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TBN-Catalyzed Dehydrative N-Alkylation of Anilines with 4-Hydroxybutan-2-one

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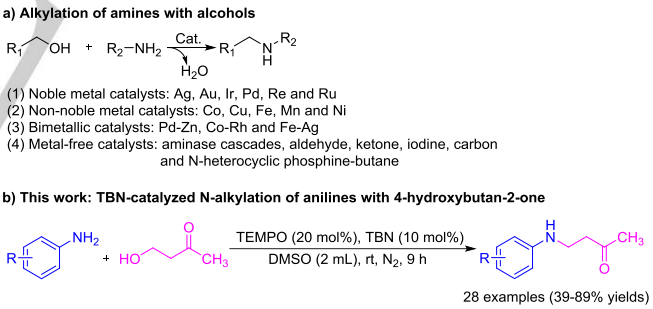
Wenchen Cheng and Shue Deng contributed equally to this work

Abstract: Substitution of alcohols by N-nucleophiles via TBN-catalyzed dehydrogenation was unknown. Herein, we reported a TBN catalyzed dehydrative N-alkylation of anilines with 4-hydroxybutan-2-one in the presence of TEMPO which was different from the TEMPO/TBN catalyzed oxidation reactions. A range of anilines reacted successfully with 4-hydroxybutan-2-one to generate the N-monoalkylation products in good yields. Mechanistic studies revealed that this reaction most possibly proceeded *α*, *β*-unsaturated ketones and aza-Michael addition. Water was the only by-product, making it more environmentally friendly. The gram-scale reactions verified the synthetic practicality of this protocol.

As one of the most useful transformations in organic synthesis, the construction of C-N bonds has long been pursued by synthetic chemists. Amines have wide applications in academic laboratories, chemical and pharmaceutical industries, and they can also be used for the synthesis of various biologically active materials.[1] Many methods have been employed to form C-N bonds, for example, substitution, addition, cycloaddition, and cross-coupling reactions, etc.[2] The direct substitution of hydroxy groups in alcohols by N-nucleophiles offers straightforward access to C-N bonds formation which has advantages of easy accessible raw materials, the sole by-product (H_2O), high increased efficiency and atom economy over the alternative stoichiometric activation and displacement protocol. However, the hydroxy group is not a good leaving group owing to the intrinsic thermodynamic and kinetic barriers. The alcohols have to be derivatized as potentially genotoxic alkyl halides, tosylates, triflates, and sulfonates, etc.[3] Direct substitution of alcohols was selected as one of the top 10 key green chemistry research areas by the ACS Green Chemistry Institute®Pharmaceutical Roundtable (GCIPR).[4]

In 1981, Grigg[5] and Watanabe[6] reported the first examples of alcohol substitution by N-nucleophiles in the presence of rhodium, iridium, and ruthenium compounds. Since then, many efficient catalytic methods for the N-alkylation of amines as well as the related reactions by activating alcohols were developed using metal catalysts (Ag,[7] Au,[8] Ir,[9] Pd,[10] Re,[11] Ru,[12] Co,[13] Cu,[14] Fe,[15] Mn[16] and Ni[17]), bimetallic catalysts[18] and non-metal catalysts[19] etc (Scheme 1a). Most of these catalyst systems needed high temperatures and strong alkalis to work.

β-Aminoketones are important structures found in many bioactive molecules and pharmaceutical agents, and are very useful intermediates in the synthesis of *β*-aminoacids, *β*-aminoalcohols, 1,3-alkamines, lactams, nikkomycins and neopolyoxines which also find wide applications in fine chemicals and pharmaceuticals.[20] We had developed a dehydrative N-alkylation of anilines with 4-hydroxybutan-2-one forming *β*-aminoketones and benzo[*h*]quinolones.[19b] During our ongoing studies, we found that TBN (*tert*-butyl nitrite) could catalyze the dehydrative N-alkylation of anilines with 4-hydroxybutan-2-one to yield *β*-aminoketones in the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) which differed from the TEMPO/TBN-catalyzed oxidation reactions (Scheme 1b). A broad range of anilines were alkylated with 4-hydroxybutan-2-one. Preliminary mechanistic investigation suggested that this reaction most possibly experienced *α*, *β*-unsaturated ketones and followed by aza-Michael addition.



Scheme 1. N-alkylation of amines with alcohols.

We began our investigations using commercially available aniline (**1a**) as amine source and 4-hydroxybutan-2-one (**1b**) as alcohol substrate with 10 mol% TEMPO and 10 mol% TBN in DMSO at room temperature for 12 h as shown in Table S1 (see the ESI). The 4-(phenylamino)butan-2-one (**1c**) was obtained in 37% isolated yield (Table S1, entry 1). A change of TBN to $NaNO_2$ and HCl contributed to the decline of the product yield (Table S1, entry 2). The reactions might involve NO• radical. In the absence of TEMPO or TBN, we did not detect 4-(phenylamino)butan-2-one (**1c**) (Table S1, entries 3 and 4). When this N-alkylation reaction was carried out in nitrogen atmosphere, 4-(phenylamino)butan-2-one (**1c**) was obtained in 73% isolated yield (Table 1, entry 1) which showed that O_2 had an impact on this N-alkylation reaction. Various conditions were tested in nitrogen atmosphere for the

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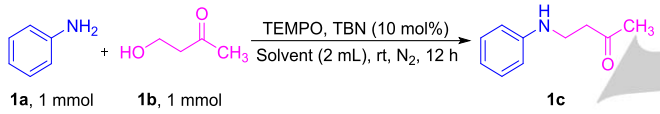
optimization of reaction parameters including TEMPO, TBN, solvents and reaction time to identify the optimal reactions conditions. First, brief screening of other solvent systems such as N, N-dimethylformamide (DMF), MeCN, MeOH, EtOH, toluene, THF, ethyl acetate (EA) and solvent-free system yielded 4-(phenylamino)butan-2-one (**1c**) in 7-65% isolated yields (Table 1, entries 2-9). This N-alkylation reaction did not occur in CH_2Cl_2, 1,2-dichloroethane (DCE) and H_2O (Table 1, entries 10-12). TBN was broken down by H_2O resulting in no N-alkylation reaction occur. Therefore, DMSO was the best choice for the next optimization study. Next, the influences of the TEMPO derivatives were investigated which revealed that TEMPO promoted this process more efficient than other derivatives (Table 1, entries 13-15). Subsequently, brief screening of the dosage of TEMPO provided a satisfactory alkylation product yield using 20 mol% TEMPO (Table 1, entries 16-19). The increase in the amount of TBN did not improve the product formation, and decrease in the amount of TBN led to the decrease of the product yield (Table 1, entries 20 and 21). It was worth noting that acceptable reaction yield was obtained when the reaction time was cut down to 9 h (Table 1, entries 22-25). Thus, further experiments were conducted with 20 mol% TEMPO and 10 mol% TBN at room temperature in DMSO for 9 h under nitrogen atmosphere.

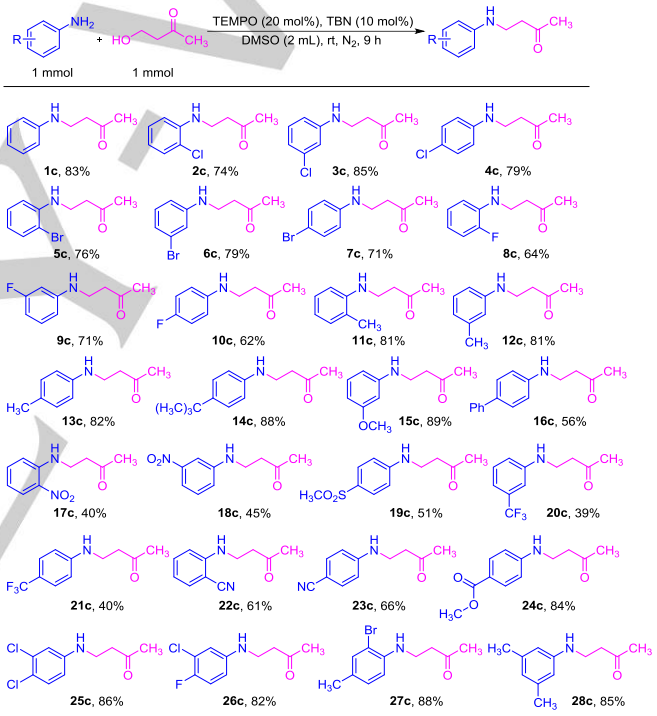
Table 1. Optimization of Reaction Conditions.



1a, 1 mmol **1b**, 1 mmol **1c**

entry	TEMPO (mol%)	solvent	yield[a] (%)
1	TEMPO (10)	DMSO	73
2	TEMPO (10)	DMF	63
3	TEMPO (10)	MeCN	7
4	TEMPO (10)	MeOH	56
5	TEMPO (10)	EtOH	57
6	TEMPO (10)	Toluene	65
7	TEMPO (10)	THF	42
8	TEMPO (10)	EA	25
9	TEMPO (10)	-	42
10	TEMPO (10)	CH_2Cl_2	n. r.
11	TEMPO (10)	DCE	n. r.
12	TEMPO (10)	H_2O	n. r.
13	HO-TEMPO (10)	DMSO	47
14	H_2NCO-TEMPO (10)	DMSO	57
15	H_2N-TEMPO (10)	DMSO	45
16	TEMPO (5)	DMSO	64
17	TEMPO (8)	DMSO	65
18	TEMPO (15)	DMSO	78
19	TEMPO (20)	DMSO	89
20[b]	TEMPO (20)	DMSO	62
21[c]	TEMPO (20)	DMSO	88
22[d]	TEMPO (20)	DMSO	53
23[e]	TEMPO (20)	DMSO	72
24[f]	TEMPO (20)	DMSO	76
25[g]	TEMPO (20)	DMSO	83

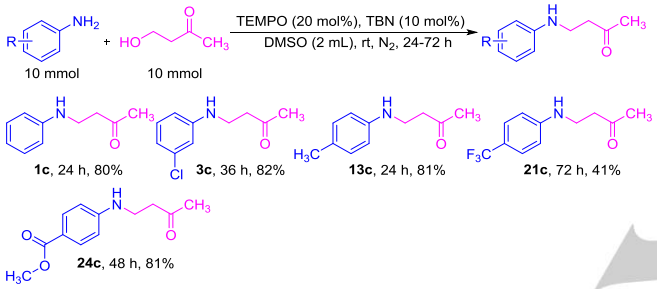
[a] Isolated yield, n. r. = no reaction. [b] The dosage of TBN was 5 mol%. [c] The dosage of TBN was 15 mol%. [d] Reaction time was 6 h. [e] Reaction time was 7 h. [f] Reaction time was 8 h. [g] Reaction time was 9 h.



Scheme 2. Scope of Substrates (isolated yield).

With the optimal conditions established, a wide range of structurally diverse anilines were subjected to the TBN-catalyzed dehydrative N-alkylation reaction (Scheme 2). Both electron-rich and electron-deficient anilines could be employed efficiently in this catalytic platform (**1c**-**28c**, 39-89%). Bromine and chlorine substituents had slight influences on our process (Scheme 2, **2c**-**7c**). By comparison, fluorine substituent had obvious effects (Scheme 2, **8c**-**10c**). It might be due to the strong electronegativity of fluorine. The halogen substituents with different positions on the phenyl groups had different influences on the reactivity. The effects of *ortho*- and *para*-substituents were greater than that of *meta*-substituents (Scheme 2, **2c**-**10c**). Substrates bearing methyl substituent at *ortho*-, *meta*-, and *para*-positions of anilines

afforded the N-monoalkylated anilines in 81%, 81% and 82% yields, respectively (Scheme 2, **11c**-**13c**). *tert*-Butyl and methoxy substitutes followed a similar trend with reasonably good yields (Scheme 2, **14c** and **15c**). Phenyl and cyano substitutes had obvious impacts on this dehydrative N-alkylation reaction, and were unfavorable for it. The yields of the products were 56%, 61% and 66%, respectively (Scheme 2, **16c**, **22c** and **23c**). The substrates with strong electron-withdrawing groups in the aromatic rings, such as -NO_2 (Scheme 2, **17c** and **18c**), -SO_2CH_3 (Scheme 2, **19c**) and -CF_3 (Scheme 2, **20c** and **21c**), were tolerated in this dehydrative N-alkylation reaction in moderate yields (40%, 45%, 51%, 39% and 40% yields, respectively). Surprisingly, electron-deficient aniline substituted with a *para*-ester group was converted into **24c** in 84% yield (Scheme 2, **24c**). Anilines bearing two substituents afforded the corresponding N-monoalkylated anilines in good yields (Scheme 2, **25c**, **26c**, **27c** and **28c**).



Scheme 3. Gram Scale Reactions (isolated yield).

To highlight the synthetic practicality of the present protocol, gram-scale (10 mmol) reactions with anilines and 4-hydroxybutan-2-one were performed until complete consumption of starting materials as monitored by TLC or 72 h. The desired products were obtained in good isolated yields (Scheme 3), indicating that this protocol was a practical process for the preparation of *β*-aminoketone.

The ^{1}H NMR was used to study the structural changes of 4-hydroxybutan-2-one (**1b**) in the presence of TBN (Figure 1). The resonance characteristics of olefins were displayed, which suggested that transformation of 4-hydroxybutan-2-one (**1b**) to methyl vinyl ketone took place in the reaction.

Encouraged by the above outcomes, further studies of this dehydrative N-alkylation reaction were carried out by various control experiments (Scheme 4). When only TEMPO or TEMPOH was used in nitrogen atmosphere, we did not detect 4-(phenylamino)butan-2-one (**1c**) (Scheme 4, eq 1 and 2) which liked the result of experiment in air atmosphere (Table S1, entry 3). 4-(phenylamino)butan-2-one (**1c**) was obtained in 19% yield when only TBN was used in nitrogen atmosphere (Scheme 4, eq 3) which was different from the result of experiment in air atmosphere (Table S1, entry 4). TBN appeared to be the real catalyst of the reaction. When TEMPOH or TEMPO was used together with TBN, 4-(phenylamino)butan-2-one (**1c**) was obtained in 83% and 45% yields, respectively (Scheme 4, eq 4 and 5). TEMPO might act as a stabilizing agent to prevent the polymerization of methyl vinyl ketone *in-situ* generated from 4-hydroxybutan-2-one. *t*-BuO$^\bullet$ radicals could react with TEMPOH forming TEMPO. Other stabilizers such as hydroquinone and 2,6-di-*tert*-butyl-4-methylphenol (BHT) were studied. The yield of 4-(phenylamino)butan-2-one (**1c**) were 36% and 44% respectively (Scheme 4, eq 6 and 7). Increase the dosage of TEMPO to 1 mmol led to the decline in yield of 4-(phenylamino)butan-2-one (32%). It was probably because a large amount of TEMPO destroyed the key radicals of this dehydrative N-alkylation reaction.

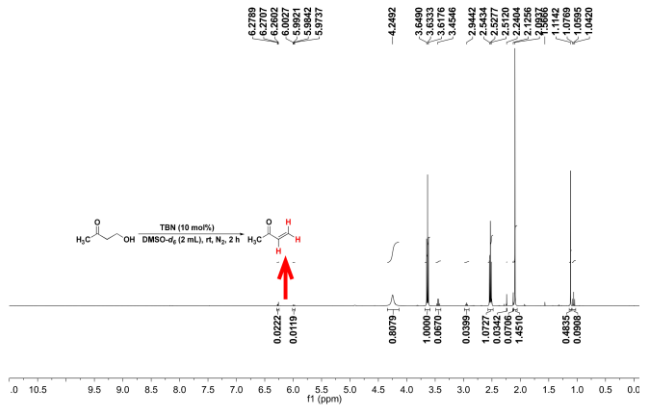
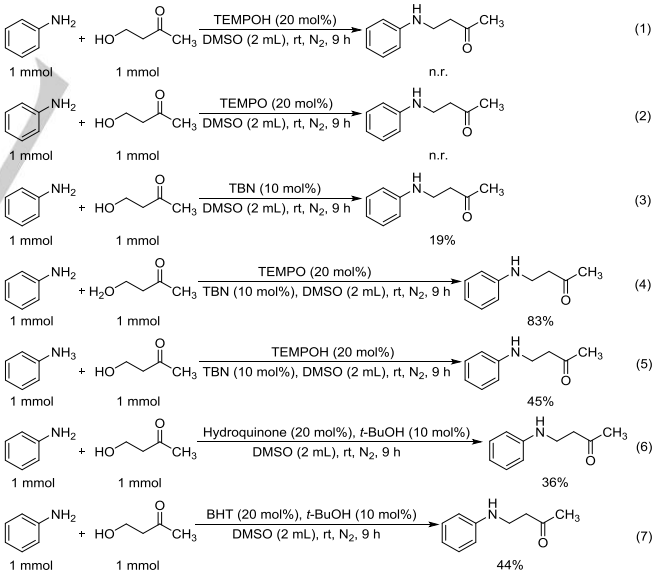


Figure 1. ^{1}H NMR spectra of 4-hydroxybutan-2-one and TBN.

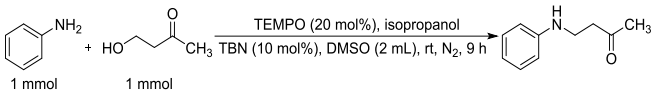


Scheme 4. Control Experiments.

We speculated this dehydrative N-alkylation reaction involved $^\bullet$OH radical. We conducted quenching tests to recognize $^\bullet$OH using isopropanol (Table 2). Low yields of 4-(phenylamino)butan-2-one (**1c**) were obtained in the cases of isopropanol, and the more isopropanol dosage, the lower product yield. These results

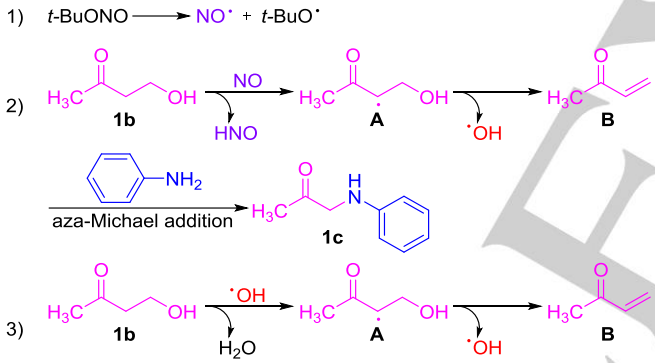
revealed the involvement of •OH radical in this dehydrative N-alkylation reaction.

Table 2. Quenching experiments (isolated yield).



entry	equivalents	yield (%)
1	0.5	52
2	1	41
3	2	33

A possible mechanism for this dehydrative N-alkylation reaction was proposed based on our results and previous literatures (Scheme 5). Initially, the decomposition of *tert*-butyl nitrite generated NO• radical. 4-hydroxybutan-2-one (**1b**) reacted with NO• to radical **A**, synchronic with generation of HNO. Then, the decomposition of radical **A** produced •OH radical and methyl vinyl ketone (**B**) which readily undergo oligomerization and polymerization. TEMPO acted as a stabilizing agent to prevent the polymerization of methyl vinyl ketone (**B**). The •OH radical reacted with another 4-hydroxybutan-2-one (**1b**) molecule to give radical **A.** Finally, aza-Michael addition between methyl vinyl ketone (**B**) with amine to afford product **1c**.



Scheme 5. Possible Reaction Pathway.

In summary, an efficient protocol for the dehydrative N-alkylation of anilines with 4-hydroxybutan-2-one using TBN as catalyst had been developed. A range of anilines reacted successfully with 4-hydroxybutan-2-one to generate the *β*-aminoketones products in good yields. A possible catalytic mechanism was proposed. Water was the only by-product, and this reaction could be scaled up. Further studies will be aimed at extending the substrate scope and investigating the reaction mechanism.

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Keywords: TEMPO • TBN • N-Alkylation • Substitution • Alcohol

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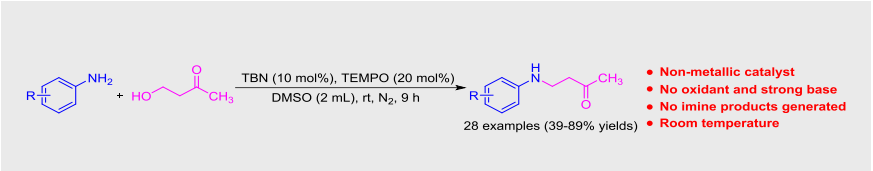

An efficient protocol for the dehydrative N-alkylation of anilines with 4-hydroxybutan-2-one using TBN as catalyst in the presence of TEMPO has been developed. Various anilines could be transformed into the N-monoalkylation products in good yields. α, β-Unsaturated ketone generated in situ from 4-hydroxybutan-2-one and aza-Michael addition were involved. Water was the only by-product.

Catalytic N-Alkylation

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TBN-Catalyzed Dehydrative N-Alkylation of Anilines with 4-Hydroxybutan-2-one