HETEROCYCLES, Vol. 67, No. 2, 2006, pp. 585 - 588. © The Japan Institute of Heterocyclic Chemistry
Received, 18th August, 2005, Accepted, 14th October, 2005, Published online, 18th October, 2005. COM-05-S(T)76

SYNTHESIS OF DIHYDROQUINOLINONES ANGULARLY-FUSED TO TETRAHYDROBENZAZEPINONE RINGS*

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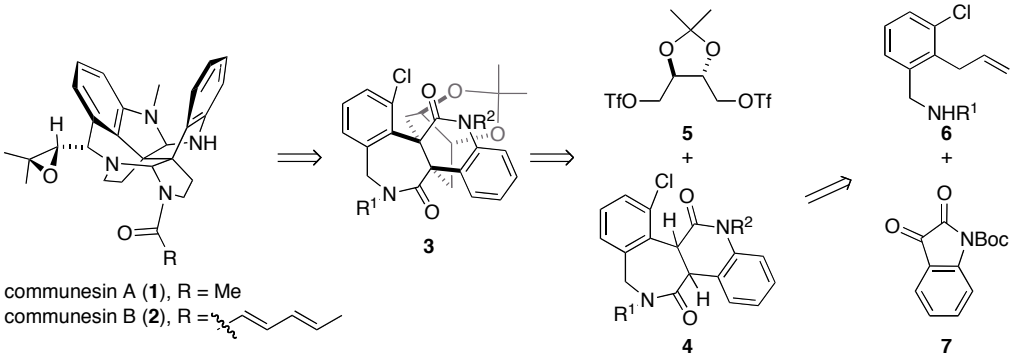
Abstract – Acylation of the dimethylaluminum derivative of a hindered secondary amine with *N*-Boc isatin, and sequential intramolecular aldol condensation–lactamization, are key steps in the first synthesis of tetrahydro-4b*H*-6,12-diazabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-5,11-diones.

*Dedicated to Professor Barry M. Trost on the occasion of his 65th birthday

In the course of total synthesis investigations targeting communesins A (**1**) and B (**2**),[1] we recently examined the possibility of constructing the contiguous quaternary carbons centers of these alkaloids in one step by the union of dienolate derivatives of tetrahydro-4b*H*-6,12-diazabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-5,11-diones (**4**) and the enantiopure, tartrate-derived, dielectrophile (**5**).[2,3] As the 6,12-diazabenzo[3,4]cyclohepta[1,2-*a*]naphthalene ring system is extremely rare, and our method for assembling this ring system from isatin derivative (**7**) has several steps of potentially more general interest, we report herein the concise synthesis of tetracyclic dilactams (**4**) developed during these studies.

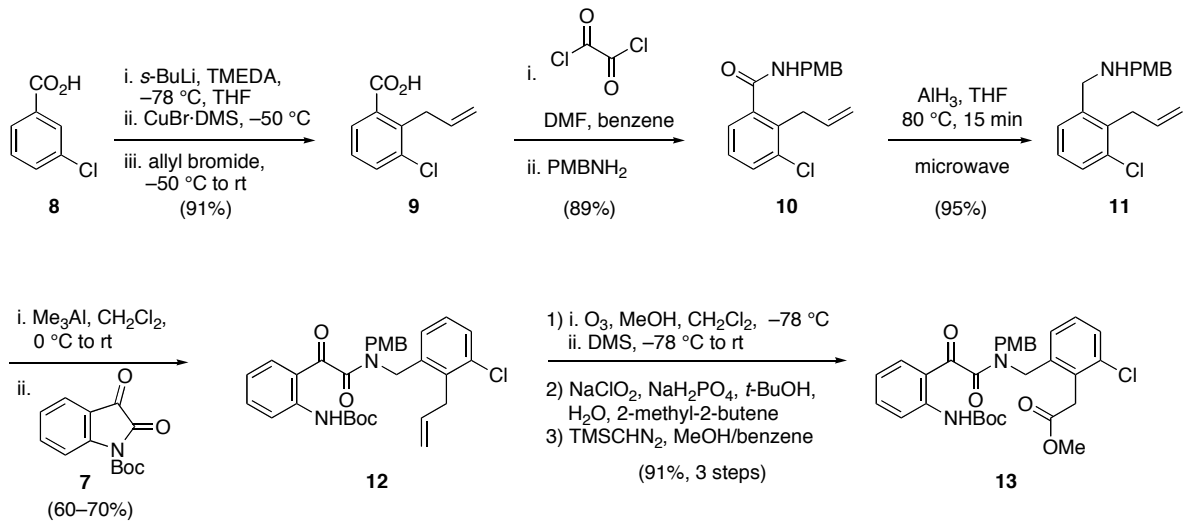
Scheme 1



The method can be illustrated by the synthesis of tetrahydro-4b*H*-6,12-diazabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-5,11-dione (**16**), which begins with carboxylate-directed *ortho*-lithiation of 3-chlorobenzoic acid (**8**) (Scheme 2). After conversion of the aryllithium intermediate to a cuprate derivative, reaction with allyl bromide provided 2-allyl-3-chlorobenzoic acid (**9**) in 91% yield

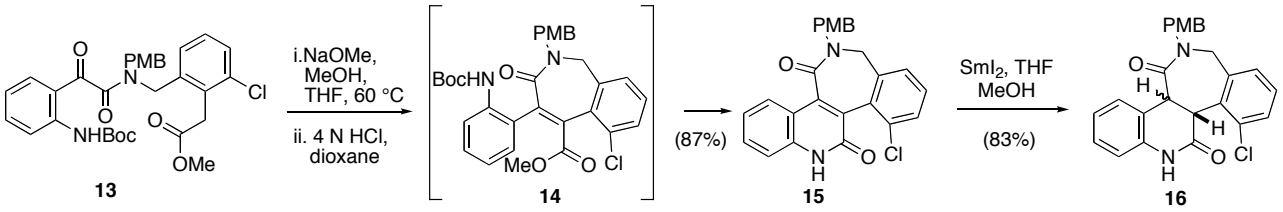
(Scheme 2).[4,5] Straightforward elaboration of acid (**9**) to amide (**10**), followed by reduction of this intermediate with alane,[6] optimally achieved by heating in a microwave reactor at 80 °C, provided benzylamine (**11**) in 77% overall yield from 3-chlorobenzoic acid.

Scheme 2



A pivotal step in the construction of (**16**) is acylation of amine (**11**) with Boc-protected isatin (**7**) to give α-keto amide (**12**) (Scheme 2). Although the reaction of *N*-acyl- and *N*-acyloxyisatins with a variety of unhindered amines has been reported, the hindered secondary amine (**11**) did not react with isatin (**7**) under conditions previously employed in similar reactions with pyrrolidine derivatives (*i*-Pr_2NEt, THF, room temperature).[7] The use of higher temperatures, stronger bases, or Lewis acid catalysts also failed to promote this acylation. However, in a reaction akin to a Weinreb aminolysis,[8] sequential reaction of secondary amine (**11**) with trimethylaluminum and isatin (**7**) provided the desired α-keto amide (**12**) in 60–70% yield. In three additional routine steps, requiring only a single purification, this product was converted in high yield to ester derivative (**13**).

Scheme 3



In a noteworthy intramolecular aldol condensation–lactamization sequence, intermediate (**13**) was transformed in two additional steps to tetrahydro-4b*H*-6,12-diazabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-5,11-dione (**16**) (Scheme 3). After screening several bases (NaH, piperidine, NaOMe, NaO*t*-Bu, DBU, LHMDS, LDA, and KOH) it was found that the intramolecular aldol condensation was

best realized by the reaction of **13** with 4 equiv. NaOMe in dry MeOH at 60 °C.[9] When this reaction was acidified at room temperature with anhydrous HCl, tetracyclic quinolinone derivative (**15**) was isolated in 87% yield. Subsequent reduction of **15** with excess SmI_2 in THF/MeOH at room temperature gave dihydro derivative (**16**) in 83% yield as a 1:1 mixture of epimers.

In conclusion, a direct synthesis of tetrahydro-4b*H*-6,12-diazabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-5,11-dione (**16**) is described. As **16** suffers from severe steric interactions between its chlorine substituent and the adjacent carbonyl group, this general strategy should be useful for the synthesis of many related sterically congested structures as well as other fused quinolinones. The use of trimethylaluminum as a mild reagent for the activation of hindered amines for acylation by isatin derivatives is likely also of more general utility.

EXPERIMENTAL

Acylation of a hindered aluminum amide with *N*-Boc-isatin. Preparation of [2-(2-allyl-3-chlorobenzyl)-(4-methoxybenzyl)aminooxalyl]phenyl)carbamic acid *tert*-butyl ester (12). To a CH_2Cl_2 (125 mL) solution of **11** (4.26 g, 13.92 mmol) at 0 °C was added a toluene solution of Me_3Al (7.3 mL, 2.0 M). The resulting solution was allowed to warm to rt. After 1 h, a CH_2Cl_2 solution of isatin derivative (**7**) (20 mL, 0.73 M) was added rapidly by syringe, giving a deep red solution. This solution was maintained at rt for 12 h at which time it was cooled to 0 °C and carefully quenched with 5 N NaOH (40 mL). The resulting mixture was stirred rapidly at rt for 1 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by silica gel chromatography (5:1 hexanes/EtOAc–3:1 hexanes/EtOAc) to yield 4.69 g (61%) of **12** as a colorless foam: (500 MHz, $CDCl_3$, a 1:1.4 mixture of rotamers, only major peaks reported) 10.69 (s, 1H); 10.54 (s, 0.74H); 8.63 (d, *J* = 8.5 Hz, 1H); 8.57 (d, *J* = 8.5 Hz, 0.74H); 7.83 (dd, *J* = 8.0, 1.4 Hz, 1H); 7.73 (dd, *J* = 8.0, 1.4 Hz, 0.74); 7.66 (t, *J* = 7.2, 1H); 7.62 (t, *J* = 7.2 Hz, 0.74H); 7.43 (d, *J* = 7.0 Hz, 1H); 7.40 (dd, *J* = 7.6, 1.5 Hz, 0.74H); 7.34–7.26 (m, 4.5H); 7.21 (d, *J* = 7.1 Hz, 1H); 7.16–7.12 (m, 3.2H); 7.08 (t, *J* = 7.2 Hz, 1H); 6.97 (d, *J* = 8.6 Hz, 1.6H); 6.88 (d, *J* = 8.6 Hz, 2H); 5.89 (dddd, *J* = 15.9, 10.3, 5.7, 5.7 Hz, 1H); 5.76 (dddd, *J* = 15.7, 10.6, 5.5, 5.5 Hz, 0.74H); 5.05 (dd, *J* = 10.2, 1.5 Hz, 1H); 4.95 (dd, *J* = 10.2, 1.4 Hz, 0.74H); 4.89 (dd, *J* = 17.1, 1.5 Hz, 1H); 4.77 (s, 2H); 4.71–4.66 (m, 2.5H); 4.41 (s, 1.7H); 4.36 (s, 2H); 3.88 (s, 2.3H); 3.83 (s, 3H); 3.57 (d, *J* = 5.7 Hz, 2H); 3.39 (d, *J* = 5.5 Hz, 1.6H); 1.62 (s, 9H); 1.58 (s, 6.7H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers, only major peaks reported) δ 194.5, 194.2, 166.8, 166.6, 159.4, 159.3, 152.5, 152.4, 143.4, 143.3, 136.5, 136.4, 135.6, 135.6, 135.3, 135.2, 135.1, 134.8, 133.9, 133.5, 133.4, 133.3, 129.9, 129.2, 129.0, 128.9, 127.62, 127.55, 127.5, 126.4, 126.0, 125.5, 121.1, 118.94, 118.88, 117.2, 117.1, 115.8, 115.6, 114.1, 114.0, 80.92, 80.86, 55.10, 55.08, 50.1, 47.3, 46.5, 43.4, 33.2,

32.8, 28.1, 28.0; IR (film) 3298, 2981, 1734, 1653, 1648, 1581, 1450, 1148 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{33}N_2O_5Cl$ (M+Na) *m/z* 571.1976; found 571.1987.

ACKNOWLEDGMENTS

This research was supported by NIGMS (GM-30859). E.A.P was supported in part by an ACS Organic Division Fellowship funded by Pfizer and a Bristol-Myers Squibb Graduate Fellowship in Organic Chemistry. NMR and mass spectra were determined at UC Irvine with instruments purchased with the assistance of the NSF and NIH shared instrumentation programs.

REFERENCES AND NOTES

1. A. Numata, C. Takahashi, Y. Ito, T. Takada, K. Kawai, Y. Usami, E. Matsumura, M. Imachi, T. Ito, and T. Hasegawa, *Tetrahedron Lett.*, 1993, **34**, 2355.
2. E. A. Peterson, Ph. D. Dissertation, University of California, Irvine, 2005.
3. For a brief discussion of our use of this strategy to prepare polyindoline alkaloids, see: E. A. Peterson and L. E. Overman, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 11943.
4. In our hands, this sequence was superior to the reported direct allylation of the aryllithium intermediate.[5]
5. B. Bennetau, J. Mortier, J. Moyroud, and J-L. Guesnet, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1265.
6. N. M. Yoon and H. C. Brown, *J. Am. Chem. Soc.*, 1968, **90**, 2927.
7. C. Y. Poon and P. Chiu, *Tetrahedron Lett.*, 2004, **45**, 2985.
8. A. Basha, M. Lipton, and S. M. Weinreb, *Tetrahedron Lett.*, 1977, **18**, 4171.
9. It is imperative to exclude adventitious water during the aldol condensation reaction because the presence of hydroxide can lead to decomposition of the α-ketoamide to give formamide (**A**), presumably by a sequence similar to a Haller-Bauer reaction.