应苯氧基碳酰胺，在碱性条件下，高温条件下与另一分子胺反应生成脲。其特点是相应的中间体苯氧基碳酰胺，

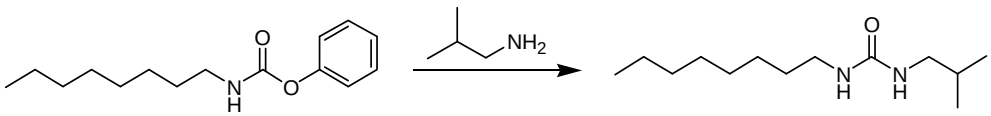
较为稳定，易于制备及纯化。若将氯甲酸苯酯用于仲胺的脲的合成，在第二步反应一般用第二个胺的负离子反应。

6.2.1 芳香伯胺的苯氧基碳酰胺和脲的合成示例 [10]



To a solution of pyridin-3-ylamine (940 mg, 10 mmol) and triethylamine (2.0. g, 20 mmol) in 50 ml of DMF was added 2.94 g of (2-tert-Butyl-5-cyano-phenyl)-carbamic acid phenyl ester at room temperature under N_2 atmosphere. The resulting mixture was heated to 100 ^oC for 5 h before poured into 200 mL of water. The mixture was extracted with DCM (3 x 100 mL). The combined organic phases were washed with 0.5 N of HCl aqueous solution (3 x 100 mL) and brine (3 x100 mL). After dried over anhydrous Na2SO4 and filtered, the filtrate was concentrated to the crude product, which was purified by column to afford 1.9 g of 1-(2-tert-Butyl-5-cyano-phenyl)-3-pyridin-3-yl-urea (64 %).

6.2.2 脂肪伯胺的苯氧基碳酰胺和脲的合成示例 [11]

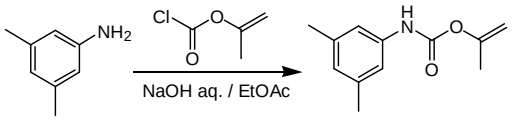


To a solution of isobutylamine (7.3 g, 0.1 mol) and triethylamine (10.1 g, 0.1 mol) in 200 ml of N,N-methylpyrrolidone was added 24.9 g of octyl-carbamic acid phenyl ester at room temperature under N_2 atmosphere. The resulting mixture was heated to 60 ^oC for 5 h before cooled to 40 ^oC. The reaction mixture was put into 500 mL of methanol and then further cooled to room temperature. The solid was collected and washed with methanol to afford 18.9 g of 1-isobutyl-3-octyl-urea (83 %).

6.3 利用氯甲酸 2－异丙烯酯合成脲

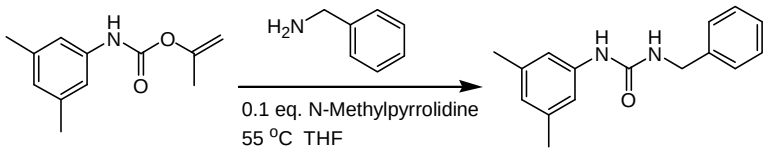
最近也有文献报道，用氯甲酸 2－异丙烯酯与伯胺生成 2 －异丙烯氧基碳酰胺，其在 N-甲基四氢吡咯的催化下与另一分子胺反应可以高收率的得到相应的脲，且许多反应经过简单后处理后就可得到较好的纯度。

6.3.1. 2-异丙烯氧基碳酰胺的合成 [12]



To an aqueous solution of sodium hydroxide (8 mL, 2.5 M in water) was added a solution of 3,5-Dimethylaniline (1.2g, 10 mmol) in 20 mL of EtOAc at 5 ^{o}C dropwise. The resulting mixture was stirred at 5 ^{o}C for 30 min before added isopropenyl chloroformate (1.1 mL, 14 mmol). The reaction mixture was stirred at r.t. for 1 h and then the mixture was separated. The aqueous phase was extracted with EtOAc (3 X 20 mL). The combined organic phases were washed with brine (3 X 50 mL), dried over anhydrous Na2SO4 and filtered. The filtrate was concentrated to the crude product, which was recrystallization from EtOAc:Heptane (1:2) to afford 1.2 g of (3,5-Dimethyl-phenyl)-carbamic acid isopropenyl ester (58 %).

6.3.2 2-异丙烯氧基碳酰胺与胺反应合成脲



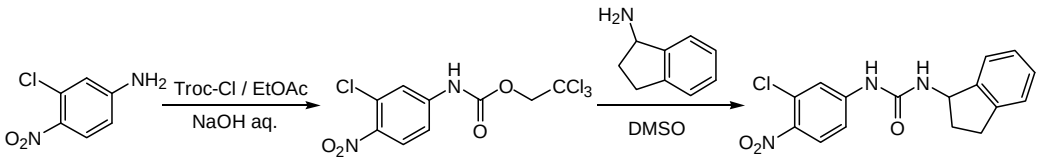
A mixture of (3,5-Dimethyl-phenyl)-carbamic acid isopropenyl ester (1.2 g, 5.8 mmol) and benzylamine (0.6 g, 5.8 mmol) in 50 mL of THF was added *N*-Methylpyrrolidine (0.06mL). The reaction mixture was stirred at 55 ^{o}C for 21 h before poured into ice-water. The mixture

was extracted with DCM (3 X 100 mL). The combined organic phases were washed with 0.5 N aq. HC1 and brine, dried over anhydrous Na2SO4 and filtered. The filtrate was concentrated to give the crude product, which was purified by column to afford 1.5 g of 1-Benzyl-3-(3,5-dimethyl-phenyl)-urea (98 %)

6.4 利用氯甲酸 2-三氟乙基酯或氯甲酸 2-三氯乙基酯合成脲

用 2-三氟乙基酯或氯甲酸 2-三氯乙基酯合成脲也是一个较好的方法，在成脲时反应一般较为干净，易于后处理。

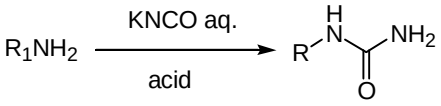
6.4.1 利用氯甲酸 2-三氯乙基酯合成脲示例 [13]



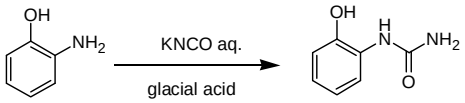
To an ice-cold suspension of 3-chloro-4-nitro-phenylamine (1.72 g, 10 mmoL) in EtOAc (50 mL) was added 3M NaOH (25 mmol, 2.50 eq). The resulting biphasic mixture was stirred briskly at 0-5 °C for 30 min. Troc-Cl (175 mg, 1.40 eq) was added dropwise. The ice bath was removed and the reaction was stirred at rt by which time the raw material was disappeared as check by LC/MS. The layers were separated and the aqueous phase was extracted with EtOAc (3 X 50 mL). The combined EtOAc layers were washed with H_2O (2× 50 mL), brine (2×50 mL), dried over anhydrous Na_2SO4 and filtered. The filtrate was concentrated to the crude product, which was used for the next reaction without further purification. A mixture of crude (3-chloro-4-nitro-phenyl)-carbamic acid trichloromethyl ester (4.2 g) and indan-1-ylaminein (1.3 g, 10 mmol) in 20 mL of DMSO was heated to 55^{o}C. The reaction mixture was stirred for 3 h when the material was disappeared as checked by LCMS. The reaction mixture was poured into ice-water and extracted with DCM (3 X 50 mL). The combined organic phases were washed with brine (5 X 50 mL), dried over anhydrous Na2SO4 and filtered. The filtrate was concentrated to give the crude product, which was purified by column to afford 1.9 g of 1-(3-chloro-4-nitro-phenyl)-3-indan-1-yl-urea (57 %)

7. 异氰酸钾与胺反应生成脲

对于没有任何取代基的脲，一般主要通过氰酸钾与胺反应得到，一般这类反应在水和醋酸的混合溶剂中进行。



7.1 异氰酸钾与胺反应生成脲示例 [14]



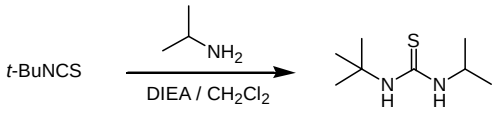
To a solution of o-aminophenol (1.1 g, 10 mmol) in 20 mL of glacial acetic acid and water (1:1) was added a solution of potassium cyanate (1.6g, 20 mmol) in water dropwise. The resulting solution was stirred at r.t. for 3 h. After removal of the solvent, the residue was dissolved in EtOAc (100 mL). The organic phase was washed with sodium bicarbonate solution and brine, dried over anhydrous Na2SO4 and filtered. The filtrate was concentrated to the crude product, which was recrystallized once from methanol and then several times from acetone-hexane to afford 1.2 g of white needles (2-Hydroxy-phenyl)-urea (80 %).

Part II：硫脲的合成

1. 前言

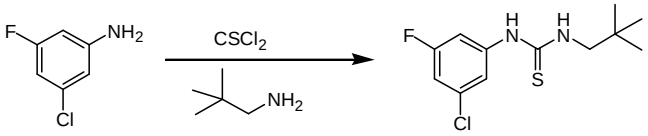
硫脲 Thiourea 在石油化工、医药化工同样具有泛的应用前景，很多医药分子中都还有硫脲的结构片断。例如目前市场上很多口服降糖药、抗甲状腺药都属于硫脲类分子。硫脲的化学合成通常有下列一些方法。

2. 异硫氰酸酯与胺反应生成硫脲 [15]



To a solution of tert-butylisothiocyanate (5.0 mL, 39 mmol) in dichloromethane (200 mL) were added isopropylamine (4.0 mL, 47 mmol) and diisopropylethylamine (DIEA) (6.8 mL, 39 mmol), and the mixture was stirred at rt for 2h. The reaction mixture was diluted with EtOAc, washed with 10 percent citric acid (2x), saturated $NaHCO_3$ (2x), H_20 (2x), and brine (1x). The organic layer was dried ($MgS0_4$) and evaporated to the crude product, which was purified by column to afford 1-*tert*-butyl-3-isopropyl-thiourea (3.3 g, 52 %).

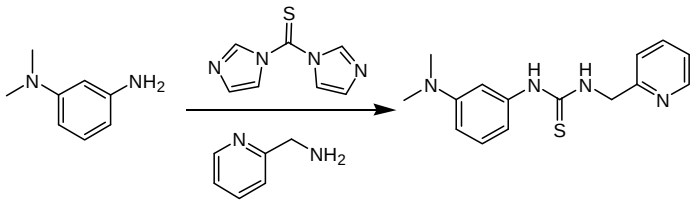
3. 硫光气与胺反应生成硫脲 [16]



To a solution of 8.5 g of 3-chloro-5-fluoroaniline in 150 ml of benzene was added a solution of 2.2 g of thiophosgene in 10 ml of benzene dropwise at room temperature under nitrogen.

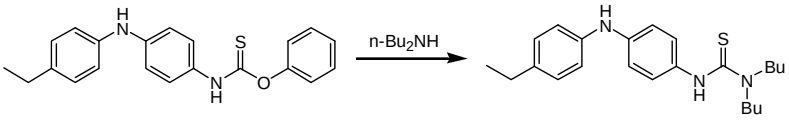
The resulting mixture was stirred at 60 ^{o}C for 3 hours and then cooled to room temperature. After filtered, the filtrate was concentrated to the oil, which was followed by a solution of t-pentylamine (3.4 g) in 30 ml of benzene. The mixture was stirred at room temperature for another 30 minutes. The reaction mixture was evaporated in vacuo and the resulting solid recrystallized from cyclohexane to give 2.2 g of the title compound as colorless needles 1-(3-chloro-5-fluoro-phenyl)-3-(2,2-dimethyl-propyl)-thiourea

4. 硫代羰基二咪唑与胺反应生成硫脲 [17]



To a mixture of 1,1'-thiocarbonyldiimidazole (535 mg) and acetonitrile (7 ml) was added a solution of 3-(N,N-Dimethyl) aniline (272 mg) in acetonitrile (7 ml) dropwise over period of 15 minutes at 0^{o}C under nitrogen. After stirring for 2 hours at ambient temperature, 2-(aminomethyl)pyridine (433 mg) was added to the mixture. The reaction mixture was then heated to 60 ^{o}C for 4 hours. After cooling to room remperature, the reaction mixture was evaporated to the residue, which was purified by column (DCM / MeOH) to give 1-(3-Dimethylamino-phenyl)-3-pyridin-2- ylmethyl-thiourea (423 mg).

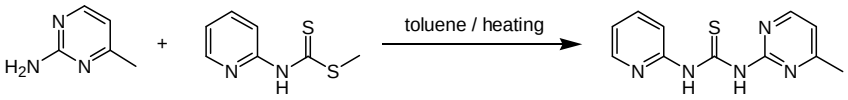
5. 利用硫代氯甲基苯酯合成硫脲 [18]



A mixture of n- Bu_2NH and [4-(4-ethyl-phenylamino)-phenyl]-thiocarbamic acid O-phenyl ester (348) in ethanol was heated to reflux under N2 atmosphere for 16 h. After removal of the

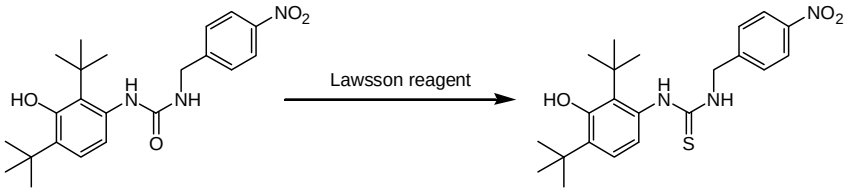
solvent, the residue was dissolved in DCM. The organic phase was washed with 1 N of sodium hydroxide (3 x 50 mL), 1 N of HCl aqueous solution and brine (5 X 50 mL). After dried over anhydrous Na2SO4 and filtered, the filtrate was concentrated to give the crude product, which was purified by column to afford 1,1-dibutyl-3-[4-(4-ethyl-phenylamino)-phenyl]-thiourea

6. 通过硫代甲巯基碳酰合成硫脲 [19]



A mixture of 4-methyl-pyrimidin-2-ylamine (2.2 g, 20 mmol) and pyridin-2-yl-dithiocarbamic acid methyl ester (3.6 g, 20 mmol) in 100 mL of toluene was heated to reflux for 10 h. After removal of the solvent, the residue was recrystallized from methanol to afford 3.4 g of 1-(4-methyl-pyrimidin-2-yl)-3-pyridin-2-yl-thiourea.

7. 硫代试剂（如 Lawsson 试剂）与脲反应得到硫脲 [20]



To 4.0 g of 1-(2,4-di-tert-butyl-3-hydroxy-phenyl)-3-(4-nitro-benzyl)-urea was added 6.0 g of a lawson reagent dissolved in 50 mL of 1,4-dioxane at room temperature under N_2 atmosphere. The resulting mixture was heated to reflux for 15 h before poured into 150 mL of water. The mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic phases were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to the crude product, which was purified by a silica gel column to give 2.5 g of 1-(2,4-Di-tert-butyl-3-hydroxy-phenyl)-3-(4-nitro-benzyl)-thiourea (60 %).

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