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Synthesis of 5,6,7,8-Tetrahydro-1,6-naphthyridines and Related Heterocycles by Cobalt-Catalyzed [2 + 2 + 2] Cyclizations

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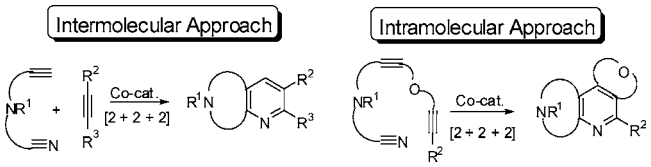
ABSTRACT



Microwave-promoted, cobalt-catalyzed intramolecular [2 + 2 + 2] cyclizations of dialkynylnitriles successfully gave 5,6,7,8-tetrahydro-1,6-naphthyridines. The efficient synthesis of these relatively simple, yet rarely addressed heterocycles enabled the preparation of a collection of these compounds.

We recently reported the preparation of 1,2,3,4-tetrahydro-1,5-naphthyridines **1a** and pyrido[3,2-*b*]azepines **1b** using inverse electron demand Diels−Alder methodology.[1] As small, nitrogen-containing heterocycles, readily prepared with various substituents, these heterocycles are attractive as library core structures for diversification.[2] To systematically vary the structure, it was of interest to locate the ring nitrogens in alternative positions. Thus, the analogous 5,6,7,8-tetrahydro-1,6- (**2**), -1,7- (**3**), and -1,8-naphthyridines (**4**) became targets, as did 1,2,3,4-tetrahydro-1,6- (**5**), -2,6- (**6**), -2,7- (**7**), and -1,7-naphthyridines (**8**) (Figure 1). To gain additional diversity, a second goal was to devise a procedure that would allow easy variation of the size of the saturated ring as accomplished with **1a** and **1b**.

These additional naphthyridine targets (**2**−**8**) are not readily accessible from the inverse electron demand Diels−Alder chemistry used to prepare **1a** and **1b,** so a different approach was pursued. Transition metal-catalyzed [2 + 2 + 2] cyclizations have proven reliable for benzannulation since Vollhardt,[3] Bonneman,[4] and Yamazaki[5] reported the now well-known cobalt(I)-catalyzed process in the 1970s.[6] Maryanoff,[7] Heller,[8] and others[9] have also shown that cobalt-catalyzed [2 + 2 + 2] cyclizations of two alkynes and a nitrile can produce pyridine rings in good yields, and cobalt-catalyzed [2 + 2 + 2] chemistry is now prominent in organic

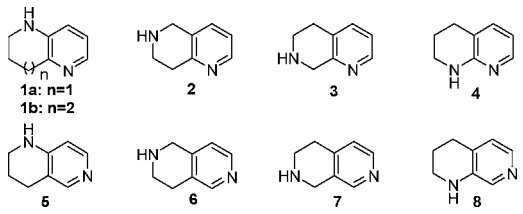


Figure 1. Tetrahydronaphthyridine isomers.

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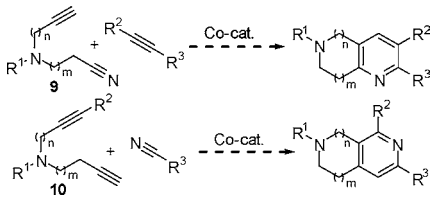
Table 1. Cobalt-Catalyzed Intermolecular [2 + 2 + 2] Cyclizations with Microwave Promotion

entry	aminonitrile	*n*	*m*	R^1	R^2	R^3	catalyst[a]	yields of **11**[b–d]
1	**9a**	1	1	H	Ph	Ph	$CpCo(CO)_2$	**11a**, 69%
2	**9a**	1	1	H	Ph	Ph	CpCo(COD)	**11a**, 67%
3	**9a**	1	1	H	Ph	Ph	InCo(COD)	**11a**, 67%
4	**9a**	1	1	H	Ph	Ph	$CpCo(CO)_2$[e]	**11a**, 60%[e]
5	**9a**	1	1	H	Ph	Ph	$CpCo(CO)_2$[f]	**11a**, 33%[f]
6	**9b**	1	1	Me	Ph	Ph	$CpCo(CO)_2$[f]	**11b,** 36%[f]
7	**9b**	1	1	Me	Ph	Ph	$CpCo(CO)_2$[g]	**11b**, 22%[g]
8	**9b**	1	1	Me	Ph	Ph	$CpCo(CO)_2$	**11b**, 68%
9	**9c**	1	0	H	Ph	Ph	$CpCo(CO)_2$	**11e**, 53%
10	**9d**	2	1	H	Ph	Ph	$CpCo(CO)_2$	**11f**, 47%
11	**9a**	1	1	H	Et	Et	CpCo(COD)	**11c**, 43%
12	**9a**	1	1	H	CH_2OH	CH_2OH	$CpCo(CO)_2$	**11d**, 36%
13	**9a**	1	1	H	CO_2Me	CO_2Me	$CpCo(CO)_2$	no rxn
14	**9a**	1	1	H	CO_2Me	CO_2Me	CpCo(COD)	no rxn
15	**9a**	1	1	H	Ph	COMe	$CpCo(CO)_2$	no rxn
16	**9b**	1	1	Me	H	TMS	$CpCo(CO)_2$	no rxn
17	**9a**	1	1	H	H	TMS	$CpCo(CO)_2$	no rxn
18	**9a**	1	1	H	H	Ph	$CpCo(CO)_2$	no rxn
19	**9a**	1	1	H	Ph	TMS	$CpCo(CO)_2$	**11g**, (**11h**),[h] 32%
20	**9a**	1	1	H	Me	TMS	$CpCo(CO)_2$	**11i**,[h] 21%
21	**9a**	1	1	H	Me	Ph	$CpCo(CO)_2$	**11j**, 44%

[a] Catalyst load 20 mol % unless otherwise noted. [b] Isolated yields. [c] All the reactions were run under microwave irradiation, 300 W, 15 min, 150 °C internal temperature, chlorobenzene as solvent unless otherwise noted. [d] See Figure 2 for product structures. [e] Catalyst load 10 mol %. [f] Reactions in refluxing toluene, 12 h. [g] Reaction in toluene with *hν* activation, 6 h. [h] Minor regioisomers could be detected in trace amounts, and isolated only for **11h**.

synthesis.[10] Thus, it became apparent that [2 + 2 + 2] pathways might prove to be a highly versatile strategy for preparing naphthyridines **2**−**8** along with ring size variants for added diversity (Scheme 1). Variation of "*n*" or "*m*", while keeping "(*n* + *m*)" constant, would locate the nitrogen at different positions in the A-ring, while the nitrogen location in the pyridine ring would be varied by using alkynylnitriles **9** and dialkynylamines **10**. Expansion of the A-ring would also be routine by increasing (*n* + *m*). We now report the successful implementation of this [2 + 2 + 2] strategy for the preparation of tetrahydro-1,6-naphthyridines **2**.

Scheme 1



Intermolecular cyclization of propargylaminonitrile **9a**, easily prepared by conjugate addition of propargylamine to acrylonitrile, with various alkynes was initially examined (Scheme 2). The reaction was probed with numerous catalysts under a variety of conditions; best results were obtained with 20 mol % $CpCo(CO)_2$,[7b] CpCo(COD),[11] or InCo(COD)[12] under microwave promotion (Table 1).

Scheme 2

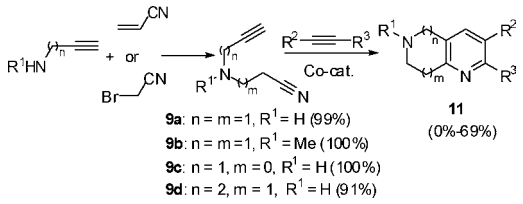


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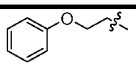
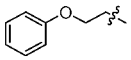
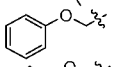
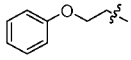
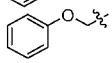
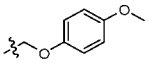
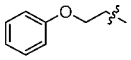
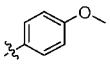
Table 2. Synthesis of the 5-, 6-, 7-Membered 1,2,3,4-Tetrahydronaphthyridines by Intramolecular Pathway (Scheme 5)

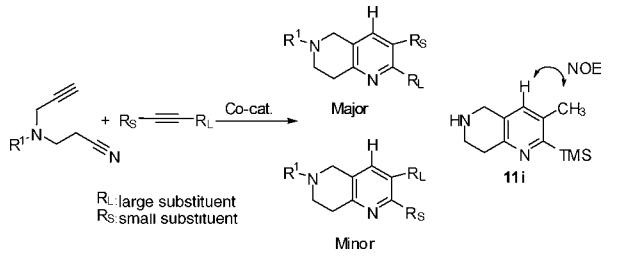
entry	R	R'	R"	n	yields of **21**[a]	yields of **22**[a,b,c]
1	Ph	Me		1	**21a** 62%	**22a** 83%
2	Ph	Me		1	**21b** 65%	**22b** 93%
3	Ph	Me		1	**21c** 77%	**22c** 86%
4		Me		1	**21d** 62%	**22d** 89%
5		Me		1	**21e** 71%	**22e** 87%
6		Me		1	**21f** 63%	**22f** 88%
7		Me		1	**21g** 66%	**22g** 99%
8	Ph			1	**21h** 63%	**22h** 86%
9		Me		1	**21i** 57%	**22i** 93%
10	Ph	Me		0	**21j** 20~30%	**22j** 71%
11	Ph	Me		2	**21k**[d] NA	**22k** 25% (2 steps)[e]

[a] Isolated yields. [b] All reactions were run under microwave irradiation, 300 W, 15 min, 180 °C internal temperature, chlorobenzene as solvent. [c] See Figure 2 for product structures. [d] **21k** is not isolable. [e] The crude mixture of **21k** was used for the [2 + 2 + 2] cyclization without further purification.

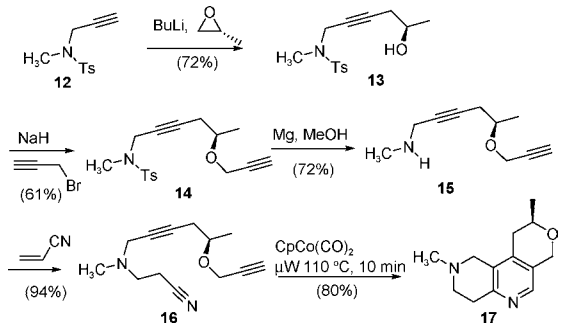
All three catalysts gave comparable yields in the reactions of **9a** with diphenylacetylene (67−69%, entries 1−3). The use of $CpCo(CO)_2$ was preferred, being more user-friendly and stable to benchtop reaction conditions and storage, while CpCo(COD) and InCo(COD) required a drybox environment. Reduction of the catalyst load to 10 mol % resulted in a slight drop in yield over the same reaction time period (60%, entry 4). Thermal (33−36%, refluxing toluene) or photochemical (22%) promotion of the cyclizations of **9a** (and **9b**) with diphenylacetylene using $CpCo(CO)_2$ gave lower yields (entries 5−7). Other intermolecular cyclizations proceeded in moderate yields, notably those with a phenyl ring attached to the alkynes (entries 8−12). Secondary and tertiary amines were tolerated (R^1 = H, Me), though alkynes with carbonyl substituents (entries 13−15) and terminal alkynes (entries 16−18) did not react. 5-Membered (entry 9, 53%) and 7-membered (entry 10, 47%) annulated pyridines could also be synthesized from aminonitriles with appropriately lengthed tethers between the nitrile and alkyne groups, though these cyclizations proceeded in lower yields than those leading to the 6-membered annulated pyridines (compare entries 1, 9, and 10). Cyclizations with unsymmetrical alkynes gave only poor to modest yields (entries 19−21), though with excellent regioselectivities; NOE studies on the products showed the bulkier alkyne substituent preferred to be adjacent to the ring nitrogen in the product (Scheme 3).

Given the modest yields of the intermolecular reactions, intramolecular cyclizations were examined. Tosyl amide **12** was deprotonated, followed by addition of (*R*)-propylene oxide to give homochiral secondary alcohol **13** (72%, Scheme 4). Ether formation with propargyl bromide yielded **14**, then deprotection and conjugate addition with acrylonitrile gave cyclization precursor **16**. Microwave irradiation

Scheme 3



Scheme 4



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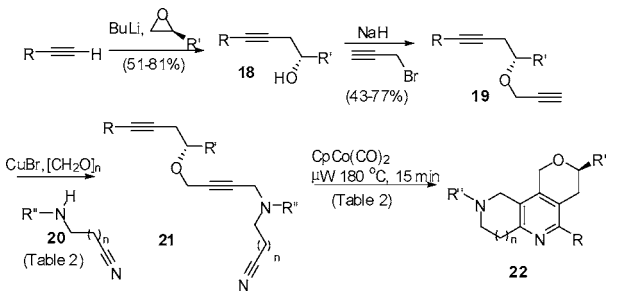
of **16** with $CpCoCO_2$ (20 mol %) produced tetrahydro-2,5-naphthyridine **17** in 80% yield, validating the intramolecular approach.

An alternative route to the cyclization precursors transposed the oxygen and stereogenic center in the C-ring (Scheme 5). Formation of dialkynyl ethers **19** by epoxide

Scheme 5



opening and propargylations of **18**, followed by copper-promoted Mannich reactions[13] with aminonitriles **20** gave cyclization precursors **21**. Cyclizations proceeded smoothly to give tetrahydronaphthyridines **22** ($n = 1$) in excellent yields (Table 2, 83−99%, Figure 2). Preparation of aminonitriles **20** from primary amines, by conjugate addition to acrylonitrile or alkylation with bromoacetonitrile or 4-bromobutyronitrile, enabled variation of the tether length between the nitrile and amino groups, resulting in 6-, 5-, or 7-membered A-rings in the products, respectively. However, formation of the dialkynylnitrile precursor **21j** ($n = 0$) by the Mannich reaction proceeded in only 20−30% yield (entry 10). In addition, the cyclization precursor **21k,** which leads to a 7-membered A-ring, was difficult to purify. The cyclization was thus performed without purification of **21k,** which may account for the low overall yield of **22k** (25%, 2 steps).

In conclusion, we have demonstrated a new route to 5,6,7,8-tetrahydro-1,6-naphthyridines **11** and **22** and related heterocycles using microwave-promoted, Co-catalyzed [2 + 2 + 2] cyclizations. Previous syntheses of these heterocycles typically relied upon annulation of a pyridine ring onto a 4-piperidone or equivalent,[14] or reductions or reductive additions to the fully aromatized 1,6-naphthyridine system.[15,16] Fully aromatized naphthyridines were not detected in any of the microwave-promoted reactions. Adaptation of this chemistry for library synthesis and the use this approach to access other naphthyridines **3**−**8** are underway.

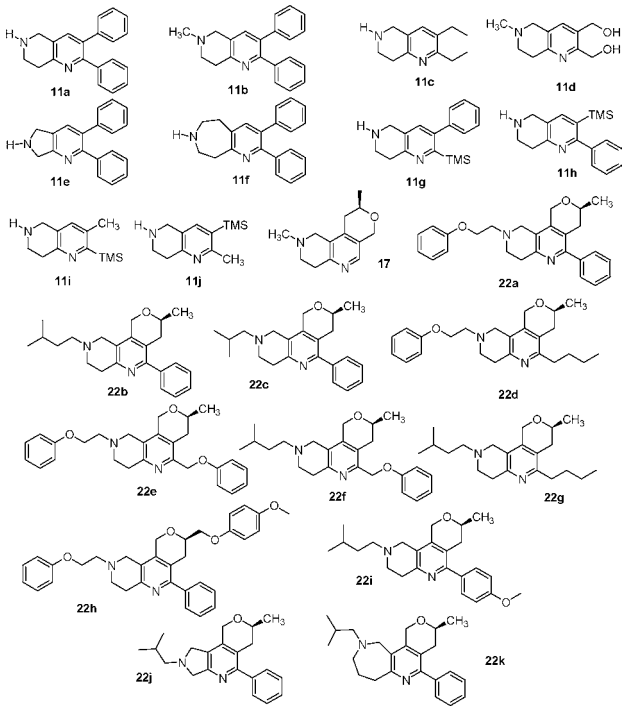


Figure 2. 5,6,7,8-Tetrahydro-1,6-naphthyridines and related heterocycles prepared by [2 + 2 + 2] cyclizations.

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Supporting Information Available: Procedures and characterization spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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