Pergamon

Tetrahedron Letters, Vol. 35, No. 37, pp. 6811-6814, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01434-5

Synthesis of a New Generation Reverse Transcriptase Inhibitor via the $BCl_3/GaCl_3$-induced Condensation of Anilines with Nitriles (Sugasawa Reaction).

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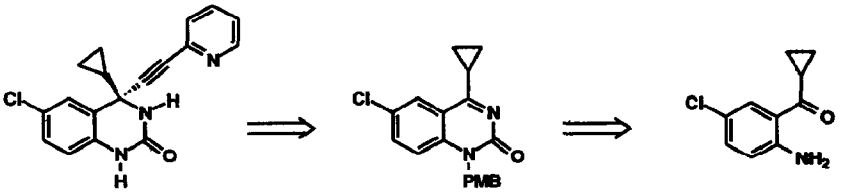
Summary: The synthesis of 1 was achieved in high overall yield through a mechanism-based improvement of the preparation of o-acyl anilines.

The rapid spread of Human Immunodeficiency Virus, the causative agent for AIDS, has prompted an intensive effort in the search for a cure or treatment of this devastating disease. Control of the reproductive cycle of the virus by inhibition of Reverse Transcriptase,[1] the enzyme responsible for transcription of viral RNA onto human DNA, has been a strategy adoped by researchers for drug treatment of the disease (AZT, DDI etc).

Resistance to these drugs by point mutation in the enzyme active site and toxic side-effects have been observed in most patients and this has spurred an effort for the development of new RT inhibitors in an attempt to overcome these problems.[2]

In this letter we disclose the efficient, economic and scaleable synthesis of **1**, one of the new generation RT inhibitors developed in the Merck Research Laboratories.[3]



1 **2** **3**

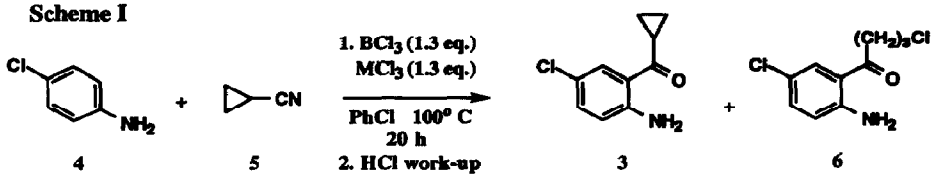
Retrosynthetic analysis indicated that **1** could be prepared by acetylide addition to quinazolinone **2** which in turn can be derived from the cyclopropyl acyl aniline **3**.

The regiospecific synthesis of *o*-acyl anilines is of great synthetic importance in the chemistry of biologically active molecules since it serves as a precursor to a large number of medicinally useful heterocyclic skeletons.[4] Despite their usefulness, synthetic methods leading to *o*-acyl anilines are lacking; the known procedures give low yields under harsh reaction conditions that are not amenable to scale-up.[5]

The most promising procedure for the synthesis of **3** appeared to be the one developed by Sugasawa,[6] in which an aniline was condensed with a nitrile in the presence of BCl_3 and $AlCl_3$ to give after hydrolysis the desired *o*-acyl aniline regiospecifically. Despite its high selectivity, the reaction suffers from low yields due to incomplete conversion. Indeed, when *p*-chloroaniline (**4**) was reacted with cyclopropyl nitrile (**5**) (Scheme I) under the Sugasawa conditions, the desired product was obtained in 30-40% yield along with the cyclopropane opened product **6** (10-20%).

In order to improve the synthetic utility of this reaction, NMR studies were conducted that identified the existence of a "super complex" intermediate, **7** (see preceding paper).[7]

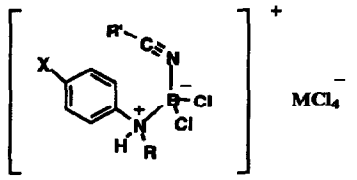
Scheme I



4 **5** **3** **6**

1.2 eq.	1.0 eq.	M= **Al**	30-40%	10-20%
2.0 eq.	1.0 eq.	M= **Ga**	74%	< 7%

These studies clearly showed that: (a) the second Lewis acid was acting as a chloride ion abstractor;[8] and (b) the reason for the low conversion was the generation of the anilinium hydrochloride salt of the starting aniline.

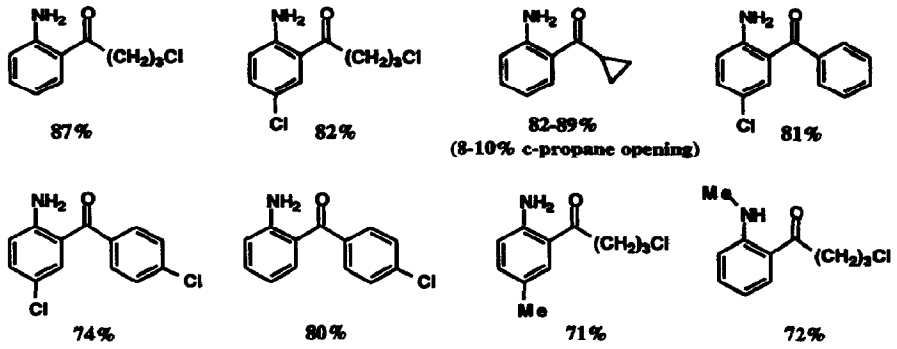


7

The first problem was solved by using $GaCl_3$[9] as the second Lewis acid while overcoming the second problem required using 2 equivalents of the reactant aniline.[10] Following this protocol we were able to double the yield of **3** while forming ≤ 7% of **6** (Scheme I).[11] The generality of the methodology was tested on a number of aliphatic or aromatic nitriles. The products and isolated yields from these reactions are shown in Scheme II, where 2 equivalents of aniline were used in all cases. The workup of the reaction was also dramatically improved; two easily separable homogeneous layers result after an aqueous HCl quench. By contrast, the $AlCl_3$ procedure produced slurries that caused operational difficulties on large scale.

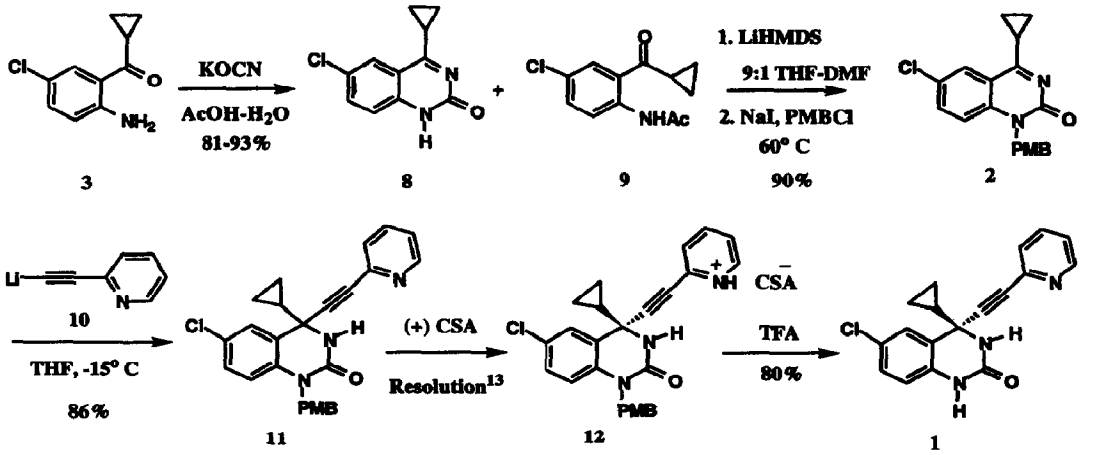
Treatment of ketone **3** (Scheme III) with KNCO in 10:1 AcOH-H_2O at 9°C for 1.5 hours followed by addition of H_2O effected precipitation of the product, **8**, in 81-93% yield along with 5-10% of the acetate **9**. The reaction time and temperature were important factors in minimizing the formation of **9**. Protection of **8** was achieved in high yield (90%) by reaction with *p*-methoxybenzylchloride (PMBCl) in the presence of LiHMDS and NaI in 9:1 THF-DMF at 60°C. This solvent system minimized O-alkylation (<3% vs 10-12% in DMF alone), while NaI was essential for complete consumption of the reactants.

Scheme II



Incorporation of the acetylenic pyridine moiety was accomplished by addition of **2** to a solution of the lithio acetylide **10** (prepared at -78°C by addition of n-BuLi to commercially available 2-ethynylpyridine) in THF at -78°C. The mixture was warmed to -15°C for 17 hours to give after extractive workup and crystallization (4:1 hexanes - EtOAc), the product **11** in 86% yield.[12] Resolution of **11** has been accomplished by crystallization of the (+) camphorsulfonic acid (CSA) salt, **12**.[13] Weaker acids were not useful due to the low basicity of the pyridine nitrogen (pKa ~3, experimentally determined). Enantiomerically pure **1** was isolated in 80% yield by deprotection with trifluoroacetic acid.

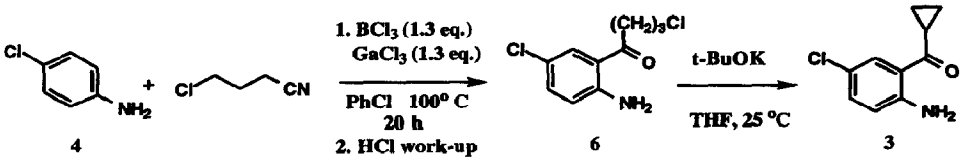
SCHEME III



In conclusion, a short synthesis of the RT inhibitor **1** was accomplished via a mechanism-based improvement of the synthesis of *o*-acyl anilines.

References and Notes

1. Mitsuya, H.; Yarchoan, R.; Broder, S. *Science*, **1990**, *249*, 1533.
2. (a) Fischl, M. A.; et al. *N. Engl. J. Med.* **1987**, *317*, 185-191. (b) Lambert, J. S.; Seidlin, M.; Reichman, R.C.; Plank, C. S.; Laverty, M.; Morse, G. D.; Knupp, C.; McLaren, C.; Pettinelli, C.; Valentine, F. T.; Dolin,R. *N. Engl. J. Med.*, **1990**, *322*, 1333-1345. Richman, D. D.; Fischl, M. A.; Grieco, M. H.; Gattlieb, M. S.; Volberding, P. A.; Laskin, O. L.; Leedom, J. M.; Groopman, J. E.; Mildvan, D.; Hirsch, M. S.; Jackson, G. G.; Durack, D. T.; Nusinoff-Lehrman, S.; and the AZT Collaborative Working Group. *N. Engl. J. Med.*, **1987**, *317*, 192-197.
3. Tucker, T.J.; Lyle, T.A.; Wiscount, C.M.; Britcher, S.F.; Young, S.D.; Sanders, W.M.; Lumma, W.C.; Goldman, M.E.; O'Brien, J.A.; Ball, R.G.; Homnick, C.F.; Schleif, W.A.; Emini, E.A.; Huff, J.R., Anderson, P.S. *J. Med. Chem*, **1994**, *37*, 0000.
4. *o*-Acyl anilines serve as intermediates for the synthesis of acridones, 1,4-Benzodiazepines, cinnolines, fluorinones, indazoles, indoles, quinazolinones, quinolines etc. See references 1-7 in reference 6a.
5. (a) Sternbach, L.H.; Fryer, R.I.; Metlesics, W.; Sach, G.; Stempel, A.J.; *J. Org. Chem.* **1962**, *27*, 3781. (b) Archer, G.A.; Sternbach, L.H. *Chem. Rev.* **1968**, 755. (c) Sternbach, L.H. *Angew.Chem. Int. Ed. Engl.* **1971**, *10*, 34. (d) *o*-Acylation by ortho-metallation followed by reaction with an aromatic nitrile has been reported: Fuhrer, W.; Gschwend, H.W.; *J. Org. Chem.* **1979**, *44*, 1133. Muchowski, J.M. Venuti, M.C. *ibid*, **1980**, *45*, 4798. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. In our hands attempts to acylate the N-Boc protected **4** with nitrile **5** gave none of the desired product **3** presumably due to deprotonation of **5** by the orthometallated dianion.
6. (a) Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* **1978**, *100*, 4842. (b)Sasakura, K.; Terui, Y.; Sugasawa, T. *Chem. Pharm. Bull.* **1985**, *33*, 1836 and references therein.
7. Douglas, A.W.; Abramson, N.L.; Houpis, I.N.; Karady, S.; Molina, A.; Xavier, L.C.; Yasuda, N. *Tetrahedron Lett.* Preceding paper this issue.
8. *Friedels-Craft and Related Reactions* Vol 1; Olah, G.H. editor; Interscience, New York, **1963**, p 201.
9. The use of $GaCl_3$ / $AgClO_4$ in the acylation of anisoles has been reported: (a) Harada, T.; Ohno, T.; Kobayashi, S.; Mukaiyama, T. *Synthesis* **1991**, 1216. (b) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Suda, S.; Kobayashi, S. *Chem. Lett.* **1991**, 1059.
10. Bases such as Et_3N, DIEA, K_2HPO_3, N,N-dimethyl-*p*-bromoaniline were not useful in preventing hydrochloride formation. No condensation product was obtained when these bases were added to the reaction mixture. Ga^0 and In^0 metal were also used as "bases" with no success.
11. The desired product **3** can also be obtained by the two-step procedure shown below:



4 — 2.0 eq. — 1.0 eq. — 6 — 82% — 3 — 97%

12. In the earlier procedures[3] the addition of the acetylide to **2** was performed by pre-complexation of the quinazolinone with $Mg(OTf)_2$ in order to avoid reduction. In our hands no such precaution was required since the anion **10** added smoothly to **2** to give **11** in high yield.
13. Yasuda, N.; DeCamp, A.; Grabowski, E.J.J. Unpublished results. Patent pending.

(*Received in USA* 20 *June* 1994; *revised* 20 *July* 1994; *accepted* 22 *July* 1994)