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COMMUNICATION

Grignard-Mediated Rearrangement of Trifluoroacetyl from Dihydroisoquinoline Enamides to Afford Tertiary Trifluoromethylcarbinols

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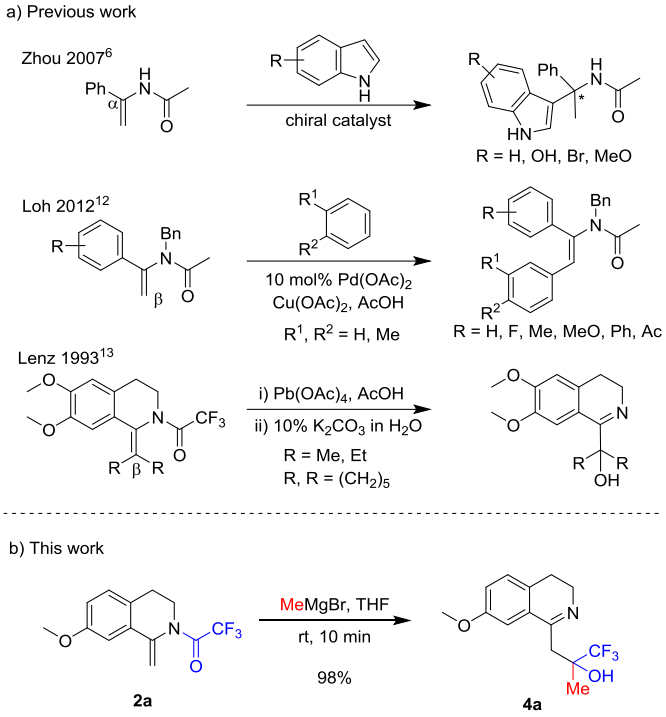
Raghavendra Achary,[a,b] Gangadhar Rao Mathi,[a,b] Seulgi Kim,[a,c] Jong Yeon Hwang,[a,b] Pilho Kim,*[a,b]

Treatment of trifluoroacetyl enamides of dihydroisoquinolines 2 with diverse Grignard reagents afforded tertiary trifluoromethyl-carbinols 4 by facilitating the addition of tertiary carbinols to the β-carbon of enamides 2. Based on the confirmed formation of vinylogous amides 3, the transformation likely proceeds via unique acyl group rearrangement to the β-carbon of the enamide and subsequent nucleophilic addition of the Grignard reagent. Given the synthetic utility and novelty of this reaction, this work may open new avenues for the synthesis of pharmaceutically important tertiary trifluoromethylcarbinols on cyclic enamide systems.

While tetrahydroisoquinoline (THIQ) fragments are prevalent in natural and pharmaceutical products,[1] the enamides of dihydroisoquinolines (DHIQs) are important structural motifs useful in the synthesis of various building blocks through diverse transformations, such as asymmetric hydrogenation,[2] metal-catalyzed α- or β-functionalization,[3] and cycloaddition.[4] In general, the α-position of enamides is electrophilic, while the β-position is nucleophilic.[3,5] Several examples of nucleophilic addition at the α-carbon of enamides have been reported. For instance, various indoles were stereoselectively introduced at the α-carbon of enamides via Friedel–Crafts reactions using chiral Brønsted catalysts (Scheme 1).[6] An alkoxide was also regioselectively and asymmetrically introduced at the α-carbon of acyclic enamides using copper(I) catalysts and iminoiodane.[7] As for additions at the β-carbon of DHIQ enamides, abundant reports have also been published,[8-11] such as palladium-catalyzed direct β-arylation,[12] oxidative rearrangement of the trifluoroacetyl group to the β-carbon of the exocyclic double bond,[13] Cu(I)-mediated radical cycloaddition using *n*-Bu_3SnH/AIBN,[14] and Heck reactions providing polyannular heterocyclic compounds.[15]



Scheme 1 (a) Previous examples of enamide reactions, (b) unique generation of tertiary trifluoromethylcarbinol **4a** in this study.

During the course of developing novel methods to prepare C1-substituted THIQs, we opted to utilize the enamide of DHIQ as a key precursor. When trifluoroacetyl enamide **2a** was treated with methylmagnesium bromide, trifluoromethyl-carbinol **4a** was unexpectedly obtained in excellent yield (Scheme 1). To our knowledge, chemistry enabling the addition of tertiary trifluoromethylcarbinols to the β-carbon of DHIQ enamides has not been previously reported.

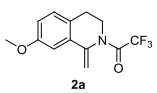
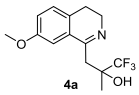
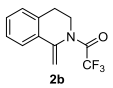
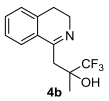
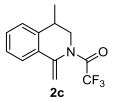
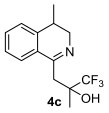
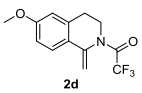
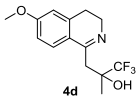
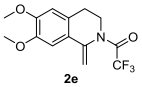
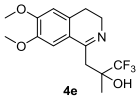
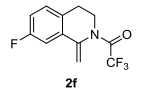
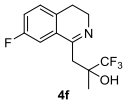
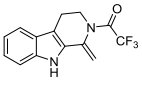
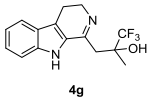
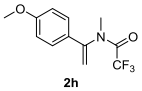
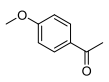
Moreover, pharmaceutically important trifluoromethyl-carbinols could be straightforwardly prepared by this synthetic methodology.[16] Trifluoromethylation has been quite instrumental in the field of pharmaceutics, agrochemicals, and

[a] Bio & Drug Discovery Division, Korea Research Institute of Chemical Technology, Daejeon 34114, Korea. E-mail: pkim@krict.re.kr
[b] Department of Medicinal Chemistry and Pharmacology, University of Science & Technology, Daejeon 34113, Korea.
[c] Department of Chemistry, Chungnam National University, Daejeon 34134, Korea
Electronic Supplementary Information (ESI) available: [Experimental and spectral data; NMR spectra of all products; crystallographic data of the products **4g** and **3d**. CCDC 1532366 and 1532365]. See DOI: 10.1039/x0xx00000x

material sciences. While numerous methods for trifluoromethylation are known,[17,18] such as those employing Umemoto reagents,[19] Togni reagents,[20] and trifluoromethyltrimethylsilane,[21] this kind of unique reaction for the construction of multi-substituted trifluoropropyl alcohols at the C1 position of THIQ is unprecedented. Considering the novelty and application potential of this reaction, the scope and limitations of this chemistry were extensively explored with the aim of preparing tertiary trifluromethylcarbinol analogs of DHIQs and cyclic imine systems in a convenient way.

At first, trifluoroacetyl enamides **2a–f** were prepared from DHIQs **1a-f** (see Supplementary Information) under modified enamide generation conditions.[22] With enamides **2a–f** in hand, the scope of the reaction was evaluated. It turned out that DHIQ enamides **2a–f** are applicable for this reaction regardless of the substituents, affording the corresponding trifluoromethylcarbinols **4a–f** in good yields (entries 1–6 in Table 1). In the case of pyrido[3,4-*b*]indole enamide **2g**, a non-DHIQ enamide, trifluoromethylcarbinol **4g** was obtained in 80% yield using three equivalents of methylmagnesium bromide (entry 7).

Table 1 Scope of the reaction with various enamides[a]

Entry	Enamides	MeMgBr (eq)	Time	Product	Yield (%)[b]
1	 **2a**	1.5	10 min	 **4a**	98
2	 **2b**	1.5	10 min	 **4b**	94
3	 **2c**	1.5	10 min	 **4c**	85
4	 **2d**	1.5	10 min	 **4d**	96
5	 **2e**	1.5	10 min	 **4e**	83
6	 **2f**	2.0	15 min	 **4f**	86
7	 **2g**	3.0	10 min	 **4g**	80
8	 **2h**	1.5	12 h		67

[a] Reaction conditions: **2a**-**h** (0.18 mmol, 1.0 eq), MeMgBr (0.27-0.54 mmol, 1.5-3.0 eq), THF (0.5 mL), rt. [b]isolated yield.

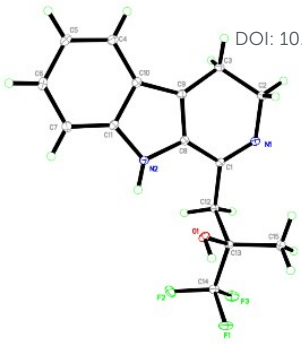
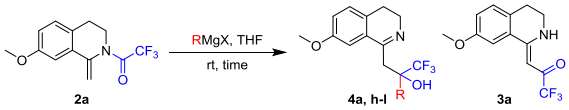


Figure 1 X-ray crystal structure of trifluoromethylcarbinol **4g**.

The structure of **4g** was unequivocally confirmed by X-ray crystallography (Figure 1; CCDC-1532366). However, acyclic enamide **2h** afforded 4-methoxy-acetophenone instead of the trifluoromethylcarbinol (entry 8), suggesting that this chemistry is only compatible with cyclic enamides. We also demonstrated that the reaction could be performed in a one-pot manner to afford trifluoromethylcarbinol **4a** directly from DHIQ **1a** in 64% yield, while the two-step processes gave 81% overall yield.

Likewise, the scope of the reaction was explored using various Grignard reagents with DHIQ enamide **2a** (Table 2). Methyl- and ethylmagnesium bromides gave instantaneously trifluoromethylcarbinols **4a** and **4h**, respectively, in high yields (entries 1 and 2). In the case of phenyl-, 4-chlorophenyl, and 4-methoxyphenyl magnesium bromides, the reactions took longer (2 h) and the yields were in the range of 61–66% (entries 3-5) without any side-products. Benzylmagnesium chloride afforded a slightly better yield than phenylmagnesium bromides (entry 6). When isopropyl, cyclopentyl, and cyclohexylmagnesium bromides were reacted with **2a**, only vinylogous amide **3a** was obtained without generation of corresponding trifluoromethylcarbinols (entries 7-9). The structure of **3a** was elucidated by X-ray crystallography (Supporting Information; CCDC-1819355). These data suggest

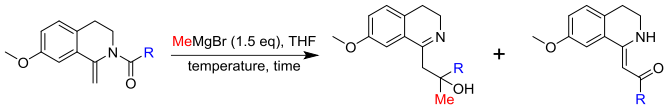
Table 2 Compatibility of Grignard reagents[a]



Entry	RMgX	Equivalent	Time	Product (%)[b]
1	MeMgBr	1.5	10 min	**4a** (98)
2	EtMgBr	1.5	10 min	**4h** (93)
3	PhMgBr	1.5	2 h	**4i** (64)
4	4-Cl-PhMgBr	1.5	2 h	**4j** (61)
5	4-MeO-PhMgBr	1.5	2 h	**4k** (66)
6	BnMgCl	1.5	2 h	**4l** (72)
7	*i*PrMgBr	3.0	30 min	**3a** (88)
8	CyPentMgBr	3.0	30 min	**3a** (76)
9	CyHexMgBr	3.0	30 min	**3a** (72)

[a] Reaction conditions: **2a** (0.18 mmol), RMgX (0.27-0.54 mmol), THF (0.5 mL), rt, 10 min to 2 h. [b]isolated yield.

Table 3 The scope of acyl groups



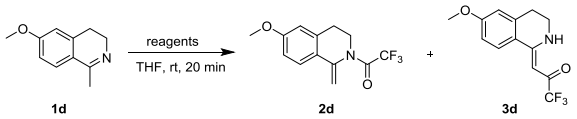
Entry	Enamide (R)	Temperature (°C)	Time	Compound (%)[a]	
1	**2a** (CF_3)	rt	10 min	**4a** (98)	**3a** (0)
2	**2a** (CF_3)	-78	2 h	**4a** (0)	**3a** (0)
3	**2a** (CF_3)	-5 to rt	2 h	**4a** (51)	**3a** (0)
4	**2i** (Me)	0 to rt	1 h	**4m** (47)	**3b** (40)
5	**2i** (Me)	rt	1 h	**4m** (55)	**3b** (35)
6	**2j** (Ph)	rt	12 h	**4n** (0)	**3c** (0)
7	**2j** (Ph)[b]	rt	2 h	**4n** (0)	**3c** (58)

[a] isolated yield. [b]MeMgBr (3 eq).

that, although the reaction appears to be compatible with alkyl and aryl Grignard reagents to afford trifluoromethylcarbinols, bulky Grignard reagents give rise to vinylogous amide **3a**, implying a hint of the reaction mechanism.

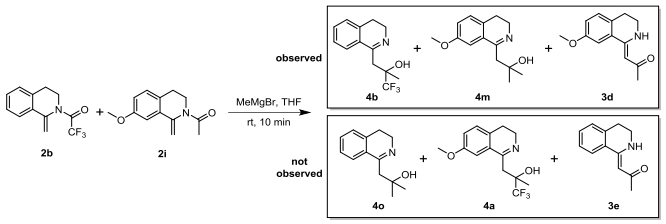
In order to understand the mechanism of this transformation, the typical reaction conditions (entry 1 in Table 3) were modified and the reactions were performed at lower temperatures. When **2a** was treated with methylmagnesium bromide at -78 °C, no product was generated and the starting material was recovered intact (entry 2). In a reaction left to warm up from -5 °C to rt, **4a** was generated in low yield (entry 3) without observing any other compounds as plausible reaction intermediates.

Additionally, acetyl enamide **2i** and benzoyl enamide **2j** were prepared to investigate the electronic effect of acyl groups in this reaction. When **2i** was treated with methylmagnesium bromide at 0 °C to rt, vinylogous amide **3b** was obtained as well as methylcarbinol **4m** (entry 4). These results imply that **3b** might be structurally related to an intermediate that also affords **4m**.[23-25] At room temperature, the yield of **4m** was slightly higher than that of **3b** (entry 5).[26] It is worth mentioning that the reaction of **2i** is much slower than that of **2a**. In the case of **2j**, 1.5 equivalents of methylmagnesium bromide were not effective for the transformation of the starting material **2j** (entry 6). When three equivalents of the Grignard reagent were used,



Entry	$(CF_3CO)_2O$ (eq)	Et_3N (eq)	Yield (%) 2d	Yield (%) 3d
1	2.5	3.0	0	90
2	2.5	0	10	68
3	1.0	0	78	0

Scheme 2 Formation of vinylogous amide **3d** during enamide synthesis.



Scheme 3 Crossover experiment.

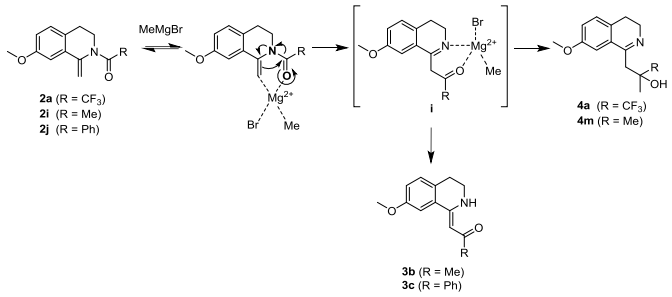
vinylogous amide **3c** was finally obtained as the sole product without the generation of **4n** (entry 7). However, neither **3b** nor **3c** was reactive with Grignard reagents to afford the corresponding tertiary carbinols. In addition to the above acyl groups, when monochloro-, dichloro-, trichloroacetyls, and trifluoromethylsulfonyl enamides were applied in this reaction, neither **4** nor **3** was observed, suggesting that the rearrangement is heavily dependent on the acyl groups.

Another crucial observation for the elucidation of the underlying mechanism was that treatment of 6-methoxy-DHIQ **1d** with trifluoroacetic anhydride (TFAA) and triethylamine gave rise to vinylogous amide **3d** in 90% yield as a sole product (entry 1 in Scheme 2). The structure of **3d** was unambiguously confirmed by X-ray crystallography (Supporting Information; CCDC-1532365). With TFAA and no triethylamine, enamide **2d** was initially observed as a major product, which was gradually converted to **3d** in 20 min (entry 2). In the presence of 1.0 equiv. of TFAA, the reaction underwent smoothly to afford only **2d** in 78% yield (entry 3). These results clearly suggest that vinylogous amide **3d** is generated from enamide **2d** through a rearrangement of the acyl group, presumably due to resonance effects of the 6-methoxy group in the enamide. Indeed, when a solution of **2d** in THF was treated with triethylamine at room temperature, the enamide was completely converted into **3d** within 30 min.[22]

On the other hand, 7-methoxy enamide **2a** was intact under basic conditions, such as triethylamine and potassium carbonate. Moreover, treatment of **2a** with Lewis acids, such as $MgBr_2$, $AlCl_3$, LiCl, did not give rise to **3a**, implying that metal chelation itself was not enough for the acyl group rearrangement. It is also worth mentioning that enamide **2a** was converted to **4a** in 57% yield by treatment of methyllithium, indicating that this chemistry might be applicable to other nucleophiles in addition to Grignard reagents.

To perform a crossover experiment, equimolar amounts of **2b** and **2i** were treated with methylmagnesium bromide, and the reaction was monitored by LC/MS (Scheme 3). While none of crossover products, **3e**, **4a**, and **4o**, were detected in LC/MS, **4b** (72%), **4m** (10%), **3d** (3%), and **2i** (62%) were isolated, complying with the reaction trends of **2b** and **2i**, respectively. This results support that the acyl group migration of enamide would go through an intramolecular fashion.

In the case of acetyl enamide **2i**, the undisputable detection of both **3b** and **4m** suggests a mechanism with a common intermediate for both products. Thus, we propose the following reaction mechanism (Scheme 4): i) facilitated by chelation of methylmagnesium bromide on the enamide,[27] rearrangement



Scheme 4 Proposed mechanism.

of the acyl group to the β-carbon of the enamide to deliver β-iminoketone **i**, an intermediate for both **3b** and **4m**, through a four-membered ring transition state;[24,28,29] ii) migration of the imine double bond in intermediate **i** to afford vinylogous amide **3b**;[23,25,30] and/or iii) nucleophilic addition of the Grignard reagent to the carbonyl carbon of intermediate **i** to afford **4m**.

Since the intermediate from trifluoroacetyl enamide **2a** would be more favorable for nucleophilic addition by the Grignard reagent due to the relatively high electrophilicity of the trifluoroacetyl group, **i** affords only trifluoromethylcarbinol **4a** with no vinylogous amide **3a**. However, bulky Grignard reagents would prefer to be utilized as a base to deliver **3a** (entries 7-9 in Talbe 2).[31] In the case of the intermediate **i** from enamide **2j**, both decreased electrophilicity and cross-conjugation may be driving forces to deliver only vinylogous amide **3c** (Table 3). It appears that intermediate **i** goes through either nucleophilic addition of the Grignard reagent to give tertiary carbinols **4** or tautomerization to furnish vinylogous amides **3** depending on the acyl group of the enamide and Grignard reagents.

In conclusion, we have shown that treatment of Grignard reagents on trifluoroacetyl enamides of 1-methyldihydroisoquinolines **2** affords tertiary trifluoromethylcarbinols **4**, resulting in the extraordinary addition of tertiary trifluoromethylcarbinols at the β-carbon of the enamides. The scope of this reaction was confirmed for a variety of Grignard reagents as well as trifluoroacetyl enamides of DHIQs and pyrido[3,4-*b*]indole. Given the irrefutable identification of β-amino vinylogous amides **3** and tertiary carbinols **4**, we have proposed a reaction mechanism featuring an unusual acyl group rearrangement to the β-carbon of the enamides, followed by nucleophilic addition of the Grignard reagent. This unique reaction has great potential for the preparation of pharmaceutically important tertiary trifluoromethylcarbinols on cyclic enamide systems.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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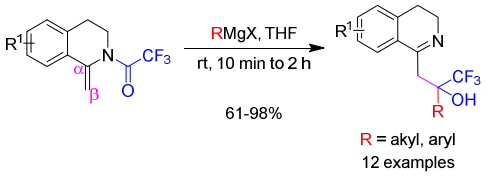
Grignard-Mediated Rearrangement of Trifluoroacetyl from Dihydroisoquinoline Enamides to Afford Tertiary Trifluoromethylcarbinols

Raghavendra Achary,[a,b] Gangadhar Rao Mathi,[a,b] Seulgi Kim,[a,c] Jong Yeon Hwang, [a,b] Pilho Kim,*[,a,b]

[a]Bio & Drug Discovery Division, Korea Research Institute of Chemical Technology, Daejeon 34114, Korea

[b]Department of Medicinal Chemistry and Pharmacology, University of Science & Technology, Daejeon 34113, Korea

[c]Department of Chemistry, Chungnam National University, Daejeon 34134, Korea



A novel approach for the addition of tertiary trifluoromethylcarbinols at the β-position of cyclic enamide has been developed.