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Thulium Triflate Catalyzed Hydration of 2-Substituted 4-Alkynones

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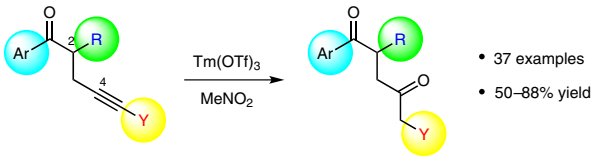

Ar = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$F_3CC_6H_4$, 4-PhC_6H_4, 2-naphthyl, 2-thienyl, 3,4-$(MeO)_2C_6H_3$, 2,3,4-$(MeO)_3C_6H_2$
R = $TolSO_2$, $PhSO_2$, $MeSO_2$, 3-$MeC_6H_4SO_2$, 4-*t*-$BuC_6H_4SO_2$, 4-$MeOC_6H_4SO_2$, 4-$FC_6H_4SO_2$; Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$F_3CC_6H_4$, 3,5-$F_2C_6H_3$, 4-PhC_6H_4, 2-naphthyl
Y = H, Me, Et, Ph

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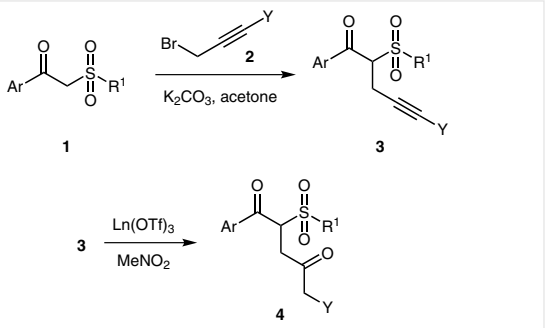
Abstract We report on a facile synthetic route for the preparation of substituted 1,4-diketones by thulium triflate mediated hydration of substituted 4-alkynones in $MeNO_2$ at 25 °C for five hours. The products were obtained in moderate to high yields.

Key words diketones, thulium triflate, hydration, alkynone, pyridazine

The transition metal complex mediated chemoselective hydration of terminal alkynes to obtain methyl ketones is one of the most straightforward functional-group transformations.[1,2] The Markovnikov-type hydration of alkynes promoted by mercuric salts is a classic procedure.[3] Because traditional mercury(II) catalysts are environmentally hazardous, alternative metal catalysts have been developed, including gold(I),[4] silver(I),[5] silver(I)/silver(III),[6] ruthenium(II),[7] rhodium(III),[8] platinum(II),[9] osmium(II),[10] iridium(III),[11] palladium(II),[12] iron(III),[13] copper(II),[14] indium(III),[15] and zinc(II).[16] Notably, some cases have been reported of metal triflate mediated hydration of alkynes using $Hg(OTf)_2$,[3] AgOTf,[5] $Cu(OTf)_2$,[14] $In(OTf)_3$,[15] and $Zn(OTf)_2$.[16] To the best of our knowledge, no examples have been performed where $Ln(OTf)_3$ (lanthanide triflates) promote the formation of carbonyl compounds.[17] In continuation of our investigation on metal triflates and α-substituted β-ketosulfones,[18,19] a facile synthesis of sulfonyl 1,4-diketones through $Ln(OTf)_3$-mediated hydration of α-propargyl β-ketosulfones[18c] was developed (Scheme 1). 1,4-Diketones are versatile building blocks in the synthesis of substituted furans, thiophenes, and pyrroles.[20]A number of articles have highlighted fascinating developments in the synthesis of functionalized 1,4-diketones, including conjugated addition, oxidative or radical coupling, nucleophilic substitution, and the umpolung process.[21,22]

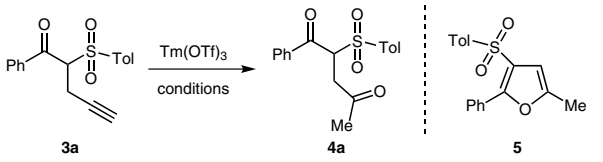


Scheme 1 Synthesis of 1,4-Diketones

After perusing literature on the synthesis of substituted 1,4-diketones and our previous studies on metal triflate promoted reactions, 13 commercially available lanthanide triflates were examined for the

$Ln(OTf)_3$-promoted hydration of substrate **3a** in $MeNO_2$ at room temperature for three hours. However, no obvious yield changes occurred with the isolation of **4a** using 5 mol% of $La(OTf)_3$, $Ce(OTf)_3$, $Pr(OTf)_3$, $Nd(OTf)_3$, $Sm(OTf)_3$, $Eu(OTf)_3$, $Gd(OTf)_3$, $Tb(OTf)_3$, $Dy(OTf)_3$, $Ho(OTf)_3$, $Er(OTf)_3$, or $Yb(OTf)_3$. Only $Gd(OTf)_3$, $Ho(OTf)_3$, and $Tm(OTf)_3$provided **4a** in 10%, 14% and 31% yields, respectively. On the basis of the results, $Tm(OTf)_3$ was used as a catalyst to screen the optimal reaction conditions, as shown in Table 1. Further variations in the reaction parameters such as the catalyst loading were examined as follows. In Table 1, entry 1, increasing the catalytic amount of $Tm(OTf)_3$ (5 mol% to 10 mol%) increased the yield of **4a** (31% to 46%) and 43% of **3a** were recovered. In Table 1, entry 2, the catalytic ability of 20 mol% $Tm(OTf)_3$ was similar to 10 mol%. With an elongat-

Table 1 Optimal Conditions[a,b]



3a 4a 5

Entry	$Tm(OTf)_3$ (mol%)	Solvent	Temp	Time (h)	Yield of **4a** (%)[c]
1	10	$MeNO_2$	25 °C	3	46 (43)[d]
2	20	$MeNO_2$	25 °C	3	48 (33)[d]
3	10	$MeNO_2$	25 °C	20	51 (38)[d]
4	10	$MeNO_2$	reflux	3	88
5	10	toluene	25 °C	3	–[e]
6	10	toluene	25 °C	20	–[e]
7	10	CH_2Cl_2	reflux	3	–[e]
8	10	CH_2Cl_2	reflux	20	–[e]
9	10	EtOAc	reflux	3	15[e]
10	10	DMF	reflux	3	46[f]
11	10	$MeNO_2$	reflux	20	36[g]

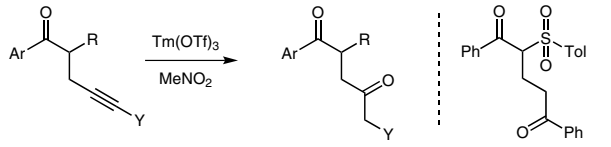
[a] Reaction was run using **3a** (1.0 mmol) and solvent (97%, 5 mL, containing at least 2–3% of H_2O).
[b] All solvents were obtained from commercial sources and used without further purification.
[c] Isolated yield.
[d] Isolated yield of **3a**.
[e] **3a** was recovered (for entry 5, 82%; for entry 6, 70%; for entry 7, 74%; for entry 8, 70%; for entry 9, 49%).
[f] A complex mixture (27%) was isolated.
[g] 30% of 3-sulfonyl furan **5** was observed.

ed reaction time (3 h to 20 h), a higher yield (51%) was observed (Table 1, entry 3). After elevating the temperature (room temperature to reflux), **4a** was isolated in 88% yield (Table 1, entry 4). After changing the reaction solvent from $MeNO_2$ to toluene and CH_2Cl_2, only **3a** was recovered (Table 1, entries 5–8) and no hydrated products could be detected at room temperature and under reflux conditions, respectively. In refluxing EtOAc (Table 1, entry 9), **4a** was isolated in low yield (15%) and **3a** was recovered (49%). Entry 10 showed that in refluxing DMF, **4a** was obtained

in 46% yield of along with 27% of complex mixture. However, treatment of **3a** with refluxing $MeNO_2$ for 20 hours afforded **4a** in low yield (36%) due to the formation of the skeleton of 3-sulfonyl furan **5** (Table 1, entry 11). On the basis of a higher yield, we believe that 10 mol% $Tm(OTf)_3$, $MeNO_2$, reflux for three hours should be the optimal reaction conditions for the formation of **4a**.

On the other hand, $Tm(OTf)_3$ has been reported as a catalyst for Ferrier rearrangements[23a] and Diels–Alder cycloadditions.[23b] Remarkably, only a few examples of thulium(III) salt mediated reactions have been performed in comparison with other commercially available metal triflates.[24] With the facile reaction conditions in hand (Table 1, entry 4), we further explored the conversion of other substrate scopes, with the results shown in Table 2. For three substituents of **3a**–**aj** (Ar, R, and Y), the Ar ring [Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$F_3CC_6H_4$, 4-PhC_6H_4, 2-naphthyl, 2-thienyl, 3,4-$(MeO)_2C_6H_3$, 2,3,4-$(MeO)_3C_6H_2$] with diversified electron-neutral, electron-donating, or electron-withdrawing groups was well tolerated. The R group included sulfonyl groups ($TolSO_2$, $PhSO_2$, $MeSO_2$, 3-$MeC_6H_4SO_2$, 4-*t*-$BuC_6H_4SO_2$, 4-$MeOC_6H_4SO_2$, 4-$FC_6H_4SO_2$) and aryl groups (Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$F_3CC_6H_4$, 3,5-$F_2C_6H_3$, 4-PhC_6H_4, 2-naphthyl). Y can be a hydrogen (H), methyl (Me), ethyl (Et), or phenyl (Ph) group. By the $Tm(OTf)_3$-mediated hydration reaction of 4-alkynones **3a**–**aj**, 1,4-diketones **4a**–**aj** were provided in moderate to good yields (73–88%, entries 1–36).[25] In all entries, no obvious yield changes for **4** were observed when different substituents of **3** were involved. However, 50% of **4ak** was isolated along with 18% of a complex mixture when H_2O was involved on the benzylic position of **3ak** (Table 2, entry 37).

Table 2 Synthesis of **4a**–**ak**[a]



3 4 4ak

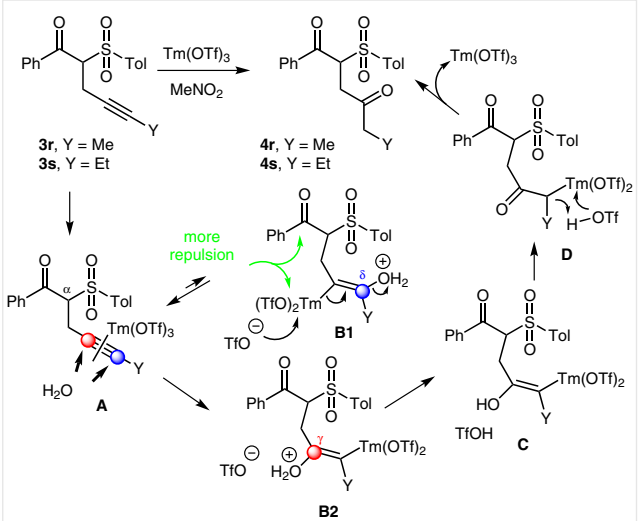
Entry	**3** Ar =, R =, Y =	Yield of **4** (%)[b]
1	**3a** Ph, $TolSO_2$, H	**4a** 88
2	**3b** 4-FC_6H_4, $TolSO_2$, H	**4b** 86
3	**3c** 4-$MeOC_6H_4$, $TolSO_2$, H	**4c** 84[c]
4	**3d** 4-MeC_6H_4, $TolSO_2$, H	**4d** 85
5	**3e** 4-$F_3CC_6H_4$, $TolSO_2$, H	**4e** 87
6	**3f** 4-PhC_6H_4, $TolSO_2$, H	**4f** 86
7	**3g** 2-naphthyl, $TolSO_2$, H	**4g** 84
8	**3h** 4-FC_6H_4, $PhSO_2$, H	**4h** 82
9	**3i** 4-$MeOC_6H_4$, $PhSO_2$, H	**4i** 84
10	**3j** 4-PhC_6H_4, $PhSO_2$, H	**4j** 80
11	**3k** 4-MeC_6H_4, $MeSO_2$, H	**4k** 80
12	**3l** 4-PhC_6H_4, $MeSO_2$, H	**4l** 82
13	**3m** Ph, 3-$MeC_6H_4SO_2$, H	**4m** 84
14	**3n** Ph, 4-*t*-$BuC_6H_4SO_2$, H	**4n** 85
15	**3o** Ph, 4-$MeOC_6H_4SO_2$, H	**4o** 80
16	**3p** Ph, 4-$FC_6H_4SO_2$, H	**4p** 80
17	**3q** 2-thienyl, $TolSO_2$, H	**4q** 82
18	**3r** Ph, $TolSO_2$, Me	**4r** 78
19	**3s** Ph, $TolSO_2$, Et	**4s** 76
20	**3t** Ph, Ph, H	**4t** 79
21	**3u** 4-$MeOC_6H_4$, Ph, H	**4u** 82

Table 2 (continued)

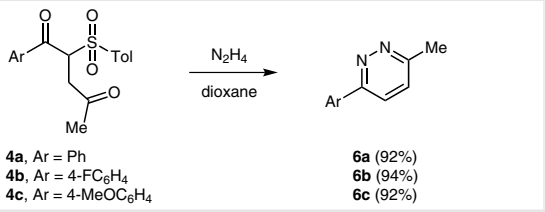
Entry	**3** Ar =, R =, Y =	Yield of **4** (%)[b]
22	**3v** 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, H	**4v** 78
23	**3w** 4-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, H	**4w** 78
24	**3x** 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, H	**4x** 80
25	**3y** 4-MeOC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, H	**4y** 76
26	**3z** 4-MeOC$_6$H$_4$, 3,5-F$_2$C$_6$H$_3$, H	**4z** 74
27	**3aa** 4-MeOC$_6$H$_4$, 4-PhC$_6$H$_4$, H	**4aa** 73
28	**3ab** 4-MeOC$_6$H$_4$, 2-naphthyl, H	**4ab** 76
29	**3ac** 3,4-(MeO)$_2$C$_6$H$_3$, Ph, H	**4ac** 75
30	**3ad** 3,4-(MeO)$_2$C$_6$H$_3$, 4-MeC$_6$H$_4$, H	**4ad** 74
31	**3ae** 3,4-(MeO)$_2$C$_6$H$_3$, 4-MeOC$_6$H$_4$, H	**4ae** 74
32	**3af** 3,4-(MeO)$_2$C$_6$H$_3$, 4-FC$_6$H$_4$, H	**4af** 76
33	**3ag** 3,4-(MeO)$_2$C$_6$H$_3$, 4-PhC$_6$H$_4$, H	**4ag** 76
34	**3ah** 3,4-(MeO)$_2$C$_6$H$_3$, 3,5-F$_2$C$_6$H$_3$, H	**4ah** 77
35	**3ai** 3,4,5-(MeO)$_3$C$_6$H$_2$, Ph, H	**4ai** 76
36	**3aj** 3,4,5-(MeO)$_3$C$_6$H$_2$, 4-FC$_6$H$_4$, H	**4aj** 78
37	**3ak** Ph, TolSO$_2$, Ph	**4ak** 50[c]

[a] The synthesis of **6** was run on a 1.0 mmol scale with **3**, Tm(OTf)$_3$ (10 mol%), MeNO$_2$ (5 mL), 3 h, reflux.
[b] Isolated yield.
[c] Complex mixture (18%) was isolated.

Based on the results, a possible reaction mechanism is shown in Scheme 2. How were regioisomers **4r** and **4s** produced? The mechanism should be initiated to form **A** by complexation of an α-alkynyl motif of **3r** and **3s** with Tm(OTf)$_3$, and participation of H$_2$O (from MeNO$_2$) could lead to the **B1** and **B2** via the intermolecular *anti* addition of H$_2$O on the δ position (blue) and γ position (red) of **A**. For the configuration of **B1** (having the δ addition of H$_2$O), a stronger repulsion between the benzoyl group and the thulium complex was generated (green arrow) such that in situ formed triflate anion mediated the reversed pathway may be occurred. Following the proton exchange of oxonium cation and triflate anion on **B2** (having the γ addition of H$_2$O), tautomerization of **C**, and then triflic acid promoted dethuliumation of **D**, the removal of Tm(OTf)$_3$ afforded **4r** and **4s**.

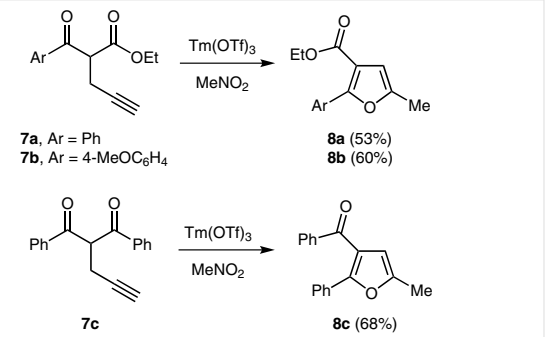


Scheme 2 Plausible mechanism of **4r**,**s**



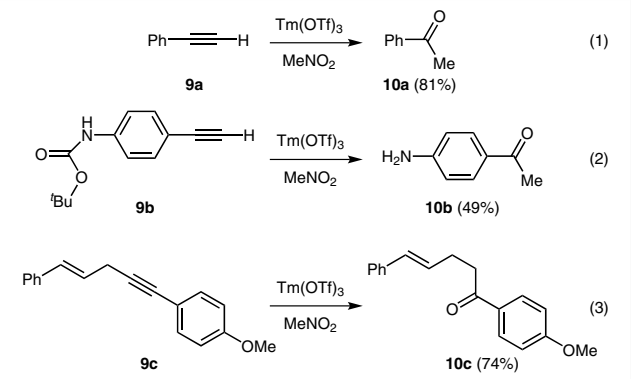
Scheme 3 Synthesis of pyridazines **6a–c**

In an extension of this method, we were able to perform a synthesis of pyridazine, as shown in Scheme 3. 2-Arylpyridazine is a versatile scaffold for useful synthetic intermediates.[26] It also exhibits versatile biological activities.[27] Many articles have highlighted fascinating developments based on two carbon–nitrogen bond formations.[28] Furthermore, condensation of sulfonyl 1,4-diketones **4a–c** with 80% hydrazine in dioxane for four hours at 25 °C provided 2-arylpyridazines **6a–c** in high yields (92%, 94%, and 92%) during the desulfonylative aromatization process. As shown in Scheme 4,Tm(OTf)$_3$-mediated reactions of α-propargyl β-ketoesters **7a**,**b** and α-propargyl β-diketone **7c** in MeNO$_2$ at reflux for three hours were examined next. In particular, 2-arylfurans **8a–c** provided as the sole isomer in 53–68% yields via the cycloisomerization process under the above conditions.



Scheme 4 Tm(OTf)$_3$-mediated cycloisomerization of **7a–c**

Furthermore, changing 1,3-diacrbonyls synthons **7** with the propargyl group to arylacetylenes **9**, substituted acetophenones **10a–c** afforded in 49–81% yields as shown in Scheme 5. In Scheme 5, eq. 1, **9a** was easily converted into **10a** in 81% yield. However, the Boc-protective group on **9b** could be removed by Tm(OTf)$_3$ and **10b** was isolated in 49% yield under the refluxing MeNO$_2$ conditions (Scheme 5, eq. 2). In Scheme 5, eq. 3, 4-alkenone **10c** afforded in 74% yield



Scheme 5 $Tm(OTf)_3$-mediated of hydration of **9a–c**

via $Tm(OTf)_3$-mediated hydration of enyne **9c** having the olefin group. The olefinic motif did not be affected under the acid-sensitive conditions.

In summary, we have developed a mild and facile synthesis of substituted 1,4-diketones **4** in good yields through a 10 mol% $Tm(OTf)_3$-mediated hydration reaction of substituted 4-alkynones **3** in $MeNO_2$ at reflux for three hours. The control of reaction parameters such as the lanthanide triflate catalyst loading, the reaction temperature, the solvent, and reaction time, had to be finely tuned in order to explore optimal reaction conditions. Furthermore, 2-arylpyridazines **6a–c** were synthesized from a concentration reaction of sulfonyl 1,4-diketones **4a–c** with hydrazine. Further investigation regarding synthetic applications of lanthanide triflates will be conducted and published in due course.

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Supporting Information

Supporting information (experimental procedures and scanned photocopies of NMR (CDCl3) spectral data) for this article is available online at http://dx.doi.org/10.1055/s-0035-1561652.

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(25) **Representative Synthetic Procedure of Skeleton 4**

$Tm(OTf)_3$ (62 mg, 0.1 mmol) was added to a solution of **3** (1.0 mmol) in $MeNO_2$ (5 mL) at r.t. The reaction mixture was stirred at reflux for 3 h. The reaction mixture was cooled to r.t. The solvent of reaction mixture was concentrated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford the crude product under reduced pressure. Purification on silica gel (hexanes–EtOAc = 8:1 to 3:1) afforded **4**.

Compound **4a**: R_f = 0.3 (hexanes–EtOAc = 8:1); yield 88% (290 mg); colorless oil. ESI-HRMS: *m/z* calcd for $C_{18}H_{19}O_4S$ $[M^+ + 1]$: 331.1004; found: 331.1010. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J*= 8.8 Hz, 2 H), 7.58–7.54 (m, 3 H), 7.43–7.39 (m, 2 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 5.51 (dd, *J* = 2.8, 10.8 Hz, 1 H), 3.49 (dd, *J* = 10.8, 18.0 Hz, 1 H), 3.29 (dd, *J* = 2.8, 18.0 Hz, 1 H), 2.40 (s, 3 H), 2.16 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.79, 191.59, 145.60, 136.58, 133.68, 133.54, 129.68 (2×), 129.36 (2×), 129.17 (2×), 128.49 (2×), 65.55, 41.87, 29.55, 21.64.

Compound **4b**: R_f = 0.3 (hexanes–EtOAc = 8:1); yield 86% (299 mg); colorless oil. ESI-HRMS: *m/z* calcd for $C_{18}H_{18}FO_4S$ $[M^+ + 1]$: 349.0910; found: 349.0918. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.94 (m, 2 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.8 Hz, 2 H), 7.13–7.07 (m, 2 H), 5.43 (dd, *J* = 2.8, 10.8 Hz, 1 H), 3.47 (dd, *J* = 10.8, 18.0 Hz, 1 H), 3.27 (dd, *J* = 2.8, 18.0 Hz, 1 H), 2.42 (s, 3 H), 2.15 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.81, 190.02, 166.13 (d, *J* = 255.5 Hz), 145.77, 133.36, 133.03 (d, *J* = 3.0 Hz), 132.97 (d, *J* = 9.1 Hz, 2×), 130.53, 129.74, 129.35, 128.84, 115.71 (d, *J* = 21.9 Hz, 2×), 65.58, 41.99, 29.49, 21.65.

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