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An expeditious synthesis of 3-(difluoromethoxy)- and 3-(trifluoromethoxy)-5,6,7,8-tetrahydro-1,6-naphthyridines

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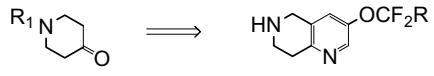
ABSTRACT

An expeditious and concise synthesis of 3-(difluoromethoxy)-5,6,7,8-tetrahydro-1,6-naphthyridine and 3-(trifluoromethoxy)-5,6,7,8-tetrahydro-1,6-naphthyridines is described. Starting from *N*-benzyl piperidone, the key intermediates leading to these two biologically desirable synthones were rapidly assembled by inverse electron demand Diels–Alder (IEDA) reaction utilizing microwave irradiation. The scope of the microwave methodology developed herein was extended to other ketones.

In biologically active molecules, replacement of hydrogen atom(s) with the more electronegative fluorine atom(s) significantly alters their electronic properties. However, because of their similar atomic radius the spatial properties are conserved.[1] The net result is the design of new entities bestowed with improved metabolic stability and increased lipophilicity. Ongoing efforts in a medicinal chemistry project required us to improve on the metabolic stability of our lead naphthyridine containing compound while maintaining potency. We reasoned that incorporation of novel 3-(difluoromethoxy) and 3-(trifluoromethoxy)-5,6,7,8-tetrahydro-1,6-naphthyridines **2** and **3** into our lead molecule might offer us analogs with improved metabolic profiles. Herein, we report a straightforward synthesis of these important pharmacophores starting from readily available 4-piperidones exemplified by **1**.



1 R = H, **2**; F, **3**

Synthesis of the naphthyridines (**2** and **3**) relied on a facile inverse electron demand Diels–Alder (IEDA) reaction between 3,5-dinitro-*N*-methyl-pyridone (**4**) and piperidone (**1**, R_1 = Bn) to afford **5**. The preparation of **4**, its congener and the relative ease with which it undergoes such a reaction have been amply documented.[2] Several variations of these reactions are known, but have been severely underutilized. In recent years because of increased efficiency, there have been burgeoning interests in the reactions that involve the use of microwave technology.[3] We further expanded on the scope and usefulness of the bis-nitro compound **4**, by extending IEDA to a wider array of ketones, but under microwave conditions.

The IEDA reaction of **4** and **1** (R_1 = Bn), with microwave irradiation in the presence of methanolic ammonia was conducted at 120 °C for 20 min.[4] Upon routine workup, **5** was isolated in 78% yield. In general, the reaction was very clean and operationally simple. Encouraged by these findings, a broader range of ketones were then subjected to similar reaction conditions, and the results from these studies are summarized in Table 1 (entries 2–8). Briefly, the protecting groups (Boc and Bz) on **1** were well tolerated under these conditions to afford products **6** and **7** as were products **8** and **9** in good to excellent yields. The successful outcomes for entries 6–8 demonstrated that ketones other than piperidones can also be utilized to afford an even wider array of products (**10**–**12**) with good to excellent yields. The only low yielding example in this study was entry 7, where the yield obtained for **11** was 28%. However, as can be seen for entry 8, protection of the OH afforded the desired product **12** in excellent yield (89%). Desilylation[5] of **12** under standard conditions gave **11**. Additional analogs could be synthesized from other ketones, but a glance at Table 1 reveals the potential for even broader applications for this microwave-assisted protocol that is beyond the scope of the present investigation.

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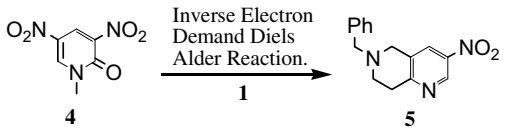
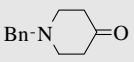
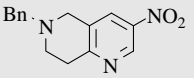
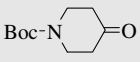
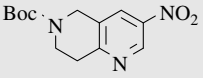
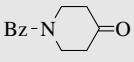
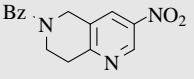
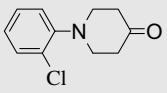
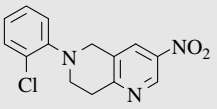
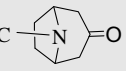
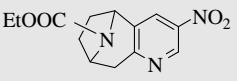
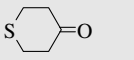
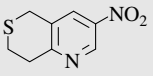
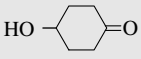
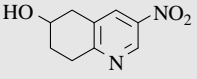
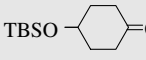
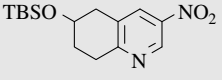


Table 1
Reaction of various ketones with **4** to afford an array of products[a]

Entry	Ketones	Product	Product ID	Yield[b,c] (%)
1			**5**	78
2			**6**	97
3			**7**	88
4			**8**	77
5			**9**	83
6			**10**	89
7			**11**	28
8			**12**	89

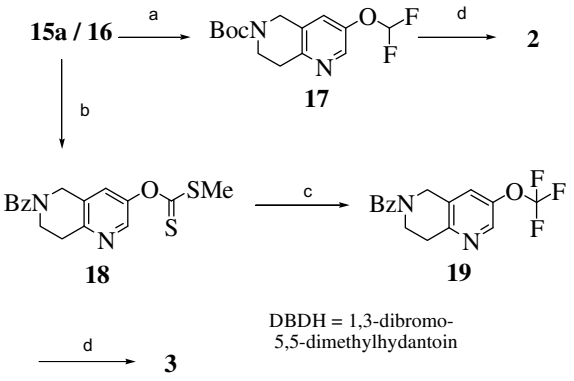
[a] Reactions performed under microwave conditions at 120 °C, 20 min.
[b] Isolated yields.
[c] Products **5**–**12** have been fully characterized by high field NMR and MS.

Upon synthesis of the key intermediates **5** and **7**, we proceeded to complete the transformations to the desired products **2** and **3** as shown in Schemes 1 and 2. Thus, a short exposure of the nitro compound **5** to catalytic hydrogenation afforded the aniline **13**. Diazotization[6] of **13** followed by thermal decomposition of the diazonium salt afforded the phenol **15**. It is important to note that the *N*-Bn protecting group remained intact during this transformation. Because the penultimate step for the synthesis of **2** required us to utilize the *N*-Boc instead of the *N*-Bn intermediate, **15** was converted to **15a**.[7] This was easily accomplished by hydrogenolysis of **15** under acidic conditions (2N HCl) followed by *N*-Boc protection to give the product **15a**.

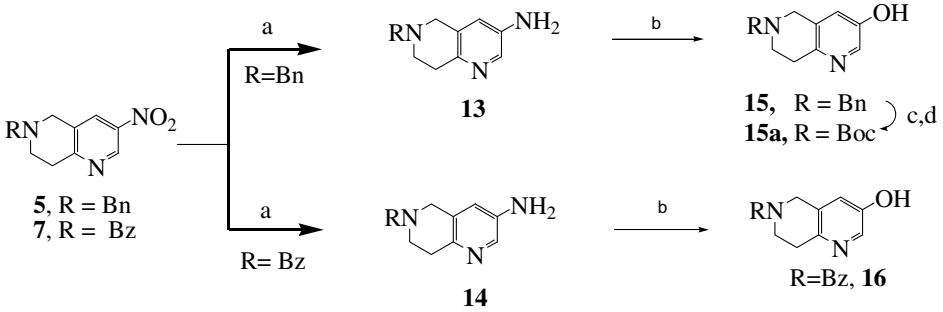
The transformation of the *N*-Bz analog **7** to the phenol **16** following the protocol discussed above for **15**, was equally facile and uneventful. Conversion of phenols **15a** and **16** to the 3-difluoromethoxy and 3-trifluoromethoxy analogs **2** and **3**, respectively, is shown in Scheme 2. A variation of literature[8] procedure that involves alkylation of **15a** under basic conditions with bromodifluoromethane ($CHBrF_2$) gave **17** in 20% yield. Attempts to improve the yield under a variety of conditions that involved diverse bases (both organic and inorganic) and temperatures were futile. By contrast, a three-step procedure[9] for the transformation of **16**–**19** proceeded in much better yields. Thus, in a sequence of reactions that involved conversion of **16** to the xanthate **18** followed by its reaction with 1,3-dibromo- 5,5-dimethylhydantoin (DBDH) and Py-HF complex, the product **19** was afforded in 90% yield.

Removal of the *N*-Boc and *N*-Bz protecting groups in **17** and **19**, respectively, was affected under acidic conditions to afford **2** and **3** as their HCl salts. The hydrochloride salts of **2** and **3** were carried forward to make the biologically active molecules. The free amine derived from **19** was also easily obtained by neutralization of the salt with $Ca(OH)_2$. The medicinal chemistry aspects related to the utilization of **2** and **3** will be the subject of communication to be followed elsewhere.

In summary, a concise synthesis of the heterocyclic synthons **2** and **3** is disclosed. The key to these pharmacologically important scaffolds involved microwave-assisted inverse electron demand Diels–Alder reaction between 3, 5-dinitro-*N*-methylpyridone **(4)**



Scheme 2. Reagents and conditions: (a) K_2CO_3, $CHBrF_2$, DMF, 75 °C; (b) NaH, CS_2, DMF, MeI, −78 °C; (c) DBDH, HF-Py complex, DCM; (d) HCl/EtOAc.



Scheme 1. Reagents and conditions: (a) Pd/C, H_2, MeOH; (b) $NaNO_2$, H_2SO_4, 90 °C; (c) Pd/C, H_2, EtOH, 2 N HCl; (d) Boc_2O, $NaHCO_3$, DCM.

and piperidone(s). We believe that our modified microwave protocol for IEDA reactions holds greater promise to the synthesis of other heterocyclic compounds.

References and notes

1. (a) Hagmann, K. W. *J. Med. Chem.* **2008**, *51*, 4359; (b) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
2. (a) Matsumura, E.; Toda, Y.; Ariga, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2174; (b) Toda, Y. T.; Ariga, M.; Kawashima, T.; Matsumura, E. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 201; (c) Marcelis, A. T. M.; Vander Plas, H. C. *Tetrahedron* **1989**, *45*, 2693; (d) Toda, Y.; Miyuki, E.; Nakagawa, T.; Usami, Y.; Ariga, M.; Kawashimaa, T.; Tani, K.; Watanabe, H.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2820; (e) Toda, Y.; Tani, K.; Yamawaki, N.; Ariga, M.; Nishiwaki, N.; Kawashima, T.; Tani, K.; Watanabe, H.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2820; (f) Toda, Y.; Tani, K.; Yamawaki, N.; Nishiwaki, N.; Kotani, K.; Matsumura, E. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1222; (g) Harling, J. D.; Harrington, F. P.; Thompson, M. *Synth. Commun.* **2001**, *31*, 787; (h) Fujita, K.; Watanabe, K.; Nishiyuchi, Y.; Honda, R.; Matsuzaki, H.; Hongo, H. *Chem. Pharm. Bull.* **2001**, *49*, 601.
3. Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2005.
4. In a typical experiment exemplified by entry 1, a mixture of **4** (0.199 g, 1 mmol) in 4 ml of 2 M methanolic ammonia and 4-piperidone **1** (R = Bn, 0.189 g, 1 mmol) in a 10 ml microwave tube was heated at 120 °C for 20 min in the Biotage Initiator Microwave. The solvent was evaporated and the crude mixture was purified by silica column on the Combiflash Companion Instrument, eluting with ethyl acetate/hexane (0–50%) to afford **5** (0.211 g, 78%). ^{1}H NMR (CD_3OD, 500 MHz): δ 9.14 (d, J = 2.5 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 7.40–7.28 (m, 5H), 3.76 (s, 4H), 3.10 (t, J = 6.0 Hz, 2H), 2.91 (t, J = 6.0 Hz, 2H). LC–MS $[M+H]^+$ calculated 269.12, found 270.05.
5. Corey, E. J.; Venkateswaralu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
6. (a) Gilbert, B. C.; Hanson, P.; Jones, J. R.; Timms, A. W. US Patent # 5,416,235; (b) Parkanyi, C.; Yuan, H. L.; Sappokstang, A.; Gutierrez, A. R.; Lee, S. A. *Montash. Chem.* **1992**, *123*, 637.
7. Attempted synthesis of **15a** directly from **6** was unsuccessful, and led to mixtures of products during the diazotization step.
8. Miller, T. G.; Thanassi, J. W. *J. Org. Chem.* **1960**, *25*, 2009.
9. (a) Kurobashi, M.; Suzuki, K.; Hiyama, T. *Tetrahedron Lett.* **1992**, *33*, 4173; (b) Kanie, K.; Tanaka, Y.; Suzuki, K.; Kurobshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 471.