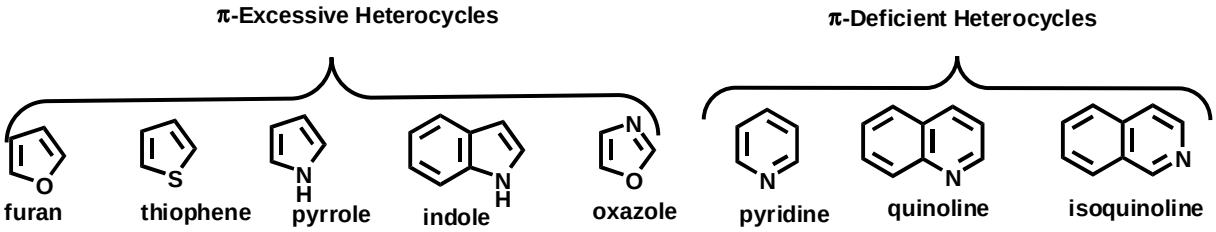
Heterocyclic Chemistry

Heterocyclic systems are widely important compounds, both in terms of commonness of occurrence and importance of consequence. For example, in 2010, 8 of the top 10 selling drugs contained heterocyclic systems – yet you have seen very little of heterocycle synthesis in your studies.

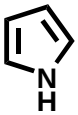
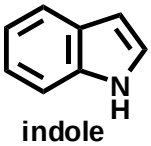
The Fundamental Heterocycles

We will be limited in the heterocycles we address, due to time constraints. We will only discuss….



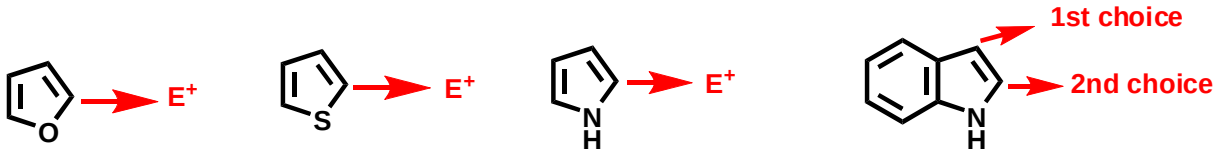
Issue #1. Are they really aromatic?

The π-excessive heterocycles use the lone pair on the heteroatom to formally make the 6π system aromatic, but in reality they have less aromatic character than benzene. Various measures of aromaticity suggest that thiophene and pyrrole are only a bit less aromatic than benzene, while furan (and oxazole) are substantial reduced in their aromatic character. This will have consequences in their properties and reactivity.

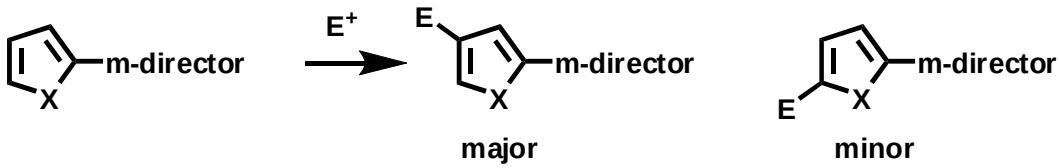
Aromaticity measurement	 furan	 thiophene	 pyrrole	 indole	 oxazole
Baran-Richter	12% rel to benzene	45%	37%		
ASE Homodesmotic	44%	56%	61%		37%
HOMA	30%	91%	89%		34%
Conclusion	not very aromatic	pretty aromatic	pretty aromatic	assume it's like pyrrole	not very aromatic

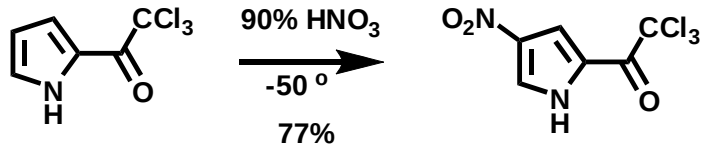
Generalities of Reactivity

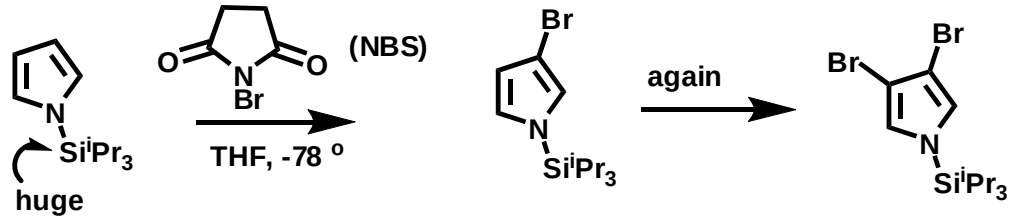
Electrophilic Aromatic Substitution – Recall, in all cases except for indole, that electrophilic substitution favours C-2 (or C-5) substitution. In indole, C-3 substitution is the first choice, and if it is blocked, then C-2 is the 2nd choice.



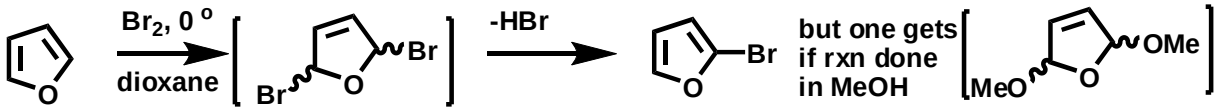
There are some, rare exception where C-4 or C-3 substitution is favoured. This is most often due to existing EWG groups disfavouring C-5, or due to mammoth steric effects.



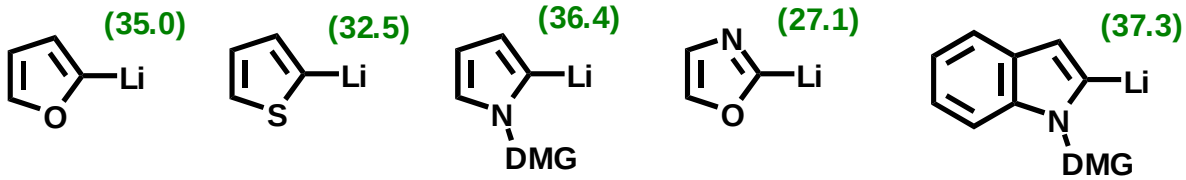




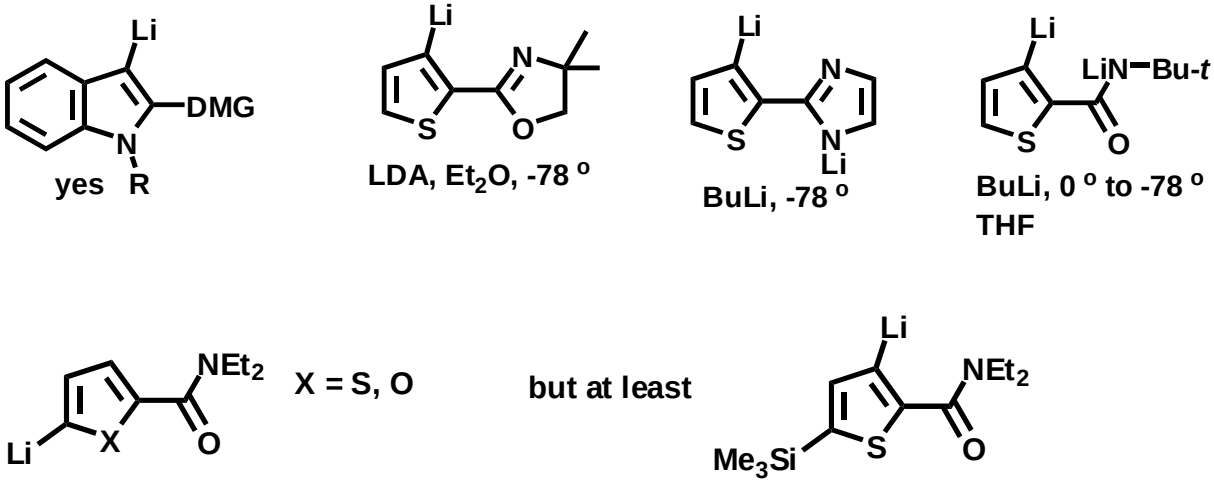
Note: In some cases with furan, the reaction products look like it's classical electrophilic substitution, but it is not really..



Directed Lithiation – Once again, the predominant lithiation site is C-2



The ability to lithiate at C-3 is hit and miss at best, other than for indoles. There is irregularly successful with thiophenes, but the overall take is that it's not generally successful.



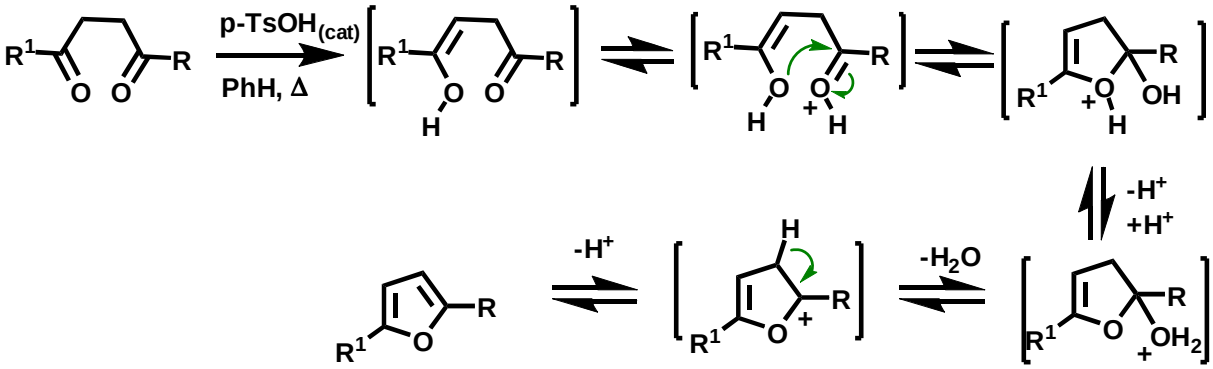
The overall take home message is that C-3 and C-4 substitution is a big issue in pyrroles, thiophenes, and furans. Conversely, C-ring substitution is a big issue in indoles.

Synthesis of π-Excessive Heterocycles

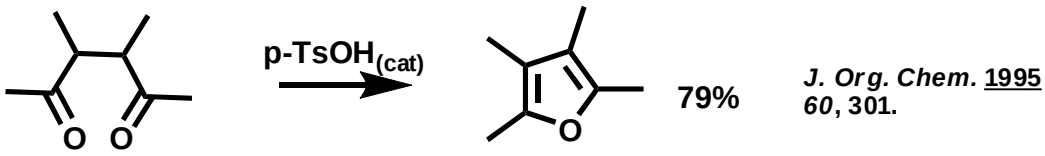
Since furan, thiophenes, and even pyrroles have much in common chemically, it is no surprise that several of the syntheses of the ring system have much in common.

The Paal-Knorr Type

Furans - The most straightforward group of syntheses come from the fact that furans are really 1,4-dicarbonyls that have been *dehydrated*. So the key is to avoid (or remove) water.

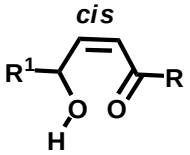


This reaction is known as the **Paal-Knorr synthesis**. Most often these 1,4-dicarbonyls are diketones, but there are examples where one or both carbonyls are aldehydes, or where one carbonyl is an ester. C-2 and C-3 substitution is well tolerated in this process, which gives furans with C-3 and/or C-4 substitution. One example is below, but there are several more on a subsequent page.

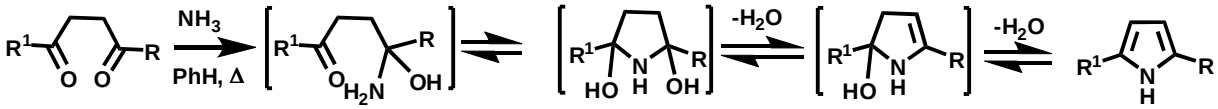


J. Org. Chem. 1995 *60*, 301.

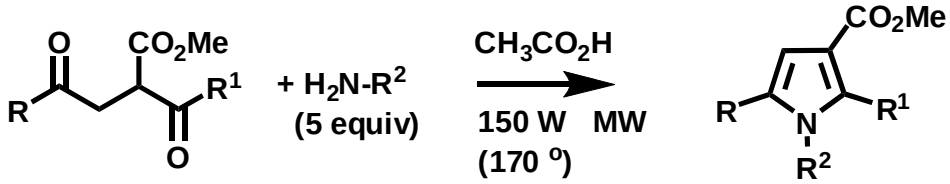
In principle, it should also be possible to initiate this type reaction from (Z)- γ-hydroxyalkenones, and this has been done.



Pyrroles -Fortunately, it is straightforward to make a modification of this to get pyrroles. If an "NH_3" equivalent is added to this reaction –sometimes NH_3 itself and sometimes H-N(TMS)$_2$ with alumina – the pyrrole is formed. Acid is often but not always present. This is also known as the **Paal-Knorr (pyrrole) synthesis.**

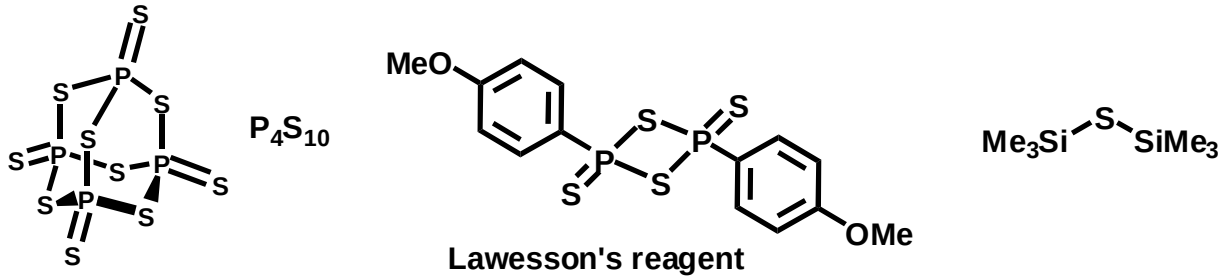


Once again, C-2/C-3 substituted starting materials and therefore C-3/C-4 substituted pyrroles are common. Furthermore, the N can be substituted and often is, with alkyl groups, aryl groups and even acyl groups (amides).

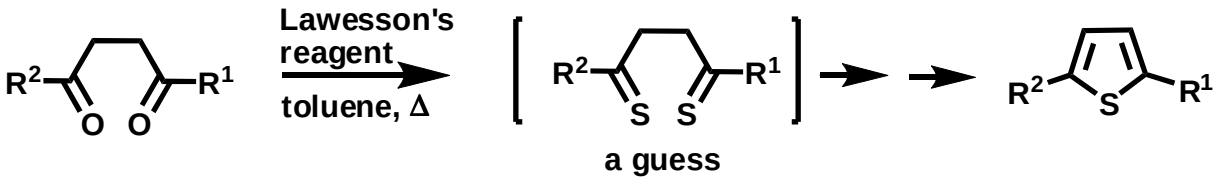


Eur. J. Org. Chem. 2005, 5277.

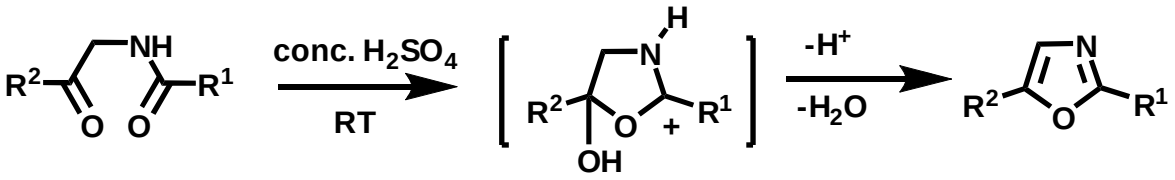
Thiophenes – For thiophenes, it might be expected that one could get the same sort of transformation to occur if only there was a reagent that could convert ketones into thioketones – and there is. Traditionally P_4S_{10} was used, but reagents such as Lawesson's reagent, or (TMS)$_2$S are much more common now. Acids are *not* additionally required for this reaction.



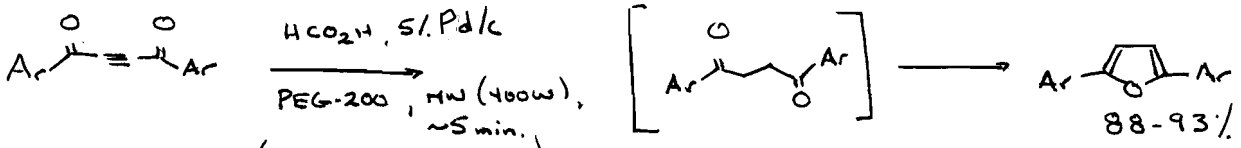
This process is known by a slightly different name, as the **Paal synthesis**. Examples are on the following pages.



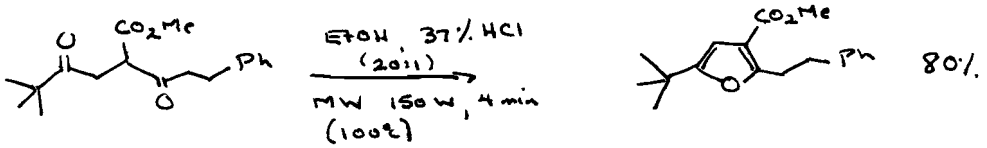
Oxazoles – Finally, if there is an N atom in the backbone (i.e., a 2° amide) , the same type of protocol is also used to make oxazoles. The only other difference is that in this case the acid tends to be a quite strong one. Curiously, this protocol is known by a completely different name – as the **Robinson-Gabriel synthesis**.



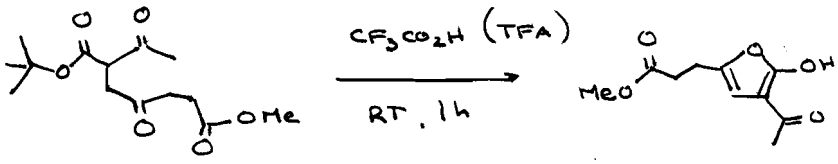
Examples of Paal-Knorr Furan Synthesis



Rao, H.S.P.; Jothilingham, S. J. Org. Chem. 2003, 68, 5392.

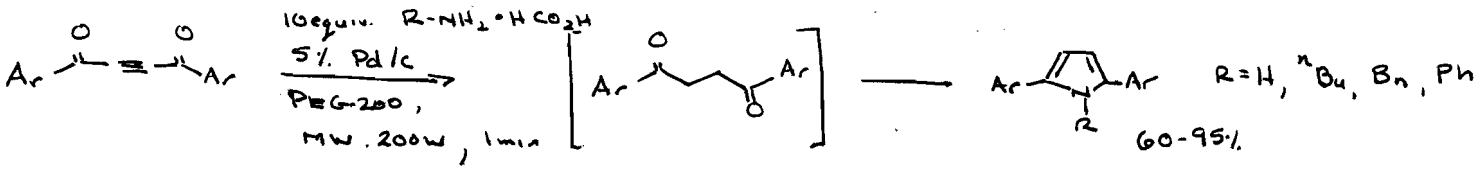


Minetto, G.; Raveglia, L.F.; Sega, A.; Taddei, M. Eur. J. Org. Chem. 2005, 5277.

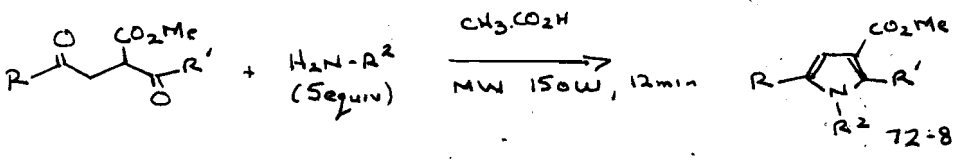


Stauffer, F.; Neier, R. Org. Lett. 2000, 2, 3535.

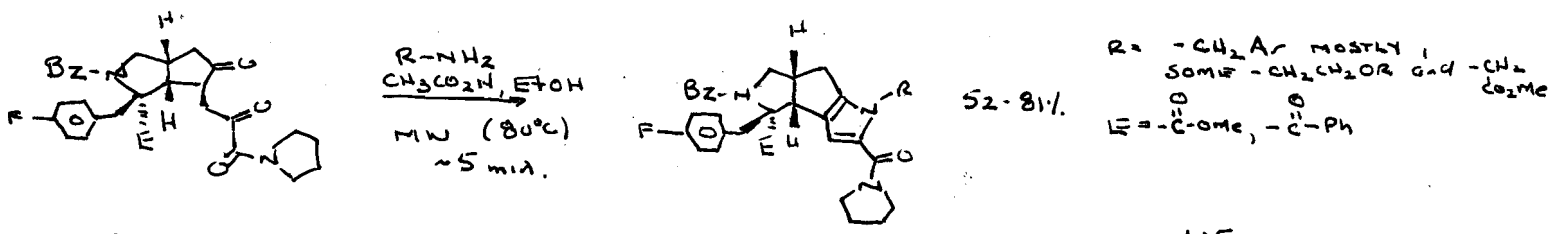
Examples of Paal-Knorr Pyrrole Synthesis



Rao, H.S.P.; Jothilingham, S., Scheeren, H.W.
Tetrahedron 2004, 60, 1625.

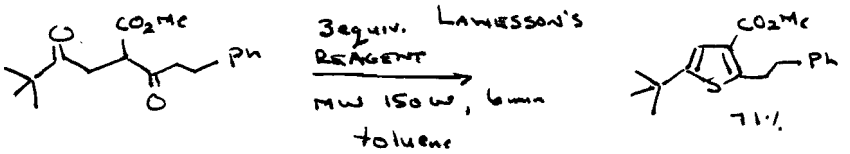


Minetto, G.; Raveglia, L.F.; Sega, A.; Taddei, M. Eur. J. Org. Chem. 2005, 5277.

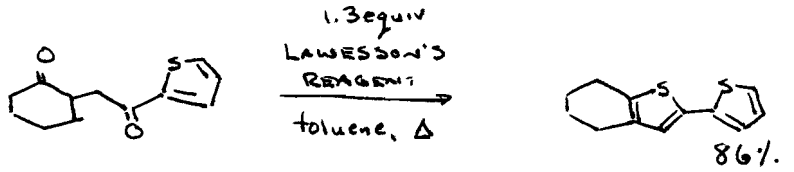


Werner, S.; Iyer, P.S. Synlett 2005, 1405.

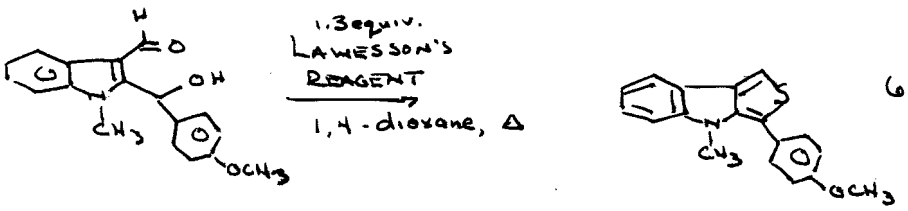
PAAR THIOPHENE SYNTHESIS



MINETTO, G.; RAVEGLIA, L.F.; SEGA, M.; TADDEI, M.
EUR. J. ORG. CHEM. 2005, 5277.

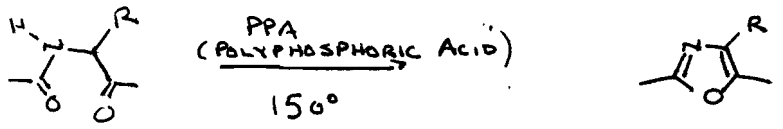


MITSCHKE, U.; OSTERITZ, E.M.; DE BAERDEMAEKER, T.; SOKOLOWSKI, M.; BÄUERLE, P. CHEM. EUR. J. 1998, 4, 2211.



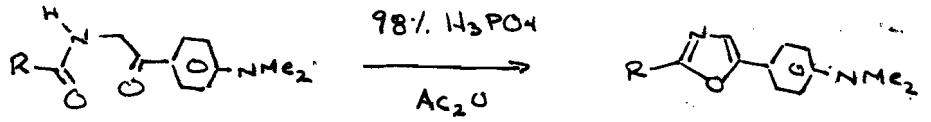
LIN, S-C.; YANG, F-D.; SHIUE, J-S.; YANG, S-M.; FANG, J-M.
J. ORG. CHEM. 1998, 63, 2909.

ROBINSON-GABRIEL OXAZOLE SYNTHESIS



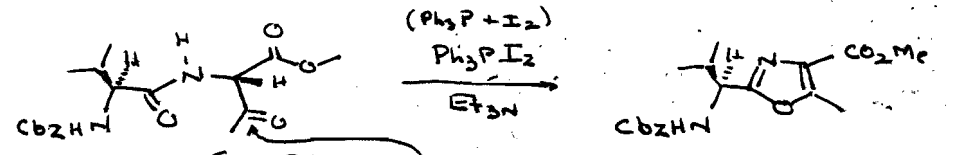
R = H, 20%.
R = Me, 40%.
R = nPr, 61%.

WIEGAND, E.E.; RATHBURN, D.W. SYNTHESIS 1970, 648.



R = Ph 95%
R = NEO- 94%
R = 90%

KERR, V.N.; HAYES, F.N.; OTT, D.G.; LIEB, R.; HANSBURY, E.
J. ORG. CHEM. 1959, 24, 1864.



55% FROM ALCOHOL.

MADE IN SITU BY DESS MARTIN OXIDN OF ALCOHOL

WIPF, P.; MILLER, C.P. J. ORG. CHEM. 1993, 58, 3604.

ALL EXAMPLES TAKEN FROM, NAME REACTIONS IN HETEROCYCLIC CHEMISTRY, LI, J.J. 2003