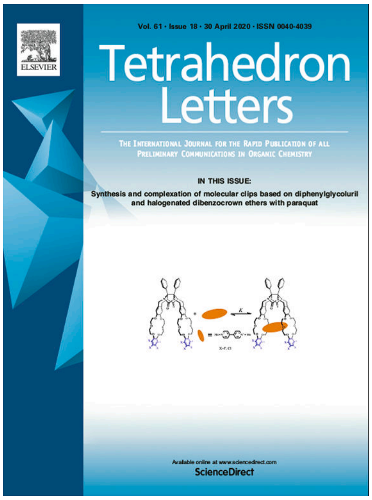

Radical addition of tetrahydrofuran to imines assisted by *tert*-butyl hydroperoxide

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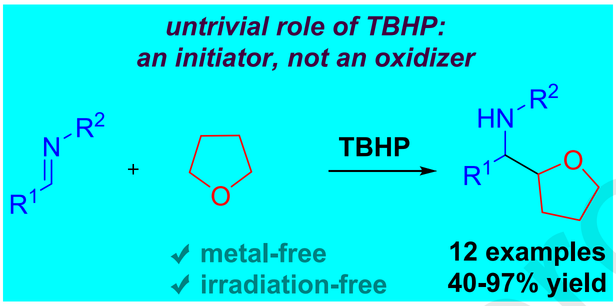

untrivial role of TBHP:
an initiator, not an oxidizer

✓ metal-free
✓ irradiation-free

12 examples
40-97% yield

Tetrahedron Letters
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Radical addition of tetrahydrofuran to imines assisted by *tert*-butyl hydroperoxide

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ABSTRACT

The TBHP-promoted selective radical addition of tetrahydrofuran to imines resulting in β-amino ethers has been developed. The presented radical method of β-amino ether synthesis is based on initiation by available TBHP and does not require metal catalysis or light irradiation. Variety of β-amino ethers are formed in good to excellent yields, despite the possible side oxidation pathways: ether α-oxidation, the transformation of starting imines into amides, target β-amino ethers dehydrogenation.

Introduction

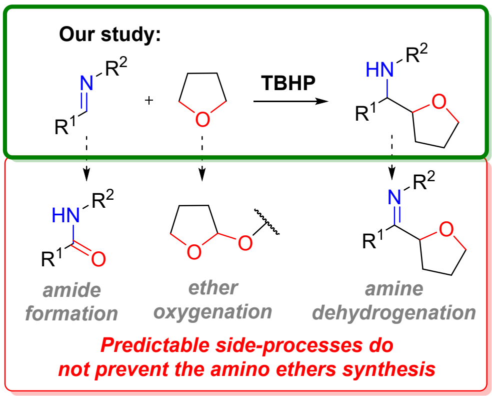
The use of radicals is a powerful tool for bond formation in organic synthesis.[1] In the last decades great advances have been achieved in the field of organic radical chemistry that was largely driven by the development of new radical precursors and methodologies.[2-12] The addition reactions of carbon–centered radicals are in the focus of synthetic chemistry because they are useful for the formation of C–C bonds considered as a basis of organic chemistry.[13, 14]

The radical addition to C=C bond was studied most thoroughly and a lot of literature was amassed over the years.[15-18] The addition of radicals to C=N bond is more challenged.[14, 19-22] Even the widespread radical Minishi-type chemistry has limitations related to the scope of heteroarenes, regioselectivity, and moderate yields of products.[23-25]

The radical addition to imine C=N bond is complicated by the several factors. An intermediate aminyl radical is less stabilized than a radical from oximes and hydrazones due to the absence of neighboring heteroatom.[26, 27] In addition, imines are easily hydrolyzed.[26, 27] The aza-enolization of the imines with an acidic α-hydrogen can reduce the content of the tautomer with the reactive C=N bond.[28] Thus, the effective radical addition to imine C=N bond is the unsolved task, progress in which is limited by scattered achievements.

Here we report a selective radical addition of tetrahydrofuran to imines with the formation of β-amino ethers. This class of compounds are of interest both as precursors in organic synthesis, and as analgesic[29] and antihistamine[30-32] compounds in medicinal chemistry. β-Amino ethers are also applied in the treatment of neuromuscular disorders.[33-36]

The addition of ethers to C=N bond[37] was performed under the action of Ti(III)/TBHP (aq.) system,[38] Ti(III)/PhN_2^+,[39] $TiO_2/(NH_4)_2S_2O_8$ under UV light irradiation,[40, 41] Alk_2Zn / oxygen,[42-46] AIBN, [47] and allyl or benzyl chloride / air system.[48] Kinetic studies were carried out using DTBP[49] as radical initiator. Later, the addition of ethers to imines [50, 51] and to other compounds with C=N bonds [52-54] was conducted using UV-light and ionizing irradiation. The Ir salt / thiol system[55] and 1,3-butanedione / NHS system [56] were designed for the addition of ethers to imines under visible light irradiation. In the present work, we disclosed a selective TBHP-promoted radical addition of tetrahydrofuran to imines in high yields (Scheme 1).



Scheme 1. Radical addition of tetrahydrofuran to imines and possible side-processes.

Despite the possibility of various oxidative side processes, in which starting ethers,[57] imines and target secondary amines[58, 59] can be involved, such as α-oxidation of ethers,[60] oxidation of imines into amides,[61-63] oxidative self-coupling of amines,[64] and

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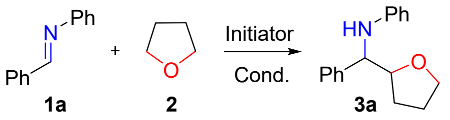
selectively formed under our conditions (Scheme 1).

Results and Discussion

To get a deeper insight into the radical addition of tetrahydrofuran to imines, firstly we investigated the reaction of (*E*)-*N*,1-diphenylmethanimine (**1a**) with tetrahydrofuran (**2**) (Table 1). The influence of initiator nature, additives, temperature, and the reaction time on the yield of β-amino ether **3a** was studied.

Table 1. Optimization of reaction conditions.[a]



Entry	Initiator (eq.)	Additives (eq.)	Cond.	Convn of **1a**, %	Yield of **3a**, %	d.r.[d]
1	TBHP [b] (0.1)	-	120 °C / 3 h	13	6	52:48
2	TBHP [b] (1.0)	-	120 °C / 3 h	90	82	52:48
3	TBHP [b] (2.0)	-	120 °C / 3 h	92	81	53:47
4	TBHP [b] (4.0)	-	120 °C / 3 h	>95	92	52:48
5	TBHP [b] (6.0)	-	120 °C / 3 h	>95	89	52:48
6[c]	TBHP [b] (4.0)	-	120 °C / 3 h	95	43	53:47
7	TBHP (70% aq.) (4.0)	-	120 °C / 3h	>95	30	52:48
8	TBHP [b] (4.0)	-	120 °C / 1 h	85	70	51:49
9	TBHP [b] (4.0)	-	120 °C / 5 h	>95	90	52:48
10	TBHP [b] (2.0)	-	80 °C / 3 h	40	20	52:48
11	BPO (4.0)	-	120 °C / 3 h	>95	0	-
12	DTBP (4.0)	-	120 °C/ 3 h	58	53	51:49
13	TBHP [b] (4.0)	$Co(OAc)_2\cdot 2H_2O$ (0.1)	20 °C / 3 h	>95	60	52:48
14	TBHP [b] (4.0)	$CoCl_2\cdot 6H_2O$ (0.1)	20 °C / 3h	85	0	-
15	TBHP [b] (4.0)	$CoSO_4\cdot 7H_2O$ (0.1)	20 °C / 3 h	40	30	53:47
16	TBHP [b] (4.0)	$Cu(OAc)_2\cdot H_2O$ (0.1)	20 °C / 3 h	83	17	52:48
17	TBHP [b] (4.0)	$Mn(OAc)_2\cdot 4H_2O$ (0.1)	20 °C / 3 h	76	50	52:48
18	TBHP [b] (4.0)	$FeCl_3$ (0.1)	20 °C / 3 h	>95	0	-

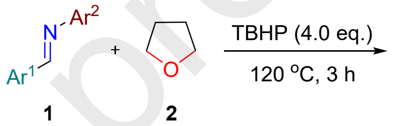
[a] **General reaction conditions:** An initiator (0.1-6.0 mmol, 0.1-6.0 eq.) and additives (0.1 eq) were added to a solution of (*E*)-*N*,1-diphenylmethanimine (**1a**) (181.2 mg, 1.0 mmol, 1.0 eq.) in THF (5 mL). The reaction mixture was stirred at 20-120 °C for 1-5 h. [b] 5.0 M solution of TBHP in decane [c] THF (2.5 mL). [d] d.r. (less polar/ more polar).

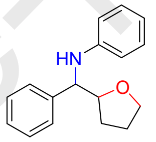
The catalytic amount of TBHP did not promote this transformation, the yield of **3a** was 6% (Table 1, entry 1), which is consistent with the previous data.[47] Increasing of TBHP

p to 92% and 89%, respectively (Table 1, entries 2-5). The use of 2.5 mL THF instead of 5.0 mL resulted in a dramatic decrease in **3a** yield to 43% (Table 1, entry 6). When the aqueous solution of TBHP was applied, the yield of **3a** was 30% (Table 1, entry 7). It may be explained by the imine hydrolysis with the formation of the aminal or aldehyde and aniline. When the reaction time was reduced to 1 h or the temperature was lowered to 80 °C, the yield of the product decreased to 70% or 20% respectively (Table 1, entries 8, 10). The increased reaction time did not affect the yield of **3a** product (Table 1, entry 9). Other peroxide initiators were found to be less effective (Table 1, entries 11, 12). When the metal salts were used for TBHP decomposition, the yield of **3a** was not higher than 60 % (Table 1, entries 13-18). The main side products in the experiments 11, 14, 18 characterized by the low yield of **3a** and high conversion of **1a** were benzaldehyde and benzoic acid.

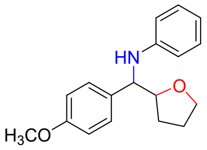
With the optimized conditions in hand (Table 1, entry 4), we next explored the substrate scope to demonstrate the generality of β-amino ethers **3** synthesis *via* the radical addition of tetrahydrofuran **2** to imines **1** (Table 2).

Table 2. Scope of the reaction.[a]

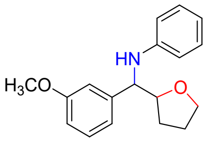




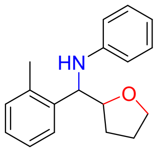
3a, 92% (52:48) [b]



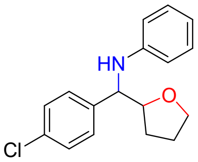
3b, 92% (50:50) [b]



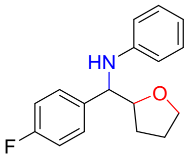
3c, 93% (50:50) [b]



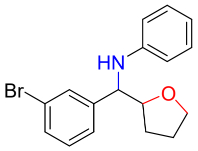
3d, 90% (51:49) [b]



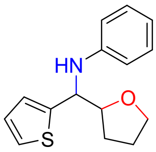
3e, 86% (52:48) [b]



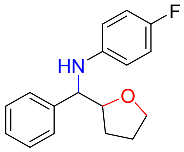
3f, 81% (52:48) [b]



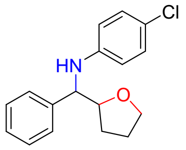
3g, 81% (51:49) [b]



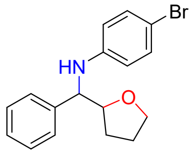
3h, 40% (50:50) [b]



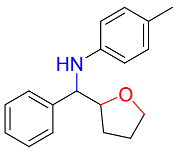
3i, 67% (51:49) [b]



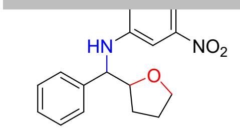
3j, 55% (54:46) [b]



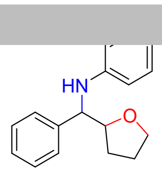
3k, 71% (55:45) [b]



3l, 97% (50:50) [b]



3m, not detected

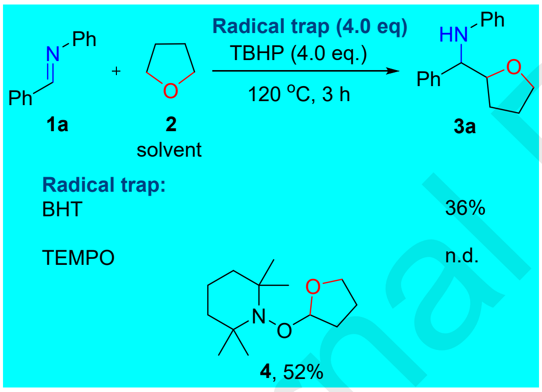


3n, not detected

[a] **General reaction procedure:** 5 M solution of TBHP in decane (4.0 mmol, 800 µL, 4.0 eq.) was added to a solution of imine **1** (1.0 mmol, 1.0 eq.) in THF (5 mL). Reaction mixture was stirred at 120 °C for 3 h. [b] d.r. (less polar/ more polar)

Various aryl-substituted imines **1a-g** with electron-donating and electron-withdrawing groups in aryl substituent Ar^1 entered the developed process resulting in the formation of the target β-amino ethers **3a-g** in high yields (Table 2). The thienyl-substituted β-amino ether **3h** was prepared in a moderate 40% yield. β-Amino ether **3l** with the electron-donating group in aryl substituent Ar^2 was obtained in a higher yield (97%) than β-amino ethers **3i-k** with electron-withdrawing groups in aryl substituent Ar^2 (55-71%) (Table 2). Imines **1m**, **1n** with strong electron-withdrawing groups in aryl substituent Ar^2 did not react with tetrahydrofuran in these conditions (Table 2). Fine-tuning of the reaction conditions allowed us to prepare target products with tetrahydrofuran core in combination with amine moiety under the action of TBHP. This selectivity is the advantage of the reaction.

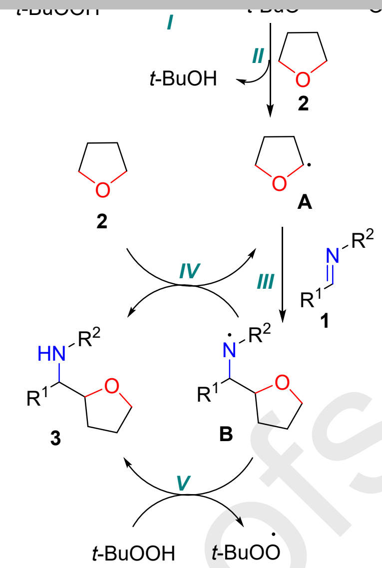
After that, we tried to confirm the radical mechanism of the developed process. For this purpose, the reaction of tetrahydrofuran with imine was carried out in the presence of the radical scavengers BHT (2,6-di-*tert*-butyl-4-methylphenol) and TEMPO (Scheme 2).



Scheme 2. Control experiments.

The yield of **3a** was reduced to 36% in the presence of BHT (the yield of **3a** in the optimal conditions is 90%). Addition of TEMPO led to the complete inhibition of the **3a** formation and practically zero conversion of **1a.** The radical-trapping product **4** was isolated in a 52% yield based on TEMPO (Scheme 2).

Taking into account the published [48, 49, 56] and experimental data, it can be proposed that the addition of tetrahydrofuran to imines occurs according to Scheme 3. Initially, the decomposition of TBHP under elevated temperature leads to the formation of the *t*-BuO radical (step I).[66] The *t*-BuO radical abstracts a hydrogen atom from tetrahydrofuran **2** to give radical intermediate **A** (step II).[67] After the generation of radical **A**, its radical addition to **1** produces aminyl radical **B** (step III),[42] which abstracts a hydrogen atom from tetrahydrofuran **2** (step IV) or TBHP (step V) to propagate the reaction chain and to generate the target product **3**.[47] TBHP can also be consumed in the ether oxidation process.[68, 69]



Scheme 3. Plausible mechanism of the reaction.

Conclusion

It was demonstrated that the radical addition of tetrahydrofuran to imines could be performed under metal- and irradiation-free conditions applying available TBHP as an initiator. A broad scope of β-amino ethers was synthesized with 40-97% yields. Using experimental data and previous reports, plausible radical mechanism of the reaction was proposed. A remarkable feature of the work is the impressive selectivity of the addition products formation in the presence of large excess of a strong oxidant despite the lability to the oxidation of substrates and products.

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Supplementary data

Supplementary data (the experimental methods and the ^{1}H NMR, ^{13}C NMR and HRMS data) associated with this article can be found, in the online version, at http://........

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