Direct C-2 Acylation of Thiazoles with Aldehydes via Metal- and Solvent-Free C–H Activation in the Presence of *tert*-Butyl Hydroperoxide

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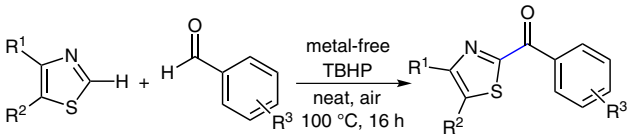
Abstract: A novel and efficient methodology for the synthesis of heteroaryl ketones by C–H activation of aldehydes and thiazoles is developed. The reaction occurs smoothly, under metal-, acid- and solvent-free conditions using *tert*-butyl hydroperoxide as the oxidant under an air atmosphere, to afford a wide range of heteroaryl ketones in moderate to good yields. The sp^2 C–H bonds in the aldehyde and thiazole undergo direct oxidative cross-coupling, resulting in C-2 acylation of the azole.

Key words: acylation, C–H activation, oxidative cross-coupling, metal-free, solvent-free

Azole derivatives are important building blocks in various natural products, agrochemicals and biologically active molecules.[1] In this regard, significant progress has been made in developing efficient methodologies for the synthesis of azoles substituted at C-2. Thus, C–C and C–N bond formation between azoles and various moieties such as alkynyl halides,[2] amines,[3] esters,[4] alkyl halides,[5] mesylates,[6] nitriles,[7] benzyl halides,[8] and alkenyl halides[9] have been achieved with considerable efficiency by cross-coupling at the C-2 position of azoles.

Acylation of azoles is an important approach to the synthesis of various heteroaryl ketones. Anderson and co-workers have developed C-2 acylations of azoles with acyl chlorides.[10] Benzaldehyde as an acylating reagent has also been explored by various groups,[11] the process requiring lithium metal along with inorganic oxidants. Beller and co-workers have reported carbonylative C–H activation of azoles using aryl halides and carbon monoxide gas.[12] Furthermore, the acylations of 2-phenylpyridine,[13] acetanilide[14] and other moieties,[15] via C–H bond activation with different acyl moieties using noble metal catalysts, have been reported.

Metal-free C–C bond formation by C–H activation using milder reaction conditions is a challenging prospect. In this regard, Wang and co-workers reported metal-free amidation[16] and alkylation[17] through oxidative cross-coupling by C–H activation. In addition, the metal-free acylation of heteroaryl moieties has been explored.[18] Thus, we aimed to develop an efficient and mild protocol for the acylation of thiazoles with aldehydes via sp^2 C–H bond activation at C-2. The present system works efficiently under metal-, acid-, and solvent-free conditions using *tert*-butyl hydroperoxide (TBHP) as an oxidant under an air atmosphere (Scheme 1).



Scheme 1 Oxidative acylation of thiazoles with aldehydes

Initially, the reaction of 4,5-dimethylthiazole (**1a**) with benzaldehyde (**2a**) was chosen as a model reaction, and the effects of various parameters such as the catalyst, solvent, oxidant, temperature and reaction time were studied. At the outset, we screened various transition-metal salts [$Pd(OAc)_2$, $Co(OAc)_2$, $Fe(OAc)_2$ and $FeSO_4$] for the oxidative cross-coupling of **1a** with **2a** using *tert*-butyl hydroperoxide as the oxidant (Table 1, entries 1–4). It was found that palladium acetate [$Pd(OAc)_2$] and iron(II) sulfate ($FeSO_4$) provided the desired product **3a** in 10% and 38% yield respectively (Table 1, entries 1 and 4). Furthermore, when the reaction was carried out in the absence of a metal salt, an improvement in the yield (45%) was observed (Table 1, entry 5). Next, we investigated the effect of different solvents on the reaction (Table 1, entries 6 and 7). However, when the reaction was carried out in the absence of a catalyst and solvent, the yield of the desired product **3a** increased to 73% (Table 1, entry 8).

We next screened various organic and inorganic oxidants under metal- and solvent-free conditions (Table 1, entries 9–16), and observed that hydrogen peroxide and *m*-chloroperoxybenzoic acid (MCPBA) were ineffective (Table 1, entries 9 and 10), whilst *tert*-butyl perbenzoate (TBPB), cumene hydroperoxide (CHP) and aqueous *tert*-butyl hydroperoxide afforded the expected product in poor yields (Table 1, entries 11–13). Inorganic oxidants did not work under the same reaction conditions (Table 1, entries 14–16). When the reaction was carried out using *tert*-butyl hydroperoxide as the oxidant without an air atmosphere the yield of the desired product decreased (Table 1, entry 17). Performing the reaction under an oxygen atmosphere also led to a lower yield of the acylation product (Table 1, entry 18). Furthermore, the effect of increasing the number of equivalents of benzaldehyde (**2a**) showed that the yield of **3a** was improved when the **1a**:**2a** ratio was 1:4 (Table 1, entries 8 and 19). We also studied the effect of the *tert*-butyl hydroperoxide loading and found that four equivalents of the oxidant were necessary to obtain ac-

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ceptable yields (Table 1, entries 8 and 20). Subsequently, the effect of the reaction time and temperature were examined, and it was found that the highest yield of the product **3a** was obtained at 100 °C within 16 hours.

Table 1 Optimization of the Reaction Conditions[a]

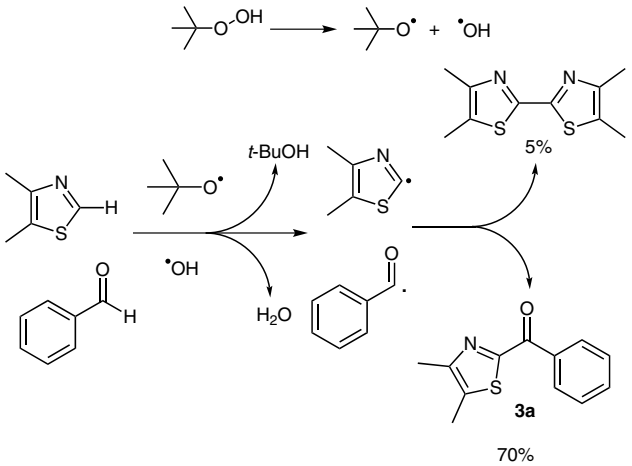
Entry	Catalyst	Oxidant	Solvent	Yield (%)[b]
Effect of the catalyst				
1	$Pd(OAc)_2$	TBHP	toluene	10
2	$Co(OAc)_2$	TBHP	toluene	–
3	$Fe(OAc)_2$	TBHP	toluene	–
4	$FeSO_4$	TBHP	toluene	38
5	–	TBHP	toluene	45
Effect of the solvent				
6	–	TBHP	PhCl	5
7	–	TBHP	MeCN	10
8	–	TBHP	–	73
Effect of the oxidant				
9	–	H_2O_2	–	–
10	–	MCPBA	–	–
11	–	TBPB	–	20
12	–	CHP	–	16
13	–	TBHP (aq)	–	25
14	–	I_2	–	–
15	–	$K_2S_2O_8$	–	15
16	–	Ag_2CO_3	–	–
17[c]	–	TBHP	–	58
18[d]	–	TBHP	–	13
19[e]	–	TBHP	–	29
20[f]	–	TBHP	–	61

[a] Reaction conditions: 4,5-dimethylthiazole (**1a**) (1 mmol), benzaldehyde (**2a**) (4 mmol), oxidant (4 mmol), catalyst (10 mol%) if necessary, solvent (3 ml) if necessary, 100 °C, air atmosphere, 16 h.
[b] Yield determined by GC.
[c] Without an air atmosphere.
[d] Under an oxygen atmosphere.
[e] Ratio of **1a**/**2a** = 1:1.
[f] TBHP (3 equiv, 5–6 M in decane).

With optimized reaction conditions in hand, the scope of the protocol was extended for the synthesis of various acylated thiazole derivatives. As shown in Table 2, the reaction worked efficiently with different aldehydes to provide a wide range of acylated thiazole derivatives in moderate to good yields. The important feature of the present protocol is that acylation of thiazole **1a** with *ortho*-, *meta*-, and *para*-substituted aldehyde derivatives proceeded well, and the corresponding 2-acylated thiazole products were obtained in good yields (Table 2, entries 1–11), indicating that the steric and electronic effects of the substituents on the aromatic rings of the aldehydes were negligible. The acylation of thiazole **1a** with aldehydes bearing electron-donating substituents proceeded smoothly to afford good yields of the corresponding products (Table 2, entries 2–6).

Aldehydes bearing halide substituents also furnished good yields of the corresponding products (Table 2, entries 7–11). The heteroaromatic aldehyde, thiophene-3-carboxaldehyde (**2l**) smoothly underwent oxidative cross-coupling and provided a moderate yield of the respective product **3l** (Table 2, entry 12). Moreover, an aliphatic aldehyde also reacted under the optimized reaction conditions to give a moderate 47% yield of the coupled product **3m** (Table 2, entry 13).[19] When the reaction was carried out using 4-methylthiazole (**1b**), satisfactory yields of the corresponding products were obtained (Table 2, entries 14–16).[20]

A tentative mechanism to rationalize this transformation is presented in Scheme 2. The reaction may proceed through the generation of free radicals, the first step involving homolysis of *tert*-butyl hydroperoxide to generate a hydroxyl radical and an alkoxyl radical. In the next step, these radicals abstract hydrogens from the sp^2 C–H (C-2) of 4,5-dimethylthiazole and the aldehydic C–H of benzaldehyde, generating the corresponding free radicals. Finally, the free radicals of 4,5-dimethylthiazole and benzaldehyde react with each other to form a new carbon–carbon bond and generate the acylated derivative (**3a**) as the major product, along with the minor homo-coupled side product through termination of two radicals of 4,5-dimethylthiazole. It should be noted that the reaction was suppressed by a radical scavenger, such as 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO).



Scheme 2 A plausible reaction mechanism for the acylation of thiazoles with aldehydes

Table 2 Oxidative Acylation of Thiazoles with Various Aldehydes[a]

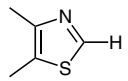
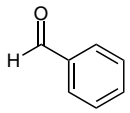
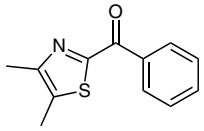
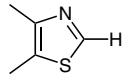
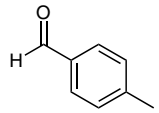
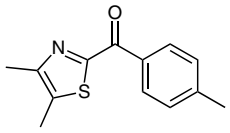
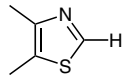
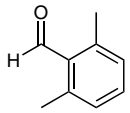
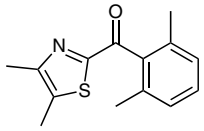
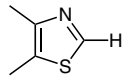
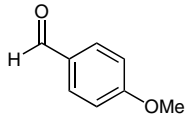
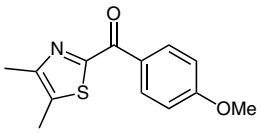
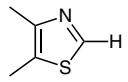
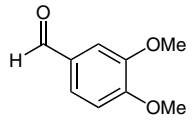
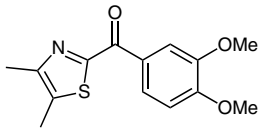
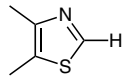
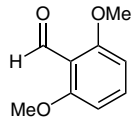
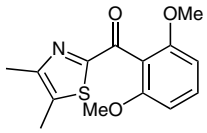
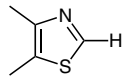
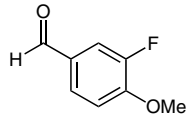
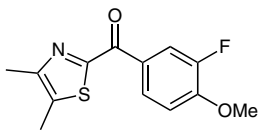
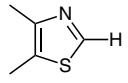
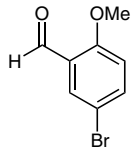
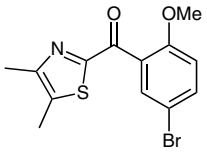
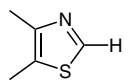
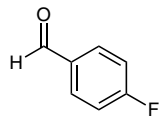
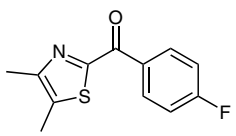
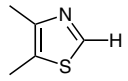
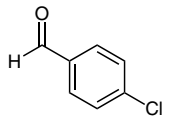
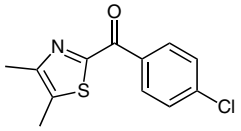
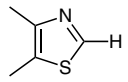
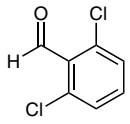
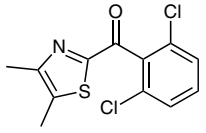
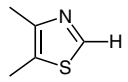
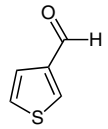
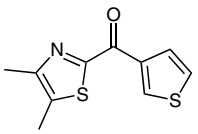
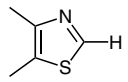
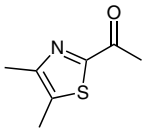
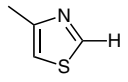
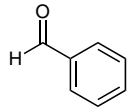
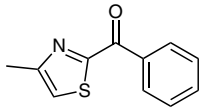
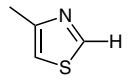
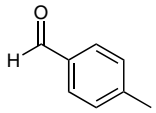
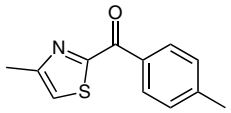
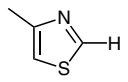
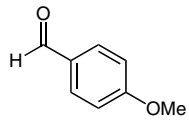
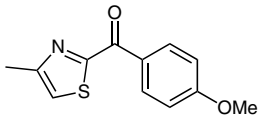
Entry	Thiazole	Aldehyde	Product	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	70
2	 **1a**	 **2b**	 **3b**	72
3	 **1a**	 **2c**	 **3c**	78
4	 **1a**	 **2d**	 **3d**	73
5	 **1a**	 **2e**	 **3e**	71
6	 **1a**	 **2f**	 **3f**	80
7	 **1a**	 **2g**	 **3g**	72
8	 **1a**	 **2h**	 **3h**	76
9	 **1a**	 **2i**	 **3i**	65

Table 2 Oxidative Acylation of Thiazoles with Various Aldehydes[a] (continued)

Entry	Thiazole	Aldehyde	Product	Yield (%)[b]
10	 **1a**	 **2j**	 **3j**	72
11	 **1a**	 **2k**	 **3k**	77
12	 **1a**	 **2l**	 **3l**	56
13	 **1a**	 **2m**	 **3m**	47
14	 **1b**	 **2a**	 **3n**	60
15	 **1b**	 **2b**	 **3o**	63
16	 **1b**	 **2d**	 **3p**	64

[a] Reaction conditions: thiazole (1 mmol), aldehyde (4 mmol), TBHP (4 mmol, 5–6 M in decane), 100 °C, 16 h, air atmosphere, neat.
[b] Yield of isolated product.

In summary, we have developed an efficient protocol for the direct C-2 acylation of thiazoles with a range of aldehydes, via C–H activation under metal-, acid-, and solvent-free conditions, to give the corresponding acylated thiazole derivatives.[21] Further applications of the present protocol for acylation of various moieties are under progress.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(21) **(4,5-Dimethylthiazol-2-yl)(phenyl)methanone (3a); Typical Procedure**

An oven-dried 15 mL glass vial containing a magnetic stir bar was charged with 4,5-dimethylthiazole (**1a**) (1 mmol) and benzaldehyde (**2a**) (4 mmol). The vial was then flushed with air and sealed with a cap. Next, TBHP (4 mmol, 5–6 M in decane) was added dropwise with stirring and the mixture was further stirred at 100 °C for 16 h under an air atm. After cooling the mixture to r.t., it was washed with sat. $NaHCO_3$ solution (1 × 30 mL). The product was extracted with EtOAc (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum and the crude residue was purified by column chromatography (silica gel, 60–100 mesh; PE–EtOAc) to afford pure coupled product **3a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44–8.41 (m, 2 H), 7.56–7.51 (m, 3 H), 2.47 (s, 3 H), 2.45 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.08, 162.58, 151.77, 135.92, 133.25, 131.10, 128.68, 124.02, 15.14, 12.02. GC–MS (EI, 70 eV): *m*/*z* (%) = 217 (20) $[M]^+$, 188 (52), 105 (100), 85 (37), 77 (87), 53 (10), 51 (31). HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{12}NOS$: 218.0640; found: 218.0634.

(4,5-Dimethylthiazol-2-yl)(*p*-tolyl)methanone (3b)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.05 Hz, 2 H), 7.29 (d, *J* = 8.05 Hz, 2 H), 2.46 (s, 3 H), 2.44 (s, 3 H), 2.42 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.69, 162.89, 151.60, 144.15, 135.57, 133.01, 131.23, 129.07, 21.80, 15.14, 12.00. GC–MS (EI, 70 eV): *m*/*z* (%) = 231 (23) $[M]^+$, 202 (55), 119 (100), 91 (55), 89 (13), 86 (27), 65 (29), 45 (30), 44 (23), 39 (11). HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}NOS$: 232.0796; found: 232.0791.

(2,6-Dimethylphenyl)(4,5-dimethylthiazol-2-yl)methanone (3c)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (t, *J* = 7.6 Hz, 1 H), 7.05 (d, *J* = 7.6 Hz, 2 H), 2.45 (s, 3 H), 2.35 (s, 3 H), 2.19 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.94, 161.71, 152.86, 138.78, 130.63, 129.32, 127.62, 119.38, 19.70, 15.06, 12.22. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{16}NOS$: 246.0953; found: 246.0947. GC–MS (EI, 70 eV): *m*/*z* (%) = 245 (38) $[M]^+$, 228 (16), 218 (18), 217 (100), 216 (63), 202 (18), 133 (37), 105 (56), 103 (24), 86 (60), 79 (32), 78 (14), 77 (41), 71 (22), 53 16), 39 (13).

