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One-Pot Three Component Synthesis of N-Arulquinolines

Shori Gerardot
Indiana University - Purdue University Fort Wayne

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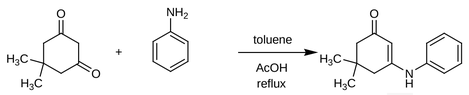
Shori Gerardot (Dr. **Daryoush** Tahmassebi)

Chemistry, IPFW, Fort Wayne, IN 46805

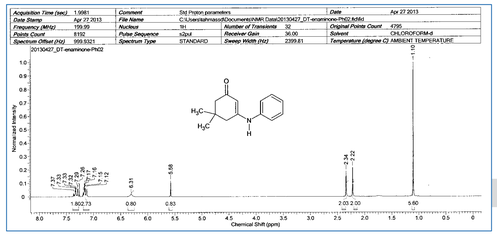
Introduction

Synthesis of bioactive materials is an important part of organic chemistry. It has been shown that N-arlquinolines have profound use as a bioactive compounds; showing useful in scaffolding of many pharmaceutical drugs that target a variety of illness [1]. They also have pharmaceutical[2] effects such as: antiplasmodial[3], cytotoxic[4], antibacterial[5], Antiproliferative[6] antimalarial[7] and even anti-cancer activity[8]. The current methods of synthesis for these compounds such as; Skraup[9], Doebner-Von Miller[10], Conrad Limbach[11], Combes[12] and Pfitzinger[13] are unappealing to many. These methods are either costly, dangerous, time consuming or inefficient [1].

Synthesis of Enaminones



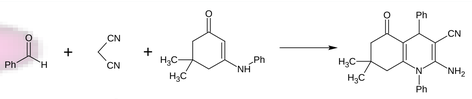
Spectral Data of Enaminone



Table

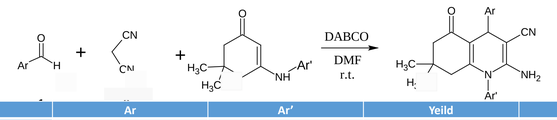
Product	Aniline	Yeild	Literature M.P	M.P.
4a	Aniline	75 %	183 – 185 °C	180 - 182 °C
4b	*p*-Bromoaniline	70 %	219 - 221 °C	218 - 220 °C
4c	*p*-Methylaniline	80 %	°C	201 - 202 °C

Optimization Reactions



Trial	Catalyst	Solvent	Percent Yeild
1	CTACl[a]	H_2O[c]	28.5 %
2	CTACl[a]	50% EtOH[c]	53.61 %
3	CTABr[b]	50% EtOH[c]	50.81 %
4	K_2CO_3	50% EtOH[c]	19.48 %
5	$NaHCO_3$	50% EtOH[c]	23.7 %
6	DABCO	50% EtOH[c]	23.04 %
7	Piperidine	50% EtOH[c]	21.66 %
8	Triethylamine	50% EtOH[c]	22.15 %
9	DABCO	EtOH[d]	12.07 %
10	K_2CO_3	DMF[c]	44.04 %
11	Piperidine	DMF[c]	33.75 %
12	Triethylamine	DMF[c]	12.72 %
13	DABCO	DMF[c]	36.79 %
14	DABCO	DMF[d]	51.82 %

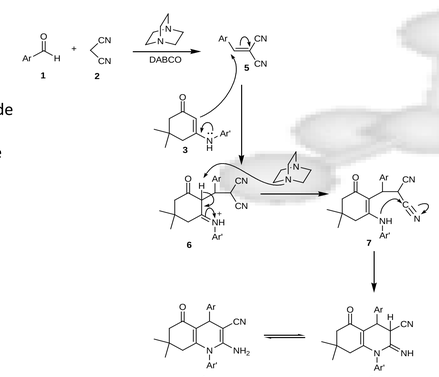
Generalization Reactions



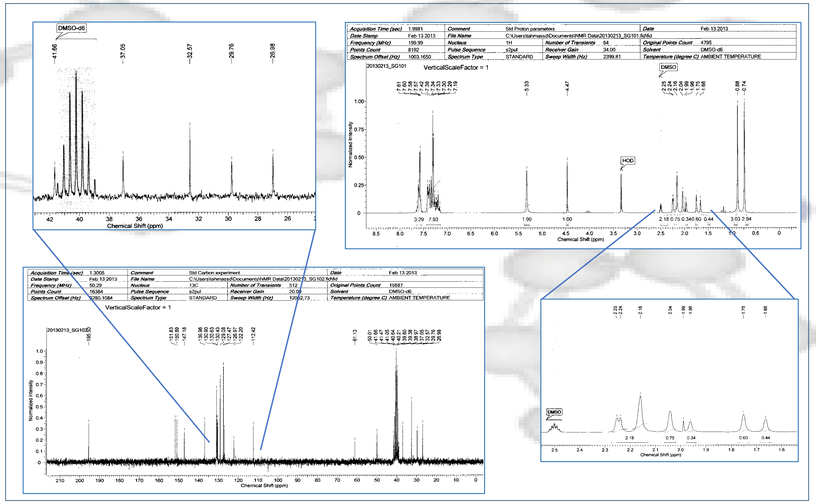
Product	Ar	Ar′	Yeild	M.P.
4a	C_6H_5	C_6H_5	52%	209-211°C
4b	4-Me C_6H_4	C_6H_5	45%	207-208°C
4c	4-MeO C_6H_4	C_6H_5	53%	225-226 °C
4d	4-Cl C_6H_4	C_6H_5	68%	252-254 °C
4e	4-NO_2 C_6H_4	C_6H_5	66%	272-275 °C
4f	4-Br C_6H_4	C_6H_5	81%	259-261 °C
4g	3-NO_2 C_6H_4	C_6H_5	83%	271-273 °C
4h	3-Cl C_6H_4	C_6H_5	81%	237-240 °C
4i	4-Br C_6H_4	4-Br C_6H_4	91%	272-276 °C
4j	3-NO_2 C_6H_4	4-Br C_6H_4	90%	240-246 °C
4k	4-Cl C_6H_4	4-Me C_6H_4	60%	243-247 °C
4l	4-Br C_6H_4	4-Me C_6H_4	66%	261-263 °C
4m	3-NO_2 C6H4	4-Me C_6H_4	57%	282-285 °C
4n	3-Cl C_6H_4	4-Me C_6H_4	60%	211-219 °C

Mechanism

- Knoevenagle condensation between malononitrile (2) and aromatic aldehyde (1) to form alkene **5**.
- **DABCO** catalyzes this reaction, and the removal of the hydrogen from intermediate 6.
- Alkene **5** reacts with enaminone **3** to from Intermediate **6**
- Cyclization through Michael addition forms intermediate **8**
- Tautomerization forms product **4**.



Spectral Data of N-arylquinolines



Conclusion

During the standardization process we found that DMF worked best at room temperature. This coupled with DABCO gave the highest yield of the product. While substituting benzaldehyde derivatives in the synthesis reaction, electron withdrawing groups seemed to fair better than the electron donating groups, with the exception of the two hydroxybenzaldehydes. The use of different enaminones with the benzaldhydes is a future goal, which will aid in determining the role of the catalyst as well as aryl substituents.

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