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Synthesis of Tricyclic Pyridones by Radical Cyclization

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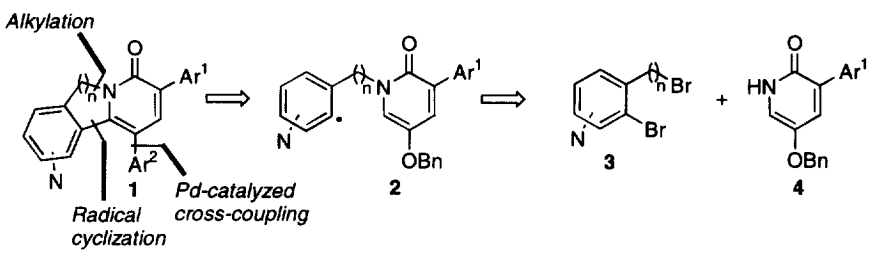
Abstract: A general and novel route for the synthesis of tricyclic pyridones by 5-, 6- and 7-*exo-trig* radical cyclization is described. The use of Pd-catalyzed cross-coupling reactions to introduce functionality at the 5-position of a pyridone is also presented.

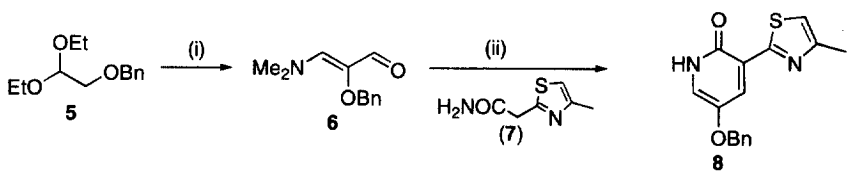
The synthesis of tricyclic pyridones has been the subject of several recent reports, most of which are concerned with the construction of the BCD ring portion of the anti-tumor agent (+)-camptothecin,[1] or the preparation of benzodiazepine receptor ligands.[2] Certain tricyclic pyridones have recently been identified as subtype-selective $GABA_A$ receptor agonists, and therefore have potential as non-sedating anxiolytics.[3]

One direct and general way to construct tricyclic pyridones **1** was envisaged to be by radical-mediated cyclization of appropriately functionalized N-alkyl pyridones **2**, themselves readily available from the two monocyclic precursors **3** and **4** (Scheme 1). Herein we report the successful completion of this strategy.

Scheme 1



The monocyclic pyridone **8** was prepared according to Scheme 2. Thus, treatment of benzyloxyacetaldehyde diethyl acetal (**5**) with PCl_5-DMF resulted in the formation of the vinylogous amide **6**[4] in 43% yield. Base-catalyzed cyclization of **6** with amide **7**[5] led to **8** in 73% yield.[8] Aryl groups other than 4-methylthiazol-2-yl (e.g. phenyl) can also be accommodated in this transformation.



Scheme 2: Reagents and Conditions: (i) PCl_5, DMF, 0-60 °C, 2 h; HCl, 43%; (ii) NaH, MeOH, DMF, 70 °C, 4 h, 73%.

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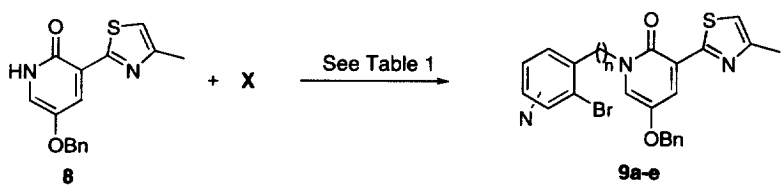
With pyridone **8** in hand, attention was turned to the N-alkylation reaction (Scheme 3). Initially this was achieved by a Mitsunobu reaction (PPh_3-DEAD, THF),[6] which gave acceptable yields for the 5-membered ring precursors **9a-b** (Table 1, Entries 1-2) but low yields for larger ring precursors **9c-e** (Entries 3-5). In these instances (e.g. Entry 6), better yields were obtained using the appropriate alkyl bromide and Curran's LiBr-mediated procedure[7] (NaH, LiBr, THF-DME), specifically developed to promote the N-alkylation of 2-pyridones.[8]

Scheme 3



8 **9a-e**

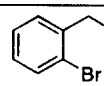
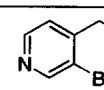
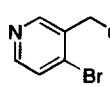
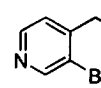
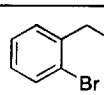
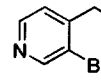
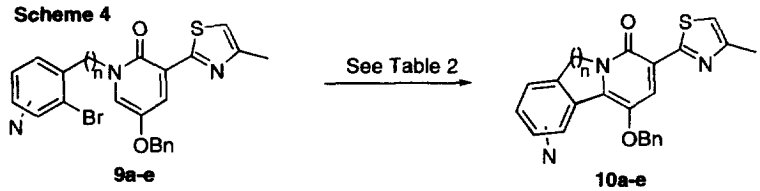
Entry	X	Product (%)	Entry	X	Product (%)
1		**9a** (74%)	4	 (b)	**9d** (17%)
2	 (a)	**9b** (58%)	5	 (c)	**9e** (33%)
3		**9c** (11%)	6	 (d)	**9e** (82%)

Table 1: Reagents and conditions: Entries 1-5: PPh_3, DEAD, ROH, THF, 0-25 °C, 1h; Entry 6: NaH, LiBr, RBr, DME-DMF (4:1), 0-75 °C.

Notes: (a) prepared by (i) bromination of 4-lithio-3-pyridinecarboxaldehyde,[18] (ii) reduction ($NaBH_4$, EtOH, 0 °C); (b) prepared by (i) lithiation of 3-bromo-4-methylpyridine, quenching with $(MeO)_2CO$,[19] (ii) reduction ($LiAlH_4$, Et_2O, 0 °C); (c) prepared by (i) lithiation of 3-bromo-4-methylpyridine, quenching with ethylene oxide;[19] (d) prepared by (i) tosylation of the corresponding alcohol (TsCl, pyridine, $CHCl_3$); (ii) bromination (LiBr, acetone, 0-70 °C).

The results for the key ring-forming step (Scheme 4) are summarised in Table 2. It was found that treatment of a solution of the aryl bromide **9a-e** in refluxing benzene with AIBN and Bu_3SnH resulted in the direct formation of the tricycle **10a-e** in moderate yield, with oxidation of the intermediate radical addition product presumably occurring spontaneously.[6,8] Addition of the AIBN/Bu_3SnH slowly via syringe pump, or degassing the reaction mixture prior to addition of the reagents did not improve the yield. The main side-products were reduced starting material (ca. 10%) or ill-characterized adducts containing AIBN fragments. The isolated yield of product is remarkably independent of substitution in the ring, with 3- and 4-pyridyl radicals forming and reacting smoothly (Entries 2,4,5).[9] A variety of ring sizes is also well tolerated, even in the uncommon 7-*exo-trig* cyclization mode (Entry 5).[10] This reaction could not be extended to include the cyclization of *alkyl* radicals: under these conditions the analogous 3-bromopropylated pyridone did not cyclize efficiently to give the bicyclic pyridone (data not shown). Despite reasonable literature precedent,[11] attempted cyclization of **9a** or **9e** under Heck-type conditions [$Pd(OAc)_2$, PPh_3, K_2CO_3, Et_4NCl] did not yield **10a** or **10e**, resulting instead in unchanged or reduced starting material and/or decomposition.

Scheme 4



9a-e **10a-e**

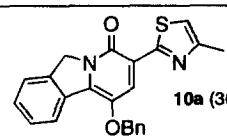
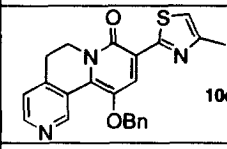
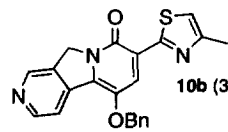
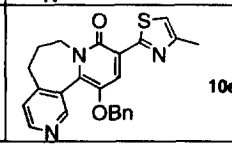
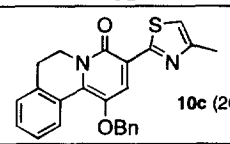
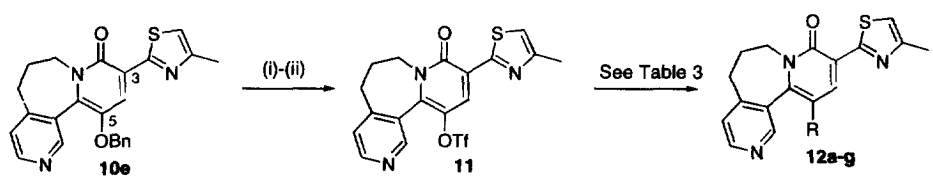
Entry	Product (%)	Entry	Product (%)
1	 **10a** (36%)	4	 **10d** (35%)
2	 **10b** (37%)	5	 **10e** (50%)
3	 **10c** (20%)		

Table 2: Reagents and Conditions: Benzene (0.01 M), AIBN (1 equiv.), Bu_3SnH (2 equiv.), 80 °C.

Attention was then turned to functionalization of the 5-position of the pyridone nucleus, as exemplified with **10e** (Scheme 5). The benzyl protecting group was removed from **10e** with BBr_3 to give the corresponding alcohol, which was treated with Tf_2O and pyridine to form triflate **11**. The debenzylation could also be accomplished by hydrogenolysis (Pd-C, H_2 or Pd-C, NH_4CO_2H), although the yields were much lower.



10e **11** **12a-g**

Scheme 5: Reagents and Conditions: (i) BBr_3, CH_2Cl_2, 0-25 °C, 0.5 h, 89%; (ii) Tf_2O, pyr., CH_2Cl_2, -78-0 °C, 1 h, 73%.

Entry	Reagent	R	Product (%)
1	2-methoxybenzeneboronic acid	2-methoxyphenyl	**12a** (93%)
2	3-methoxybenzeneboronic acid	3- methoxyphenyl	**12b** (76%)
3	4-methoxybenzeneboronic acid	4-methoxyphenyl	**12c** (84%)
4	4-formylbenzeneboronic acid	4-formylphenyl	**12d** (74%)
5	*trans*-PhCH=CHB(OH)2	*trans*-CH=CHPh	**12e** (69%)
6	HC≡CPh	C≡CPh	**12f** (67%)
7	HCO_2H, Et_3N	H	**12g** (60%)

Table 3: Reagents and Conditions: (Entries 1-5): $Pd(PPh_3)_4$ (10 mol%), boronic acid (2 equiv.), 2 M Na_2CO_3(aq)-DME (1:3), 100 °C, 3 h; (Entry 6): $PdCl_2(PPh_3)_2$, Et_3N, DMF, acetylene, 100 °C, 3 h; (Entry 7): Et_3N, $Pd(OAc)_2$, PPh_3, HCO_2H, DMF, 100 °C, 16 h.

Although there are now instances of the Pd(0)-catalyzed arylation of 3- and 4-OTf- pyridones,[12,13] to the best of our knowledge there are no reports concerning the arylation of 5-OTf pyridones.[14] Accordingly, it was pleasing to find that the coupling of **11** with a variety of boronic acids under Suzuki conditions[15] (Table 3,

Entries 1-5) gave the aryl-substituted pyridones **12a-e** in excellent yield. Even quite hindered and electron-deficient boronic acids proved good coupling partners. Heck couplings[16] (e.g. Entry 6) and reduction (Entry 7) were also effective, although Buchwald-Hartwig amination[17] (BINAP, NaO*t*Bu, $Pd(OAc)_2$, toluene) led to reduction of the triflate moiety, and introduction of the amine (benzylamine) at the 2-position of the pyridine ring in 36% yield.

In summary, we have shown that a range of tricyclic pyridones can be rapidly and convergently assembled using (i) pyridone N-alkylation, and (ii) radical-mediated cyclization reactions. These reactions are readily scaled to yield multi-gram quantities of products. We have also shown that the so-derived 5-OTf tricyclic pyridones are excellent substrates for a variety of Pd-catalyzed cross-coupling reactions. These results extend the availability and scope of substituted pyridones in organic chemistry.

Notes and References.

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8. Representative procedures are as follows:

8: 2-(4-Methyl-thiazol-2-yl)-acetamide (0.016 mol), 2-benzyloxy-3-dimethylamino-propenal (**6**) (0.017 mol), NaH (0.032 mol), MeOH (1.3 ml) and DMF (100 ml) were heated at 70 °C for 4 h. The reaction was cooled, acidified with 5.0 N HCl(aq), and poured into water. The resulting precipitate was collected by filtration and dried to give 5-benzyloxy-3-(4-methyl-thiazol-2-yl)-1*H*-pyridin-2-one (**8**) (11.7 mmol, 73%). δ_H (360 MHz; $CDCl_3$) 9.38 (1H, s), 7.47-7.34 (7H, m), 7.09 (1H, s), 5.21 (2H, s), 2.69 (3H, s). **9e:** 5-Benzyloxy-3-(4-methyl-thiazol-2-yl)-1*H*-pyridin-2-one (**8**) (3.3 mmol) was dissolved in DMF (5 ml) and DME (20 ml). The reaction mixture was cooled to 0 °C and treated with NaH (3.5 mmol). After 10 min, the reaction mixture was treated with LiBr (6.6 mmol) and stirred for 15 min at room temperature. The reaction mixture was treated with a solution of 4-(3'-bromopropyl)-3-bromopyridine (5.0 mmol) in DME (5 ml) and then it was heated at 75 °C for 60 h. Aqueous work-up and purification by column chromatography gave the product, 5-benzyloxy-1-[3-(3-bromo-pyridin-4-yl)-propyl]-3-(4-methyl-thiazol-2-yl)-1*H*-pyridin-2-one (**9e**) (2.74 mmol, 82%). δ_H (250 MHz; $CDCl_3$) 8.65 (1H, s), 8.60 (1H, brd), 8.41 (1H, d, J = 7.2), 7.40-7.33 (5H, m), 7.16 (1H, d, J = 7.2), 7.03 (1H, s), 7.00 (1H, d, J = 4.6), 5.02 (2H, s), 4.13 (2H, t, J = 10.4), 2.79-2.72 (2H, m), 2.53 (3H, s), 2.17-2.04 (2H, m). **10e:** 5-benzyloxy-1-[3-(3-bromo-pyridin-4-yl)-propyl]-3-(4-methyl-thiazol-2-yl)-1*H*-pyridin-2-one) (**9e**) (2.0 mmol) was dissolved in benzene, treated with Bu_3SnH (4.0 mmol) and AIBN (2.0 mmol) and refluxed for 16 h. The reaction mixture was evaporated in vacuo, and aqueous work-up and column chromatography gave 4-benzyloxy-2-(4-methyl-thiazol-2-yl)-1-(5,6,7,9-tetrahydro-pyrido[3,4-*c*]azepin-8-yl)-penta-2,4-dien-1-one (**10e**) (1.0 mmol, 50%). δ_H (360 MHz; $CDCl_3$) 8.83 (1H, s), 8.81 (1H, s), 8.60 (1H, d, J = 6.0), 7.37-6.99 (7 H, m), 5.17-5.09 (2H, m), 4.85 (1H, d, J = 11.6), 3.07-2.99 (1H, m), 2.58-2.39 (5H, m), 2.17-2.08 (1H, m), 1.97-1.87 (1H, m).

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