A Mild Protocol for Parallel Solution Phase Synthesis of Cyclic Imides

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Efficient drug discovery?

- **Why do we perform parallel synthesis?**
  - Rapid production of molecules for exploration and follow-up of biological activity
  - Design tools allow compounds to be tailored to meet ‘druglike’ criteria
  - Diverse libraries possible from few reagents
- **Where is the catch?**
  - Logistical problems
    - Isolation of products
    - Apparatus might not allow sensitive chemistry
    - Large numbers of reactions often need facilities to deal with large amounts of hazardous chemicals

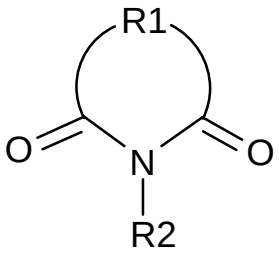
Efficient drug discovery?

- **Solution phase vs. solid phase[1-4]**

	Solution Phase	Solid Phase
Development	May use existing knowledge. Minimal development time needed if purifying anyway. May use development time to minimise purification required.	Extensive development often necessary
Scale	0.25mmol readily achievable	0.2mmol max?
Speed	Limited by hardware/processes – 7500 compounds synthesised per week average H1 2004 at TDR	Combinatorial numbers possible
Purification	Potentially time consuming. 3-4000 MS triggered purifications performed at TDR per week	Potentially simple, given well developed chemistry
Isolation	Discrete reactions do not lead to a loss of efficiency	Sorting/deconvolution necessary if combinatorial advantage exploited.

- **Solution phase chemistry more commonly used at TDR**

Why Cyclic Imides?



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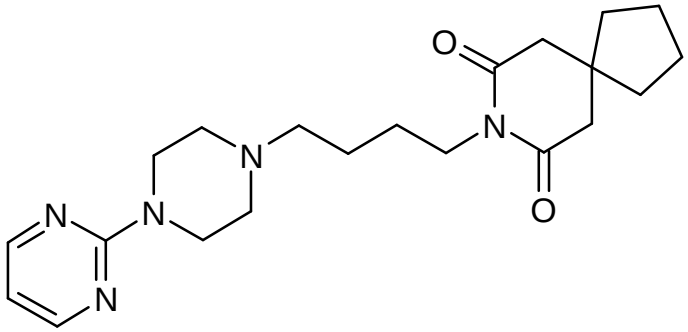

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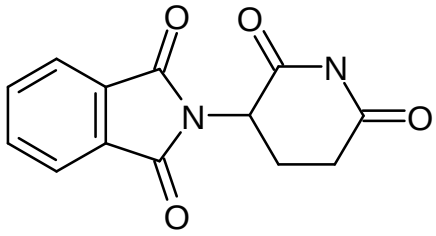

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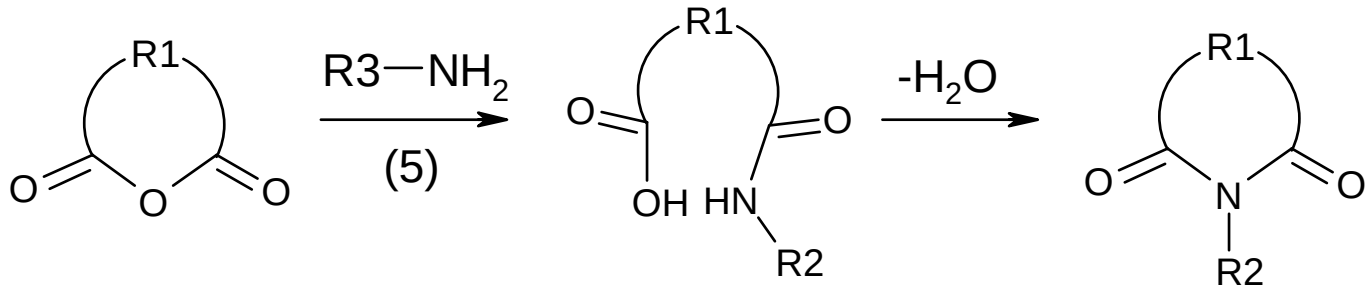
- Structural template selected for similarity to known biologically active molecules.
  - Buspirone (2) as a 5-HT1A inhibitor, clinically effective for the treatment of anxiety and depression[5] and
  - Thalidomide (3), developed as a sedative in the 1950's but removed from the marketplace after its teratogenic effects were discovered[6]
- Possible use both as building block for inclusion in several libraries or as a general screening library of cyclic imides.

Phase 1 – Conventional Protocols Applied to HTC



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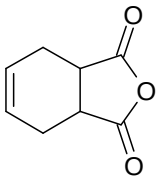
- Synthesis of cyclic imides well documented in literature.
  - Acidic conditions and heating are the most common[7,8], followed by activation of acid functionality in (6) to allow dehydration to products (1)[9].
  - Highly acidic & corrosive reagents (and, to a lesser extent, by-products) not well tolerated by high throughput equipment or chemists, so it was necessary to use another route.
  - Initial approach was to look at simple literature methods alongside control acylation experiment, performed in vials rather than plates.

Phase 1 – Conventional Protocols Applied to HTC

Cyclic Anhydrides Used:



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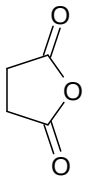

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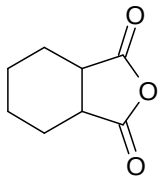

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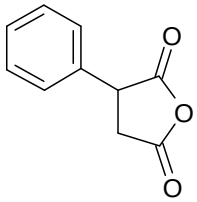

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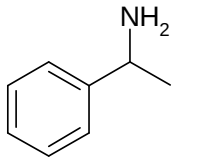
Amines Used:



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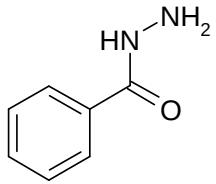

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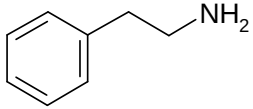

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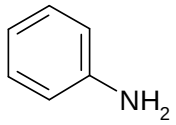

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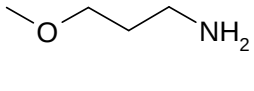

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Summarised Results

LCMS purity, UV detection@254nm for given condition
Purity of compound (6) given in brackets where observed

Compound	Cyclic Anhydride	Amine	RT 72h	RT 72h, 1 eq thionyl chloride	150°C 6h	150°C 72h
1(1)	4(1)	5(1)	0%	0%	0% (8%)	45% (11%)
1(2)	4(1)	5(2)	0%	35%	6%	65%
1(3)	4(1)	5(3)	0%	0% (13%)	0% (6%)	40%
1(4)	4(1)	5(4)	0% (47%)	0% (47%)	0% (29%)	11%
1(5)	4(1)	5(5)	0% (30%)	0%	5% (25%)	36% (16%)
1(6)	4(2)	5(1)	0% (89%)	13% (76%)	0% (75%)	0%
1(7)	4(2)	5(2)	0% (91%)	0% (14%)	67% (33%)	86%
1(8)	4(2)	5(3)	0% (98%)	11% (70%)	0% (54%)	20% (6%)
1(9)	4(2)	5(4)	0% (81%)	0%	0% (97%)	72% (18%)
1(10)	4(2)	5(5)	0%	0%	0% (41%)	27%
1(11)	4(3)	5(1)	3%	0%	0% (23%)	40% (24%)
1(12)	4(3)	5(2)	0% (42%)	1%	10%	62% (20%)
1(13)	4(3)	5(3)	0% (94%)	4% (67%)	13% (8%)	33% (11%)
1(14)	4(3)	5(4)	0% (72%)	8% (77%)	5% (95%)	11% (14%)
1(15)	4(3)	5(5)	0%	0%	0%	0%
1(16)	4(4)	5(1)	0% (92%)	0% (29%)	3% (67%)	65% (6%)
1(17)	4(4)	5(2)	24% (56%)	47% (42%)	34% (23%)	74% (14%)
1(18)	4(4)	5(3)	2% (56%)	0% (6%)	12% (71%)	75% (7%)
1(19)	4(4)	5(4)	0% (100%)	56%	0% (100%)	46% (9%)
1(20)	4(4)	5(5)	5% (55%)	2%	13% (58%)	11%

- Cyclic imides are formed most successfully with extended heating at elevated temperature.
- Hydrazide is most successful amine – perhaps electron withdrawing character is beneficial in this substituent.
- LCMS detection issues with aliphatic reagents?

Phase 2– Dehydrating Conditions

- Temperatures >120^{o}C for production of large numbers of compounds in HTC awkward.
  - Tendency to melt consumable PTFE plates.

- Ability of dehydrative conditions to reduce temperatures for cyclic imide synthesis was therefore examined on a small subset of reactions.
  - Reactions performed at room and elevated temperatures.

- Amine, cyclic imide and dehydration reagents all added simultaneously.
  - Examined HATU, CDI, sodium acetate/acetic anhydride and thionyl chloride.

Phase 2 – Dehydrating Conditions

- Only conditions which produced desired material with aliphatic amines involved using HATU as dehydrating reagent.
  - After work up, comparable to crude high temperature reactions from Phase 1.
  - Aniline works with HATU and thionyl chloride.

Summarised Results

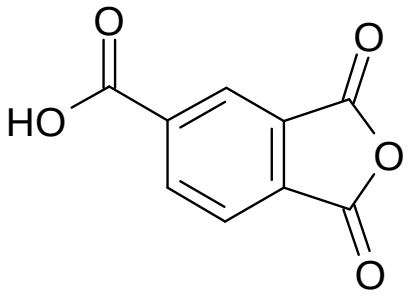
LCMS purity, UV detection@254nm for given condition - purity of compound (6) given in brackets where observed

	Compound	1(16)	1(18)	1(19)
	Cyclic anhydride	4(4)	4(4)	4(4)
	Amine	5(1)	5(3)	5(4)
HATU/DCM/DMF	RT O/N	4% (10%)	6% (9%)	17% (47%)
	80°C 18h	19% (7%)	17% (7%)	25% (8%)
	80°C 18h Post W/U	60% (23%)	62% (26%)	62%
CDI/THF	RT O/N	0% (29%)	0% (55%)	0% (82%)
	80°C 18h	0% (64%)	0% (36%)	0% (78%)
1 eq NaOAc	RT O/N	0% (54%)	0% (42%)	0% (26%)
40 eq Ac_2O, DCM	80°C 18h	0%	0%	0%
$SOCl_2$, DCM	RT O/N	0% (6%)	0%	34%
	80°C 18h	0%	0%	55%

Phase 3 – Combine Best Conditions

- Use of HATU (added simultaneously with other reagents) with extended reaction times, compared against heating only.
- Also examined shortened heating times and microwave heating.
- All products purified by automated aqueous workup (1 x 10% K2CO3, 1 x water wash).

Additional Reagents Used:



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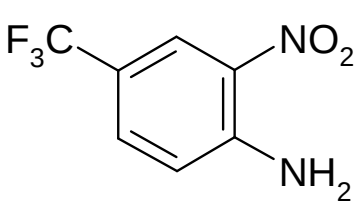

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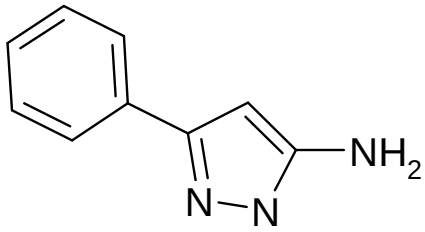

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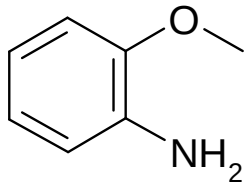

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Phase 3 – Combine Best Conditions

LCMS purity, UV detection@254nm for given condition - purity of compound (6) given in brackets where observed

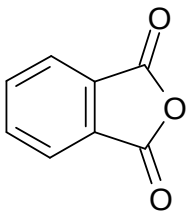
			Conventional Heating				Microwave Heating	
Compound	Cyclic Anhydride	Amine	80°C 18h, 100°C 18h	80°C 18h, HATU 100°C 18h	80°C 18h, 100°C 72h	80°C 18h, HATU 100°C 72h	80°C 18h, 60°C uw 150W 15 mins	80°C 18h, 60°C uw 150W HATU 15 mins
1(7)	4(2)	5(2)	74% (21%)	31%	91% (21%)	30%	0% (98%)	1%
1(8)	4(2)	5(3)	0% (68%)	0%	0% (32%)	0%	0% (42%)	0%
1(9)	4(2)	5(4)	19% (63%)	13% (72%)	63% (25%)	25% (50%)	2% (97%)	0%
1(21)	4(2)	5(6)	0% (10%)	0% (24%)	0% (8%)	0% (28%)	0%	0%
1(22)	4(2)	5(7)	31% (55%)	42% (44%)	85% (15%)	57%	0% (97%)	50%
1(23)	4(2)	5(8)	9% (82%)	11%	23% (35%)	26%	4% (46%)	12%
1(18)	4(4)	5(2)	68%	17%	94%	23%	6% (70%)	10%
1(19)	4(4)	5(3)	6% (12%)	10% (12%)	67% (22%)	0% (13%)	0% (78%)	0%
1(20)	4(4)	5(4)	0% (94%)	6% (52%)	39% (53%)	6% (19%)	0% (100%)	0%
1(24)	4(4)	5(6)	0%	0%	0%	0%	0%	0%
1(25)	4(4)	5(7)	29% (48%)	29% (29%)	40% (48%)	29%	0% (100%)	23%
1(26)	4(4)	5(8)	6% (82%)	21% (35%)	43% (53%)	29% (15%)	0% (92%)	18% (10%)
1(27)	4(5)	5(2)	85%	52%	93%	25%	59% (41%)	0%
1(28)	4(5)	5(3)	54%	37%	71%	42%	5% (95%)	3%
1(29)	4(5)	5(4)	80%	64%	86%	55%	18% (80%)	10%
1(30)	4(5)	5(6)	6% (44%)	0%	21%	1%	0%	0%
1(31)	4(5)	5(7)	18%	20%	43%	33%	24% (55%)	7%
1(32)	4(5)	5(8)	65%	52%	73%	53%	18% (77%)	25% (9%)

- Reactions heated without a dehydrating agent appear to be the more successful than those heated with HATU.
- Heating with microwaves at a power which is not destructive to consumable PTFE reaction plates is insufficient driving force for these reactions.
- Amine 5(6) is forms little desired material, perhaps due to the deactivating substituents on the aromatic ring.

Phase 4 – Change of Tack

- It is notable that acylation proceeds well and cyclisation begins to occur without dehydrating agents.
- Would performing the cyclic imide formation using a two step process therefore offer any insights/improvements?
- Reactions performed at raised temperature, dehydrating the product of reaction between amine and anhydride with i) further heating ii) CDI and iii) HATU, then purified with aqueous workup as in Phase 3.

New Cyclic Anhydrides Used:



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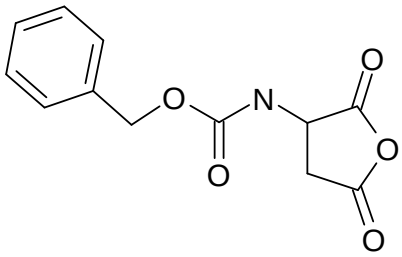

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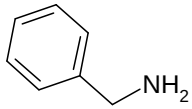
New Amines Used:



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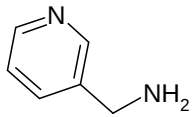

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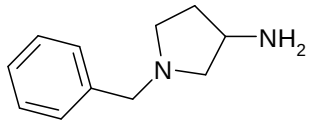

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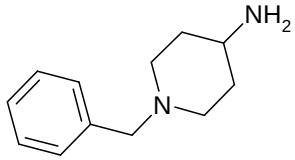

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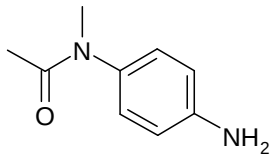

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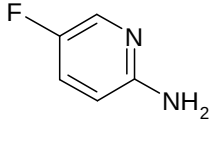

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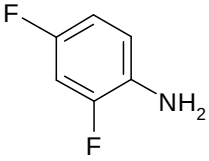

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Phase 4 – Change of Tack

- Reactions heated with CDI proceed more successfully than their counterparts heated without a dehydrating agent in a few cases, and are comparable in the rest.
- Conventionally heated reactions are still more successful than those heated with HATU.
- Anhydride 4(3) produces desired compounds, yet LCMS purities are low, perhaps due to poor absorbance characteristics of these materials.
- Amines 5(14) and to a lesser extent 5(15) often produce low purity products, perhaps due to the deactivating substituents on the aromatic ring. Amines 5(11) and 5(12) appear more successful at 210nm than at 254nm.

			LCMS purity, UV detection@254nm for given condition Purity of compound (6) given in brackets where observed		
Compound	Cyclic Anhydride	Amine	80°C 18h, 100°C 18h	80°C 18h, 100°C CDI 18h	80°C 18h, 100°C HATU 18h
1(14)	4(3)	5(4)	14%	22%	8%
1(33)	4(3)	5(9)	27%	84%	0%
1(34)	4(3)	5(10)	94%	96%	37%
1(35)	4(3)	5(11)	23%	23%	8%
1(36)	4(3)	5(12)	37%	46%	26%
1(37)	4(3)	5(13)	91%	91%	81%
1(38)	4(3)	5(14)	33%	15%	3%
1(39)	4(3)	5(15)	72%	76%	0%
1(19)	4(4)	5(4)	39%	60%	36%
1(40)	4(4)	5(9)	70%	68%	81%
1(41)	4(4)	5(10)	98%	93%	88%
1(42)	4(4)	5(11)	33%	50%	38%
1(43)	4(4)	5(12)	49%	69%	47%
1(44)	4(4)	5(13)	91%	87%	90%
1(45)	4(4)	5(14)	8%	26%	12%
1(46)	4(4)	5(15)	59%	49%	25%
1(47)	4(6)	5(4)	100%	96%	92%
1(48)	4(6)	5(9)	76%	95%	0%
1(49)	4(6)	5(10)	99%	100%	87%
1(50)	4(6)	5(11)	86%	88%	36%
1(51)	4(6)	5(12)	88%	88%	68%
1(52)	4(6)	5(13)	100%	98%	100%
1(53)	4(6)	5(14)	78%	28%	35%
1(54)	4(6)	5(15)	100%	98%	0% (55%)
1(55)	4(7)	5(4)	25%	42%	53%
1(56)	4(7)	5(9)	70%	84%	68%
1(57)	4(7)	5(10)	87%	97%	90%
1(58)	4(7)	5(11)	33%	53%	49%
1(59)	4(7)	5(12)	51%	77%	56%
1(60)	4(7)	5(13)	94%	87%	86%
1(61)	4(7)	5(14)	4%	31%	5%
1(62)	4(7)	5(15)	24%	41% (21)	74%
			254 Average: 61%	254 Average: 67%	254 Average: 46%

Conclusions

- The combination of using high temperatures and coupling reagents allows production of cyclic imides rapidly and in higher purity than heat or coupling agents alone.
- In addition, the method developed is within the limits readily achievable in high throughput synthesis.
- The method is applicable to a wide range of R2 reagents
  - **Hydrazides**
  - **Anilines - reasonably nucleophilic anilines may be used successfully**
  - **Primary 'aliphatic' amines (although need to be careful about chromophores if using LCMS analysis)**

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