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Isonitrile Trapping Reactions under Thermolysis of Alkoxyamines for the Synthesis of Quinolines

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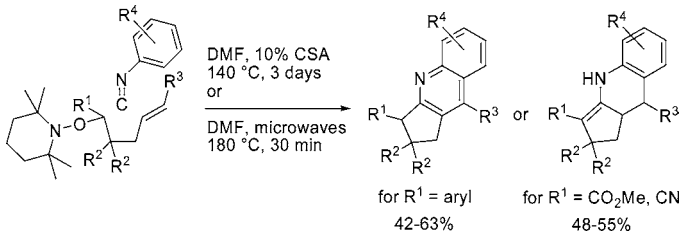
ABSTRACT



An efficient tandem radical process comprising a thermal alkoxyamine homolysis, an isonitrile trapping reaction, a 5-*exo*-trig cyclization, and a homolytic aromatic substitution leads to substituted dihydroquinolines. Depending on the substituent R^1, oxidation to dihydro-1*H*-cyclopenta-[*b*]quinolines (for R^1 = aryl) or tautomerization to tetrahydro-1*H*-cyclopenta[*b*]quinolines (for $R^1 = CO_2Me$, CN) occurs. The heterocycles are obtained in moderate to good yields. Upon using microwave-induced heating, the reaction time can be shortened from 3 days to 30 min.

Over the last few decades, radical chemistry has gained increasing importance in synthetic organic chemistry.[1] Along with other radical acceptors, isonitriles have been shown to react efficiently with various C-radicals and sulfanyl radicals to provide the corresponding imidoyl radicals which can further react with various radical acceptors to afford interesting heterocycles.[2,3] Curran has elegantly used these tandem reactions for the synthesis of substituted quinolines in radical [4+1] annulation reactions.[3b,4] Over the past few years, we have successfully used alkoxyamines as clean sources for the generation of C-centered radicals.[5,6] C-radical formation using this approach is reversible and is controlled by the persistent radical effect (PRE).[7] Alkoxyamine isomerizations and intermolecular alkoxyamine additions have been conducted using this methodology. In most of the cases, the

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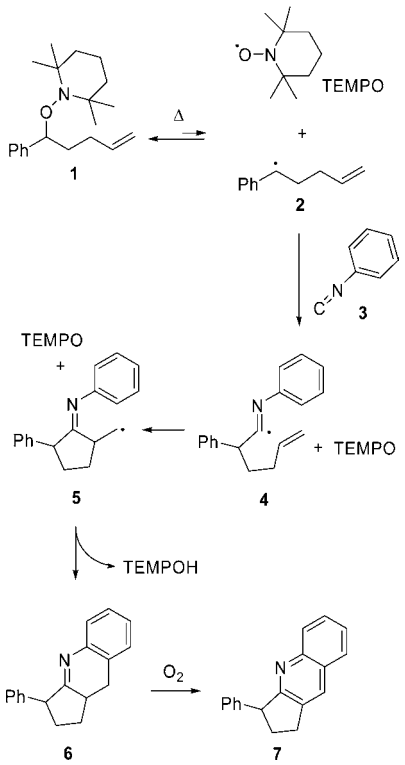
commercially available TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) radical was used as persistent nitroxide in these tin-free PRE-controlled processes.

In this communication, we present first results on the use of aryl isonitriles as radical acceptors in TEMPO-mediated radical cyclization processes for the synthesis of quinolines. The synthetic strategy is depicted in Scheme 1. As a model

Scheme 1. PRE-Mediated Quinoline Synthesis



compound, we prepared alkoxyamine **1** (see Supporting Information). We anticipated that the C-radical **2** generated via thermal C−O bond homolysis will react either with TEMPO to reform starting material **1** in a degenerate process or with phenyl isonitrile (**3**) to afford the corresponding imidoyl radical **4**. Radical **4** can further react in a 5-*exo*-type cyclization to give the primary alkyl radical **5** which can undergo homolytic aromatic substitution to provide imine **6** which readily oxidizes during workup to the corresponding quinolines **7**.[3b] We have previously shown that homolytic aromatic substitutions can be performed using TEMPO−alkoxyamines as radical precursors.[5c] In these reactions, TEMPO oxidizes the intermediately formed cyclohexadienyl radicals (TEMPOH). It is also possible that the intermediately formed cyclohexadienyl radicals are oxidized by the isonitrile.[3a,c,8]

The tandem process was optimized using phenyl isonitrile (**3**) as the radical trapping reagent. The first experiment was conducted in DMF (0.1 M) at 140 °C (sealed tube) with equimolar amounts of **1** and the isonitrile (Table 1, entry 1).

Table 1. Reaction of **1** with **3** under Different Conditions

entry	**1** (M)	time	solvent	temp (°C)	**3** (equiv)	**7** (%)[a]
1	0.1	3 days	DMF	140	1	traces
2	0.1	3 days	DMF	140	2	13
3	0.1	3 days	DMF	140	5	50
4	0.1	3 days	DMF	140	10	54
5	0.1	3 days	$ClCH_2CH_2Cl$	140	5	42
6[b]	0.1	3 days	DMF	140	5	56
7[b]	0.25	3 days	DMF	140	5	53
8[b]	0.05	3 days	DMF	140	5	49
9[c]	0.1	30 min	DMF	180	5	51
10[b,c]	0.1	30 min	DMF	180	5	28

[a] Isolated yields. [b] 10% CSA was added. [c] Microwave-induced heating.

Disappointingly, only trace amounts of the desired quinoline **7** were obtained. We found that at least 2 equiv of the isonitrile are necessary to get sufficient amounts of **7** for product isolation (entry 2). A 50% yield was obtained using a 5-fold excess of the radical acceptor (entry 3). The yield could be further increased if 10 equiv of **3** were added (54%, entry 4); however, isolation of the product turned out to be more difficult in that case. Therefore, a 5-fold excess was used for all the following experiments. Any side products could not be isolated in these experiments. We know that the starting material slowly decomposes at 140 °C in DMF.[9] Reaction in $ClCH_2CH_2Cl$ was less efficient (entry 5). Importantly, we found that the yield could be further increased upon adding 10% of camphorsulfonic acid (CSA, see entry 6). We have previously shown that CSA accelerates TEMPO-mediated radical cyclization processes.[5a] Reaction at a lower concentration (0.05 M) was less efficient (entry 8), whereas increasing the concentration did not affect the yield to a large extent (entry 7). Pleasingly, we could shorten the reaction time from 3 days to 30 min upon switching to microwave-induced heating (entry 9).[10] Microwave heating in the presence of CSA provided lower yields of the desired quinoline **7** (entry 10). The starting material rapidly decomposes under the harsh reaction conditions applied. It is important to note that there are only a few papers published on microwave-induced free-radical chemistry.[5c,d,f,11]

Under the optimized reaction conditions (method A: 140 °C, 3 days, 10% CSA, DMF; method B: 180 °C, microwaves, 30 min, DMF), a series of quinolines were synthesized. We first tested the tandem reaction with alkoxyamine

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(10) The microwave experiments were conducted using professional laboratory microwave equipment. A MLS-Ethos 1600 Mikrowellen System (Milestone) was used for the present studies. The reactions were run in 40 mL MLS-reaction high-pressure vessels (up to 15 bar) which contain pressure-control valves. An advanced temperature control system from MLS allowing direct contactless temperature monitoring was used. The microwave power is continuously and dynamically adjusted to follow the defined temperature profile. Temperature profile for the quinoline synthesis: from 25 to 100 °C in 10 s; from 100 to 150 °C in 10 s; from 150 to 180 °C in 10 s and then keep the temperature at 180 °C for 30 min.

1 using various isonitriles **8a**−**d**. Reactions with para-substituted aryl isonitriles worked well under both conditions tested. Quinolines **9a**,**c** and **9d** were obtained in 43−56% yield (Table 2, entries 1, 3, and 4). Similar yields were obtained for both protocols (A or B). Importantly, bromo-substituted aryl isonitriles, which are dehalogenated under tin hydride conditions, can be used in the radical quinoline synthesis presented herein. Ortho-substituted aryl isonitriles can also be applied as shown in entry 2 (→ **9b**).

Table 2. Synthesis of Quinolines **9a**−**g** from Alkoxyamine **1**, **10a**−**c**, and Various Aryl Isonitriles[a]

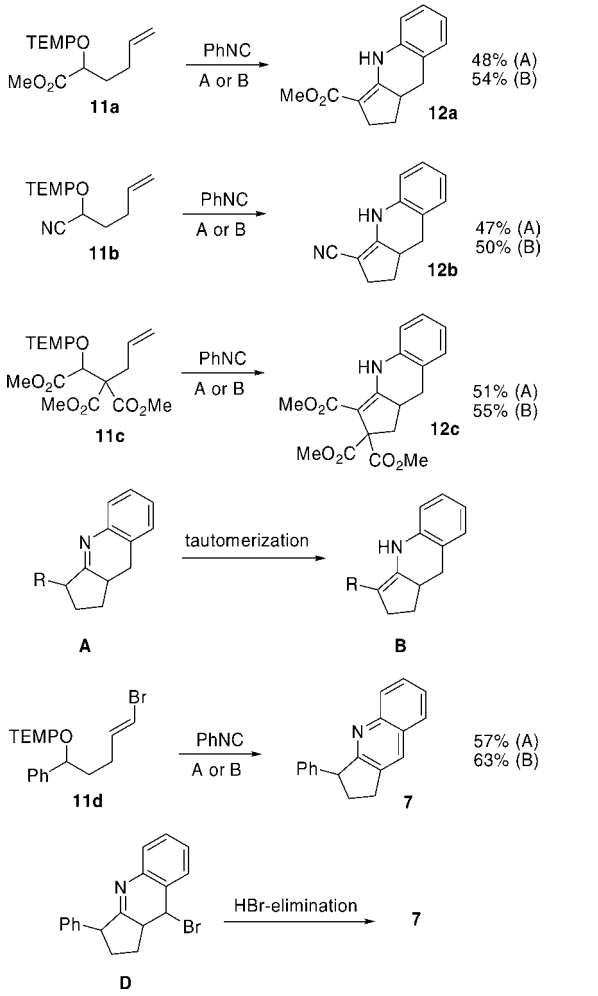
entry	alkoxyamine	isonitrile	quinoline	isolated yield (%)
1	**1**	**8a**	**9a**	56% (A) 51% (B)
2	**1**	**8b**	**9b**	48% (A) 52% (B)
3	**1**	**8c**	**9c**	55% (A) 49% (B)
4	**1**	**8d**	**9d**	43% (A) 46% (B)
5	**10a**	**3**	**9e**	52% (A) 53% (B)
6	**10b**	**3**	**9f**	59% (A) 61% (B)
7	**10c**	**3**	**9g**	42% (A) 45% (B)

[a] Conditions: (A) DMF, 140 °C, 10% CSA, 3 days; (B) DMF, 180 °C, microwaves, 30 min.

To further study the scope and limitations of our method, the alkoxyamine component was varied. Again, both protocols were tested for the substrates investigated. These studies were performed using **3** as an isonitrile component. The syntheses of the alkoxyamines **10a**−**c** are described in the Supporting Information. Reaction using bromide **10a** with phenyl isonitrile (**3**) provided quinoline **9e** in 52 and 53% yields using method A or B, respectively (entry 5). Importantly, the aryl bromides available via our route are ready for further synthetic manipulations using transition-metal-mediated C−C coupling reactions. Geminally disubstituted system **10b** provided slightly higher yields under both conditions tested (entry 6). To our delight, homolytic aromatic substitution works also for secondary alkyl radicals, as documented by the successful transformation of alkoxyamine **10c** into the the corresponding quinoline **9g** (entry 7).

We next tested whether the aryl substituent in the starting alkoxyamines can be replaced by other radical stabilizing groups. As previously shown, cyano and alkoxycarbonyl-substituted TEMPO−alkoxyamines undergo clean thermal C−O bond homolysis.[5a] Therefore, we decided to test alkoxyamines **11a**−**c** in the quinoline synthesis. The tandem

Scheme 2. Synthesis of Tetrahydro-1*H*-cyclopenta[*b*]quinolines



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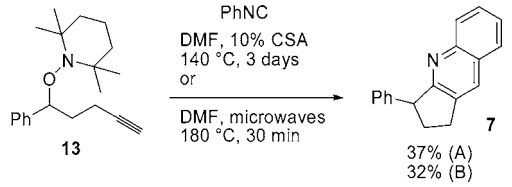
reaction was conducted under the optimized conditions using phenyl isonitrile as an acceptor. To our surprise, the targeted quinoline of type **7** was not formed in these cases. Instead, tetrahydro-1*H*-cyclopenta[*b*]quinolines **12a**−**c** were isolated in acceptable yields (Scheme 2, 48−55%). Hence, for heterocycles of type **A** obtained after homolytic aromatic substitution bearing acidifying R groups such as CN or CO_2Me, tautomerization to **B** occurs after homolytic aromatic substitution. The compounds **12a**−**c** are stable toward further oxidation. Interestingly, reaction of vinyl bromide **11d** with **3** afforded quinoline **7** in good yields. In this reaction, the intermediately formed dihydroquinoline **D** undergoes HBr elimination to provide **7**. Air oxidation is not necessary in this case.

Scheme 3. Quinoline Synthesis Using Alkyne **13**



Finally, we tested whether the tandem reaction can also be conducted with alkyne terminated alkoxyamines. As expected, reaction of alkyne **13** with phenyl isonitrile under the optimized conditions afforded the desired quinoline **7**. However, as compared to the above-described experiments performed with olefin-terminated alkoxyamines, slightly lower yields were obtained (Scheme 3).[12]

In summary, we presented an efficient method for the preparation of quinolines starting from readily available alkoxyamines. The reactions are very easy to conduct. Simple mixing and heating of the starting compounds delivers the desired quinolines in moderate to good yields. For alkoxyamines bearing acidifying R groups at the α-position of the alkoxyamine, tetrahydro-1*H*-cyclopenta[*b*]quinolines are obtained. These thermal radical tandem processes can be conducted without the use of toxic tin compounds.[13] Furthermore, bromides are tolerated under the applied conditions. These tandem reactions can also be performed under microwave conditions. Reaction times can be reduced by a factor of 140 upon using microwave-induced heating.

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Supporting Information Available: Experimental procedures and analytical data of all new quinolines and alkoxyamines. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) As compared to the alkene-terminated alkoxyamines, compound **13** turned out to be thermally less stable for unknown reasons. This may lead to the lower yields observed.

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