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Cyclization of unsaturated amides with triflic anhydride and samarium diiodide

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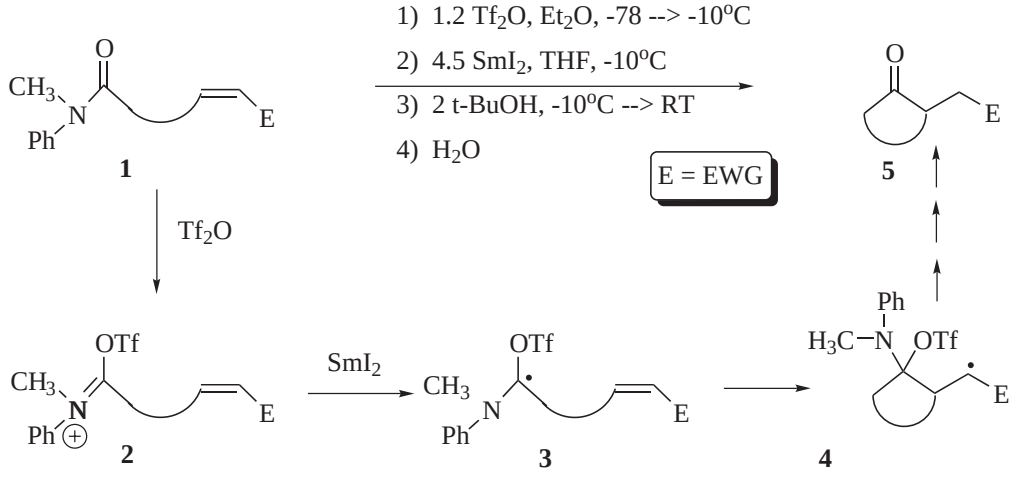
Abstract—A new approach to the generation of acyl radical equivalents has been developed. Treatment of amides with triflic anhydride followed by samarium diiodide allows for cyclization onto appropriately substituted olefins.

The generation of acyl radicals and their subsequent cyclization onto a pendant olefin has drawn substantial interest over the past decade.[1] The most synthetically relevant procedures involve acid chlorides,[2] acyl selenides,[3] acyl tellurides,[4] acyl germanes,[5] acyl cobalt derivatives[6] and carbonylation of alkyl radicals.[7] Acyl radical equivalents are also known. Acetals[8] and thioacetals[9] have shown utility in this capacity. In this letter we report that *N*-alkyl-*N*-phenylamides can serve as useful precursors for the generation of a new class of acyl radical equivalents and that they are capable of cyclization to form five- and six-membered rings. Amides have received little attention as radical precursors. Ogawa et al. have reported that amides will dimerize with deoxygenation upon treatment with samarium diiodide and samarium metal in refluxing THF.[10] Kamochi has directly reduced amides to the corresponding aldehydes and primary alcohols using samarium diiodide with phosphoric acid catalysis.[11]

Our approach to using amides as radical precursors is outlined in Scheme 1. Unsaturated amide **1** is initially treated with an electrophilic species, such as triflic anhydride, to generate an intermediate iminium triflate (**2**).[12] An initial one electron reduction by samarium diiodide is thought to generate radical **3** (an acyl radical



Scheme 1.

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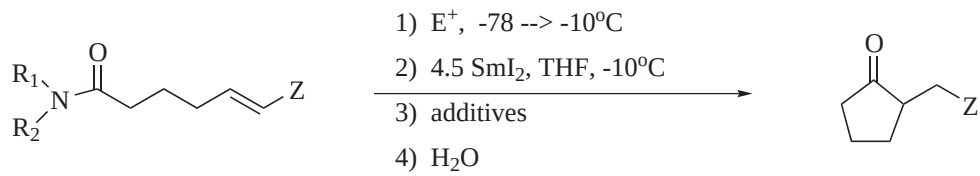
Table 1.



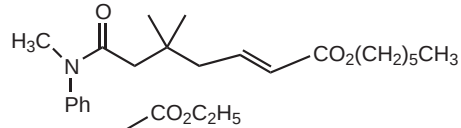
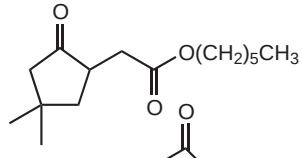
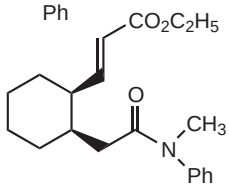
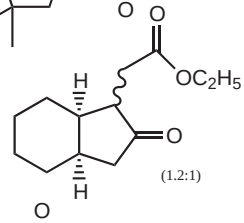
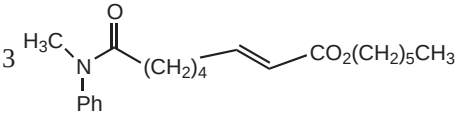
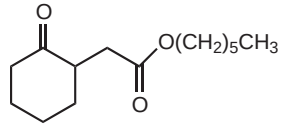
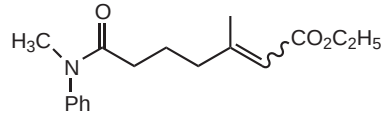
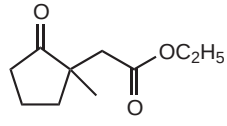
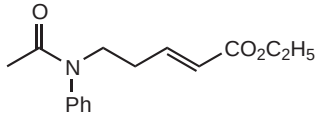
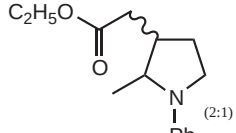
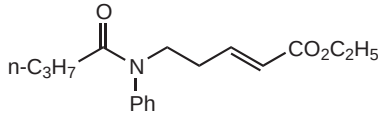
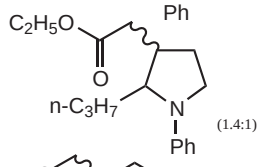
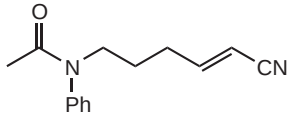
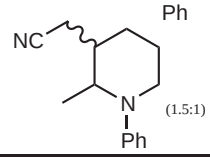
Entry	R_1	R_2	Z	Electrophile	Additives	Yield (%)
1	Ph	CH_3	$CO_2(CH_2)_5CH_3$	2.5 TMSCl	4.0 HMPA	20[a]
2	Ph	CH_3	$CO_2(CH_2)_5CH_3$	1.2 Tf_2O	4.0 HMPA	39
3	Ph	CH_3	$CO_2(CH_2)_5CH_3$	1.2 Tf_2O	0.2 NiI_2	66
4	Ph	CH_3	$CO_2(CH_2)_5CH_3$	1.2 Tf_2O	0.2 NiI_2, 2 *t*-BuOH	87
5	Ph	Ph	$CO_2(CH_2)_5CH_3$	1.2 Tf_2O	2.0 HMPA	5
6	*n*-Bu	*n*-Bu	$CO_2(CH_2)_5CH_3$	1.2 Tf_2O	2.0 HMPA	0
7	$-(CH_2)_4-$		$CO_2(CH_2)_5CH_3$	1.2 Tf_2O	0.2 NiI_2, 2 *t*-BuOH	37
8	Ph	CH_3	$(CH_2)_8CH_3$	1.2 Tf_2O	0.2 NiI_2, 2 *t*-BuOH	0

[a] The E^+ was added last at 0°C.

equivalent) which can then cyclize forming **4**. Further reduction, protonation and rapid hydrolysis upon addition of water affords cyclic ketone **5**.

Our initial efforts towards radical cyclization used chlorotrimethylsilane as the electrophile because it had previously been shown to be compatible with samarium

Table 2.

entry	starting material	product	yield
1			68%
2		 (1.2:1)	74%
3			17%[a]
4			15%[b]
5		 (2:1)	70%
6		 (1.4:1)	58%
7		 (1.5:1)	49%

[a]18% aldehyde also isolated. [b]34% aldehyde also isolated

diiodide.[13] This reaction proceeded best by adding 2.5 equiv. of TMSCl to a mixture of the amide, 4.5 equiv. of SmI_2 in THF, and 4.0 equiv. of HMPA at 0°C to afford a modest yield of the target cyclic ketone (entry 1, Table 1).[14] A somewhat better result was obtained by adding 1.2 equiv. of Tf_2O to a mixture of the amide and dry Et_2O (−78 to −10°C), then adding 4.5 equiv. of SmI_2 and 4 equiv. HMPA at −10°C (entry 2). It was then determined that the inclusion of NiI_2, which has been shown to facilitate a variety of different SmI_2 reactions (presumably as an electron transfer catalyst),[15] afforded a substantially improved yield of cyclized product (entry 3). The inclusion of *t*-BuOH as a proton source (entry 4) was found to further increase the yield. Entries 5–7 in Table 1 summarize our further examination of the effect of modifying the amide nitrogen substituents. Clearly the initial choice of *N*-alkyl-*N*-phenyl was the best at effecting cyclization. Entry 8 illustrates the importance of alkene activation by an electron withdrawing group. In cases where little or no cyclized products were isolated (entries 5, 6 and 8), substantial amounts (>50%) of starting amide were isolated from the reaction mixtures.

Table 2 summarizes our efforts at generalizing this reaction. Entries 1 and 2 provide further examples of *5-exo-trig* cyclizations using the optimized conditions described in entry 4 of Table 1.[16] Six-membered carbocyclic rings can be formed, albeit in low yield, as shown in entry 3. Entry 4 is noteworthy because it examines the steric sensitivity of the reaction at the site of ring closure. In all cases, side reactions typically afforded small amounts of amide reduction products (aldehydes, amines, alcohols). In entries 3 and 4, significant amounts of the corresponding aldehydes were isolated. The last three entries in Table 2 examine an interesting variant of the reaction where the amide nitrogen is internal to the incipient ring. In such cases, after cyclization, further reduction occurs to produce good yields of 2,3-disubstituted nitrogen heterocycles.[17] Note (entry 7) that this particular *6-exo-trig* cyclization is apparently significantly more favorable than that described in entry 3. If the reduction reaction described in entry 5 is conducted at lower temp (SmI_2 added at −30°C instead of −10°C), substantial preference for the *cis* isomer (8:1) is observed (although the yield dropped to 37%).[18]

In conclusion, a new radical generation system has been uncovered which allows for the efficient cyclization of appropriately substituted unsaturated amides. We are currently working on acyl radical equivalents that will allow for the production of carbocycles in enantioselective fashion.

Acknowledgements

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References

1. A thorough review of acyl radical chemistry has recently appeared: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991–2070.
2. Sasaki, M.; Collin, J.; Kagan, H. *Tetrahedron Lett.* **1988**, *29*, 6105–6109.
3. Crich, D.; Fortt, S. *Tetrahedron* **1989**, *45*, 6581–6598.
4. Crich, D.; Chen, C.; Hwang, J.; Yuan, H.; Papadatos, A.; Walter, R. *J. Am. Chem. Soc.* **1994**, *116*, 8937–8951.
5. Kiyooka, S.; Kaneko, Y.; Matsue, H.; Hamada, M.; Fujiyama, R. *J. Org. Chem.* **1990**, *55*, 5562–5564.
6. Coveney, D.; Patel, V.; Pattenden, G.; Thompson, D. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2721–2728.
7. Tsunoi, S.; Ryu, I.; Yamasaki, S.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1996**, *118*, 10670–10671.
8. Stien, D.; Crich, D.; Bertrand, M. *Tetrahedron* **1998**, *54*, 10779–10788.
9. Nashida, A.; Kawahara, N.; Nishida, M.; Yonemitsu, O. *Tetrahedron* **1996**, *52*, 9713–9734.
10. Ogawa, A.; Takami, N.; Sekiguchi, M.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 8729–8730.
11. Kamochi, Y.; Kudo, T. *Tetrahedron* **1992**, *48*, 4301–4312.
12. Charette, A.; Chua, P. *Tetrahedron Lett.* **1997**, *38*, 8499–8502.
13. Lautens, M.; Ren, Y. *J. Org. Chem.* **1996**, *61*, 2210–2214.
14. All new compounds exhibited spectroscopic (IR, ^1H and ^{13}C NMR) and analytical (HRMS) data in accord with their assigned structures.
15. Machrouhi, F.; Namy, J. *Tetrahedron Lett.* **1999**, *40*, 1315–1318.
16. Typical procedure for cyclization—Entry 1, Table 2: A solution of 121 mg (0.337 mmol) of (*E*)-*n*-hexyl 6-*N*-methyl-*N*-phenyamidohex-2-eneoate and 21 mg of NiI_2 (0.067 mmol) in 3.0 mL of dry Et_2O under argon was cooled to −78°C. Triflic anhydride (68 μL, 0.40 mmol) was added and the resultant solution was allowed to warm to −10°C over 20 min. A solution of 0.1 M SmI_2 in THF (15.2 mL, 1.52 mmol) was added rapidly followed immediately by 64 μL of *t*-butanol (0.67 mmol). The mixture was allowed to stir for 2 h and warm to rt. A solution of saturated $NaHCO_3$ (5 mL) was added and the mixture was extracted with ether (3×10 mL). The combined ether extracts were washed with 1 M HCl (2×5 mL), water, and saturated $NaHCO_3$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, solvent gradient ranging from 1% EtOAc: 99% hexane to 6% EtOAc: 94% hexane) yielded 58 mg of the cyclized product (0.23 mmol, 68%) as a colorless oil. IR (film) ν 2875, 2864, 1738 (br) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 4.00 (t, $J=6.8$ Hz, 2H), 2.68–2.61 (m, 2H), 2.42–2.36 (m, 1H), 2.10–2.08 (m, 2H), 2.01–1.94 (m, 1H), 1.57–1.46 (m, 3H), 1.29–1.23 (m, 6H), 1.20 (s, 3H), 1.13 (s, 3H), 0.82 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 218.1, 171.1, 63.8, 51.6, 43.5, 42.2, 33.5, 33.0, 30.4, 28.7, 27.5, 26.9, 24.5,

21.5, 13.0; LRMS (EI) m/z (%): 254 (27), 239 (17), 171 (15), 153 (70), 152 (100), 137 (27), 111 (65), 83 (44), 56 (45), 55 (61); HRMS (EI) m/z: calcd for (M^+) requires: 254.1883. Found: 254.1884.

17. For recent examples of radical cyclization for the synthesis of pyrrolidines, see: (a) Senboku, H.; Hasegawa, H.; Orito, K.; Tokuda, M. *Tetrahedron Lett*. **2000**, *41*, 5699–5703; (b) Andrés, C.; Duque-Soladana, J.; Pedrosa, R. *J. Org. Chem*. **1999**, *64*, 4282–4288.
18. The *cis* isomer was assigned using the method of Hashimoto for differentiating *cis* and *trans* isomers in 2,3-disubstituted pyrrolidines: Hashimoto, K.; Konno, K.; Shirahama, H. *J. Org. Chem*. **1996**, *61*, 4685–4692.