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An Expedient Route to the Tricyclic Pyridone Derivative Ro 41-3696, a Novel Non-Benzodiazepine Sleep Inducer

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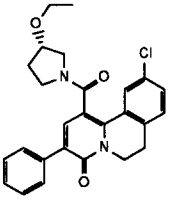
Abstract: A short, technical synthesis of (S)-10-chloro-1-(3-ethoxypyrrolidin-1-yl)-3-phenyl-6,7-dihydro-4H-benzo[a]-quinolizin-4-one (**1**) from 2-(4-chlorophenyl)ethylamine (**2**) is described.

The benzo[a]chinolizinone derivative **1** (Ro 41-3696) is a promising candidate as an effective non-sedative hypnotic for the induction and maintainance of sleep.[1a] This compound represents the culmination of an extensive research program undertaken at Roche aimed at developing a new class of non-benzodiazepine heterocycles for the treatment of anxiety and sleep disorders.[1] Despite a considerable effort to successfully develop a technical synthesis based on the original laboratory route,[1a] the overall yield could not be significantly ameliorated (from ca. 10 to 20%). Furthermore, the procedure would not have been amenable to scale-up and production. Attention was therefore directed towards an alternative approach and a more viable route was established (Scheme).[2]



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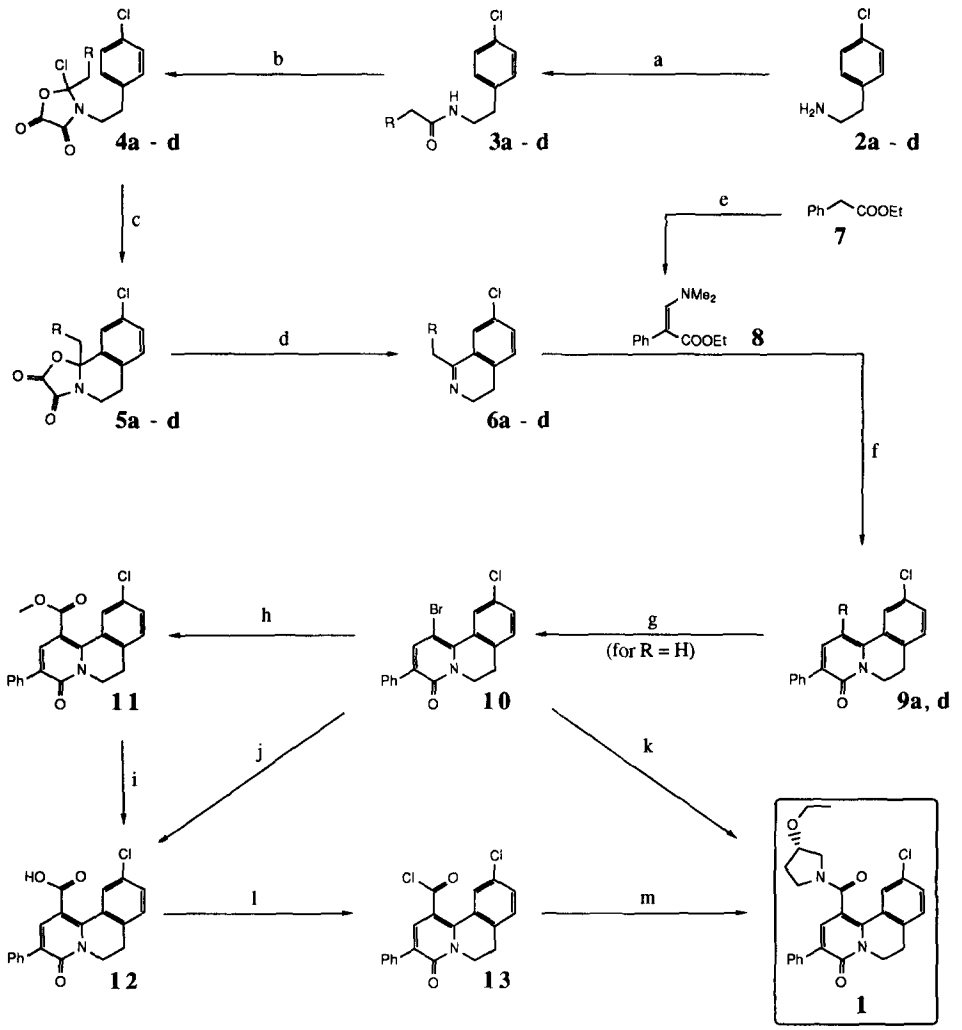
Direct manipulation of the acetamide **3a** derived from the commercially available amine **2** (1.05 eq. Ac_2O, 100%) to construct the second ring element under Bischler-Napieralski type conditions was unsuccessful. However, this difficulty, often encountered in the cyclization of un- or deactivated arylamides, was overcome by the application of a recently disclosed process.[3] Thus, activation of the amide functional group of **3a** with $(COCl)_2$ gave the chlorooxazolidinedione intermediate **4a** which behaved in the presence of $FeCl_3$ as a superior acylating agent (*via* the acyliminium species) to produce the oxalyl-adduct **5a** in 85-90% yield (over multiple runs).

Methanolysis of the crude product (3 eq. conc. H_2SO_4) released the cyclic oxalyl-protecting group and provided the known dihydroisoquinoline **6a**[4] in 80-85% overall yield from amine **2**.

Scheme



a: R = H; **b**: R = MeCOO; **c**: R = Br; **d**: R = Me

Reagents: a) 1.05 eq. Ac_2O/tol, r.t./0.75 h, 100%; b) 1.1 eq. $(COCl)_2/CH_2Cl_2$, r.t./1.5 h; c) 1.2 eq. $FeCl_3$, r.t./16 h, 85-90% from **3a**; d) 3 eq. conc. H_2SO_4/MeOH, 65 °C/24 h, 80-85% (isol) or AcOH, 110 °C/1 h; e) 1.4 eq. DMF-diethylacetal, 130-150 °C/ 22 h, 95%; f) 1.1 eq. **8**/AcOH, 95 °C/3 h, 70-75% (isol) from **6a**; g) 1.25 eq. NBS/AcOH, 95 °C/1 h, 75-80% (through process) from **5a**; h) 0.05% $Pd(OAc)_2$/dppp/MeOH, 2 eq. $KHCO_3$, 10 bar CO, 95 °C/8 h, 95%; i) 2.5 eq. KOH/aq. MeOH, 75 °C/4 h, 90-95% from **10**; j) 1% $Pd(OAc)_2$/dppp, 2 eq. $KHCO_3$/aq. DMSO, 20 bar CO, 95 °C/ 20 h, 85-90%; k) 1.05 eq. (S)-3-ethoxypyrrolidine (**14**)/1% $Pd(OAc)_2$/dppp, 4 eq. K_2CO_3/MeCN, 20 bar CO, 95 °C/24 h, 80-85%; l) 1.1 eq. $(COCl)_2$/cat. DMAP[9]/EtOAc, 60 °C/3 h, 100%; m) 1.1 eq. (S)-3-ethoxypyrrolidine/1.2 eq. NEt_3/tol, r.t./4 h, 80-85% from **12**.

Introduction of the pyridone ring was effected by a novel condensation reaction of the dihydroisoquinoline **6** with the amino acrylate **8** (AcOH, 70-75%) which was readily prepared (1.4 eq. DMF-diethylacetal, 95%) from ethyl phenyl acetate (**7**).[5] Treatment of the initially formed quinolizinone **9a**[10] *in situ* with NBS (1.25 eq., 100%) afforded the bromide **10**[10] which crystallized directly from the reaction mixture upon dilution with water in 70-75% yield from precursor **6a**. The conversion of oxazoledione **5a** to the dihydroisoquinoline **6a** could also be performed efficiently in refluxing AcOH and indeed, this deprotection step, involving the loss of CO_2 and CO, could be carried out in the presence of the amino acrylate **8** to provide, after subsequent addition of NBS, the bromide **10** in 75-80% yield in a one pot, three step procedure from the oxazoledione **5**. More reliable yields[6] were realized when the aminoacrylate was added *after* the transformation of the oxazoledione **5** to the dihydroisoquinoline **6** due to its thermal instability towards hot acetic acid.

Unfortunately, no method could be found to effect the conversion of the amidoester **3b**, eg. *via* **4b** & **5b**, to the dihydroisoquinoline **6b**,[7] thus enabling the ester group to be present from the outset of the synthesis. Attempts at introducing the ester group into the dihydroisoquinoline **6a** were also thwarted as N- rather than C-acylation always predominated. Direct acylation of pyridone **9a** by a variety of methods ($ClCOOCH_3 \pm FeCl_3$ or BF_3. Et_2O, $ClCONMe_2/AlCl_3$, $(COCl)_2 \pm AlCl_3$ or $FeCl_3$ or $CoCl_2$, Ac_2O or $AcCl \pm CoCl_2$, DMF-$POCl_3$, CO_2, $CO/Pd(OAc)_2$-$K_2S_2O_8$) to produce the ester **11**, the acid **12** or related useful products, were similarly unavailing.

Inclusion of the bromine moiety at the beginning of the reaction sequence would also have saved one operational step but in view of the only moderate yield obtained for the cyclization of the bromoacetamide **3c**-> **4c**-> **5c** (Scheme), this approach was abandoned. The carbonyl-carbon atom presumably could have been fashioned in a masked form as a methyl group by subjecting the propanamide **3c** to a similar series of reactions, i.e. **4d**-> **5d**->**6d**->**9d**, as with the acetamide **3a** (Scheme). Oxidation of the methylpyridone **9d** would then have delivered the acid **12**. However, owing to the success of a far more facile route (*vide infra*), this possibility was not examined in detail.

The bromine atom of intermediate **10** served as a handle for the incorporation of the carboxyl-moiety *via* a palladium catalyzed carbonylation reaction.[8] In MeOH, this step proceeded smoothly (0.05% $Pd(OAc)_2$/dppp) and provided the ester **11**[1a] in 95% yield. Saponification of this ester was carried out directly by the addition of aqueous KOH to the crude carbonylation mixture and afforded the acid **12**[1a] in 90-95% yield for the two steps. Acid **12** was converted into the acid chloride **13** and treated with (*S*)-3-ethoxypyrrolidine[1a] delivering the product **1** in 80-85% overall yield after recrystallization and thus establishing an overall yield of 45-50% for the entire synthetic sequence.

In contrast to the preceding methoxycarbonylation reaction, hydroxycarbonylation of bromide **10** required a much higher loading of catalyst to achieve an acceptable yield of the acid **12** (1% $Pd(OAc)_2$/dppp, 85-90%). However, ~10% of the reduced compound **9a** was also formed as the major side product compared to <0.5% for the alternative reaction **10** -> **11**. A similar observation was made in the direct amidation reaction of bromide **10** with (S)-3-ethoxypyrrolidine which furnished the amide **1** in 80-85% yield. Of practical relevance for a technical synthesis of the amide **1** was the fact that all byproducts from the carbonylation reactions could be removed more readily at the stage of the acid **12** (as the potassium salt) rather than after the final product **1** where the presence of any impurity significantly affected the recovery yield upon recrystallization.

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5. a) Biere H.; Russe, R. *Tetrahedron Lett.*, **1979**, 1361-1362; see also b) Gupton, J. T.; Lizzi, M. J.; Polk, D. *Synth. Commun.*, **1982**, *12*, 939-946. c) Wasserman, H. H.; Ives, J. L. *J. Org. Chem.*, **1985**, *50*, 3573-3580. d) Schuda, P. F.; Ebner, C. B.; Morgan, T. M. *Tetrahedron Lett.*, **1986**, *27*, 2567-2570. The parallel reaction of methyl phenyl acetate with DMF-dimethylacetal was in contrast significantly slower due to the lower boiling point of the acetal (bp. 104 °C cf. 130 °C for the diethyl derivative) and required a much larger excess of this reagent (≥3 eq.) to drive the reaction to completion.
6. Alternative reagents to **8** such as methyl formyl- or methoxymethylenephenyl acetate were inferior options due to their lower yielding syntheses (from methyl phenyl acetate) and their use for the preparation of the pyridone **9a**.
7. The amidoester **3b** proved to be recalcitrant towards cyclization under all of the following conditions: $(COCl)_2$; $FeCl_3/ClCH_2CH_2Cl$/r.t.-80 °C, $AlCl_3/Cl_2CHCHCl_2$ or $MeNO_2$/r.t.-reflux, $POCl_3 \pm SnCl_4$ or P_2O_5/100 °C $P_2O_5 \pm ZnCl_2$/PPA/100-180 °C and $P_2O_5/Cl_2CHCHCl_2$ or $MeSO_2OH$/r.t.-110 °C.
8. The corresponding chloride was much less reactive and regioselective than the bromide **10** whereas the iodo analogue was not viewed as an economically viable alternative. Methods other than carbonylation (eg. Mg or $nBuLi/Me_2CO_3$ or $ClCOOCH_3$ or CO_2) failed to yield the ester **11** or acid **12** from bromide **9**.
9. With DMF instead of DMAP as catalyst, traces of the dimethylamide derivative of **12** were sporadically detected in the crude final product and this interfered with the purification of **1**.
10. All new compounds gave correct microanalytical and spectroscopic data. Selected physical data:

    9a: mp. 166-167°C (iPrOH/H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 3.00 (t, 2H, H-7), 4.36 (t, 2H, H-6), 6.76 (d, 1H, H-1), 7.24 (d, 1H, H-8), 7.35 (dd, 1H, H-9), 7.58 (d, 1H, H-2), 7.76 (d, 1H, H-11), 7.33-7.72 (m, 5H, ArH). IR (KBr) ν cm^{-1} 1636, 1592, 1547, 1480, 786, 756, 696. EIMS m/z 307 (M^+).

    10: mp. 186-187°C (AcOH/H_2O); ^1H NMR 400 MHz, $CDCl_3$) δ 2.92 (t, 2H, H-7), 4.27 (t, 2H, H-6), 7.24 (d, 1H, H-8), 7.45 (dd, 1H, H-9), 7.77 (s, 1H, H-2), 7.36-7.75 (m, 5H, ArH), 8.37 (d, 1H, H-11). IR (KBr) ν cm^{-1} 1637, 1583, 1526, 1476, 787, 733, 695. EIMS m/z 387 (M^+).

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