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Photoinduced, Copper-Catalyzed Alkylation of Amides with Unactivated Secondary Alkyl Halides at Room Temperature

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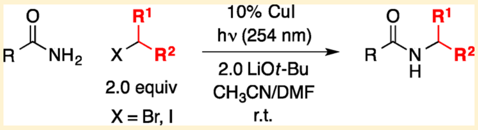
Supporting Information



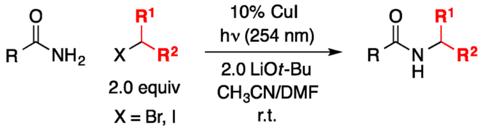
ABSTRACT: The development of a mild and general method for the alkylation of amides with relatively unreactive alkyl halides (i.e., poor substrates for S_N2 reactions) is an ongoing challenge in organic synthesis. We describe herein a versatile transition-metal-catalyzed approach: in particular, a photoinduced, copper-catalyzed monoalkylation of primary amides. A broad array of alkyl and aryl amides (as well as a lactam and a 2-oxazolidinone) couple with unactivated secondary (and hindered primary) alkyl bromides and iodides using a single set of comparatively simple and mild conditions: inexpensive CuI as the catalyst, no separate added ligand, and C−N bond formation at room temperature. The method is compatible with a variety of functional groups, such as an olefin, a carbamate, a thiophene, and a pyridine, and it has been applied to the synthesis of an opioid receptor antagonist. A range of mechanistic observations, including reactivity and stereochemical studies, are consistent with a coupling pathway that includes photoexcitation of a copper−amidate complex, followed by electron transfer to form an alkyl radical.

INTRODUCTION

Because a wide array of important compounds (such as natural products, pharmaceuticals, and functional polymers/materials) contain nitrogen,[1] the development of methods for the efficient formation of C−N bonds is a central challenge in organic chemistry.[2,3] The formation of a C_{sp^3}−N bond through a substitution reaction (S_N2) between a nitrogen nucleophile and an alkyl halide is a classic method[4] that is widely used, despite its limitations. In the case of the N-alkylation of an amide, the coupling can proceed in good yield with electrophiles that are generally useful in S_N2 processes (e.g., primary halides), but the yield can be poor with less reactive alkyl halides.[5] Consequently, the development of a mild and general method for amide N-alkylation with electrophiles such as unactivated secondary halides is a worthwhile objective.

In recent years, significant advances have been described in the discovery of transition-metal-catalyzed approaches to C−N bond formation (e.g., C_{sp^2}−N: Buchwald−Hartwig couplings;[6,7] C_{sp^3}−N: reductive amination[8] and olefin hydroamination[9]); however, to the best of our knowledge, there are few reports of metal-catalyzed N-alkylations of amines with alkyl halides.[10] Building on our earlier studies of the photophysics of discrete copper−carbazolide complexes,[11] we recently reported that photoinduced, copper-catalyzed couplings of carbazoles with unactivated secondary alkyl bromides and iodides can be achieved under mild conditions.[12] Whereas that investigation provided proof of principle for such transition-metal-catalyzed N-alkylation reactions, we sought to demonstrate that this photoinduced, copper-catalyzed approach has broader generality and can be applied to more ubiquitous nitrogen nucleophiles, for example, an amide.

In view of our hypothesis that a copper−nucleophile complex undergoes excitation in these and related photoinduced processes,[12,13] it was unclear at the outset that a copper−amidate complex would have the necessary absorption/reactivity profile to engage in a copper-catalyzed N-alkylation analogous to that observed with a copper−carbazolide complex. Indeed, all of our previous photoinduced, copper-catalyzed reactions of alkyl or of aryl electrophiles had employed nucleophiles in which the nucleophilic site either was part of an aromatic ring (carbazoles, indoles, or imidazoles)[12,13a,c] or was directly attached to an aromatic ring (thiophenols).[13b] Nevertheless, as described in this report, we have now established that the photoinduced coupling of an amide with an alkyl halide can in fact be achieved: specifically, that C−N bond formation proceeds with a wide range of coupling partners with a simple catalyst under mild conditions (room temperature; eq 1).



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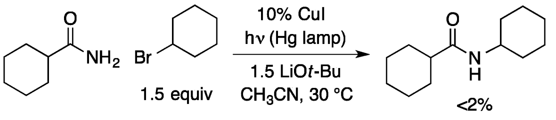
RESULTS AND DISCUSSION

In a preliminary study, we determined that the conditions that we had developed for photoinduced, copper-catalyzed N-alkylations of carbazoles with alkyl bromides[12] were ineffective when cyclohexanecarboxamide was employed as the nucleophile (<2% yield; eq 2).[14] However, optimization of the various reaction parameters,



(2)

with the most critical one being the wavelength of light used, led to N-alkylation of the amide in good yield (Table 1, entry 1).

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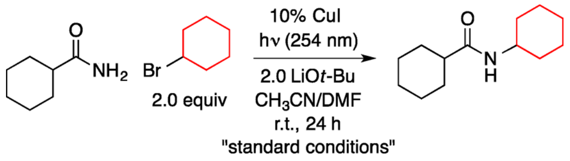
Control reactions established that, in the absence of CuI, light, or LiO-*t*-Bu, essentially no C−N bond formation was observed (Table 1, entries 2−4). Copper(I) complexes other than CuI could be utilized with a small loss in yield (entries 5 and 6), whereas the use of several other Brønsted bases resulted in a substantial drop in yield (entries 7−10). The omission of DMF as a cosolvent was deleterious (entry 11),[15] as was the use of a smaller excess of electrophile/LiO-*t*-Bu (entry 12). A catalyst loading as low as 2.5% could be employed with only a minor impact on N-alkylation (entries 13−16).[16] Little C−N coupling was observed when the reaction mixture was irradiated with longer-wavelength light (entries 17 and 18). Furthermore, a household Honeywell 36 W UVC air-treatment lamp[17] could be used as the light source, affording the N-alkylation product in good yield at room temperature (entry 19), whereas bond formation was slow at 0 °C (entry 20). Finally, this method is not highly water-sensitive (entry 21).

Table 1. Photoinduced, Copper-Catalyzed N-Alkylation of an Amide by an Unactivated Secondary Alkyl Halide: Effect of Reaction Parameters

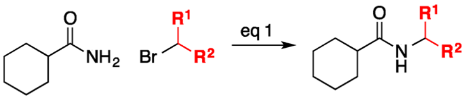


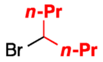
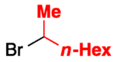
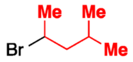
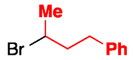
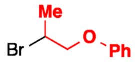
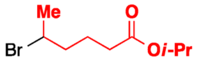
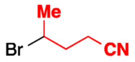
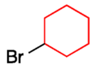
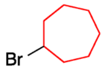
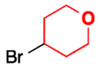
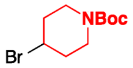
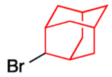
entry	change from the "standard conditions"	yield (%)[a]
1	**none**	**90**
2	no CuI	<2
3	no *hν*	<2
4	no LiO-*t*-Bu	<2
5	CuBr, instead of CuI	82
6	CuCl, instead of CuI	78
7	NaO-*t*-Bu, instead of LiO-*t*-Bu	38
8	KO-*t*-Bu, instead of LiO-*t*-Bu	10
9	Cs_2CO_3, instead of LiO-*t*-Bu	9
10	K_3PO_4, instead of LiO-*t*-Bu	4
11	no DMF	83
12	1.2 equiv CyBr and 1.2 equiv LiO-*t*-Bu	40
13	5.0% CuI	87
14	2.5% CuI	83
15	1.0% CuI	69
16	0.5% CuI	30
17	*hν* (300 nm)	10
18	*hν* (100 W Hg lamp)	<2
19	Honeywell 36 W UVC air-treatment lamp	90
20	Honeywell 36 W UVC air-treatment lamp, 0 °C	33
21	1.0 equiv H_2O	85

[a] Determined through GC analysis (average of two experiments).

This photoinduced, copper-catalyzed C−N bond-forming process can be applied to the room-temperature alkylation of an amide with a wide range of unactivated secondary alkyl bromides (Table 2). Thus, both acyclic and cyclic electrophiles couple with cyclohexanecarboxamide in generally good yield. Functional groups such as an ether, nitrile, and carbamate are compatible with the reaction conditions, although we observe a modest yield for the ester-containing electrophile illustrated in entry 6.

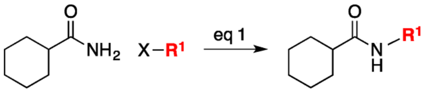
Table 2. Copper-Catalyzed N-Alkylation of an Amide at Room Temperature: Scope with Respect to the Secondary Alkyl Bromide



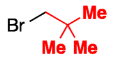
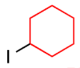
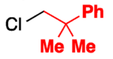
entry	electrophile	yield (%)[a]
1		65
2		85
3		82
4		75
5		63
6		38
7		56
8		88
9		58
10		91
11		90
12		74

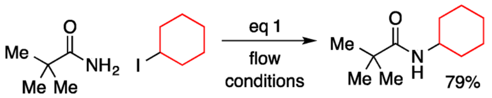
[a] Yield of purified product (average of two experiments).

Under the same conditions, cyclohexanecarboxamide also undergoes N-alkylation with neopentyl bromide, a primary electrophile that is typically a relatively poor substrate for S_N2 reactions,[18] as well as a secondary alkyl iodide (eq 3; for a flow reaction, see eq 4[19,20]).[21] Furthermore, we have established for the first time that an alkyl chloride (neophyl chloride) can serve as an effective electrophile in a photoinduced, copper-catalyzed N-alkylation (eq 3).



(3)

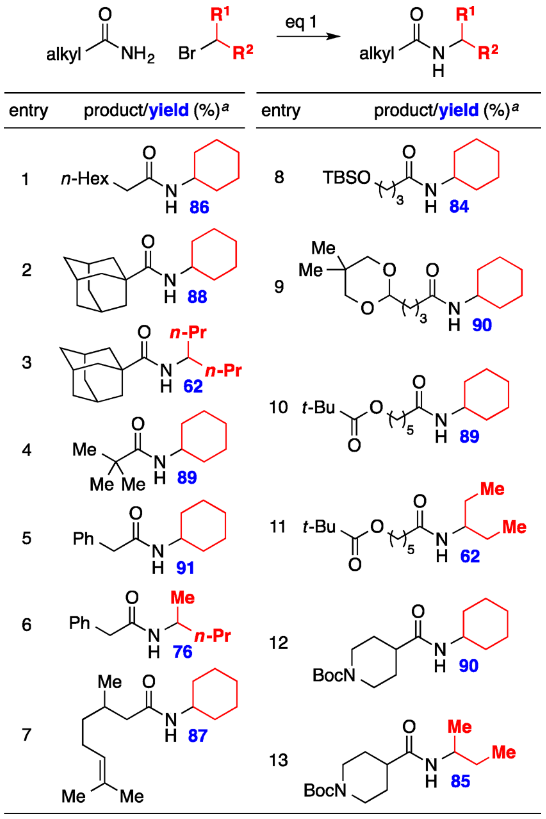
X−R1	yield (%)
	80
	88
	67



(4)

The scope of this transition-metal-catalyzed method for N-alkylation is also fairly broad with respect to the amide nucleophile (Table 3). Thus, a range of aliphatic primary amides (including sterically demanding ones: entries 2−4) couple with unactivated secondary alkyl bromides at room

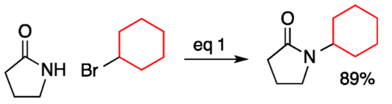
Table 3. Copper-Catalyzed N-Alkylation of Aliphatic Amides at Room Temperature



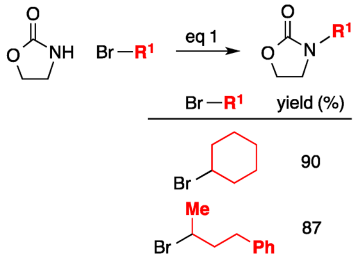
^{a}Yield of purified product (average of two experiments).

temperature. An array of functional groups, including an olefin, silyl ether, acetal, ester, and carbamate, are compatible with the C−N bond-forming conditions.

For the photoinduced couplings illustrated in Tables 2 and 3, we have not observed a significant amount of double-alkylation of the primary amide to form a tertiary amide (<2%). Nevertheless, a lactam and a 2-oxazolidinone *can* serve as useful nucleophiles under the same conditions, coupling with cyclic and acyclic unactivated secondary alkyl bromides at room temperature (eqs 5 and 6).[22]

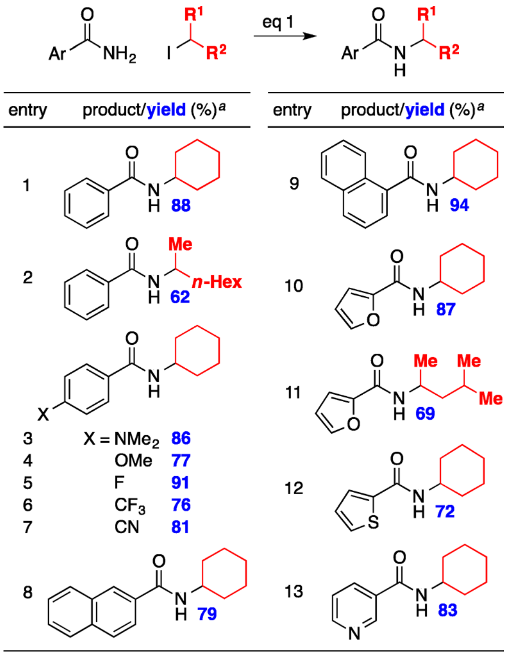


(5)



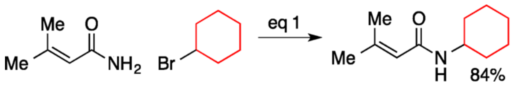
(6)

Table 4. Copper-Catalyzed N-Alkylation of Aromatic Amides at Room Temperature



^{a}Yield of purified product (average of two experiments).

The N-alkylation of an α,β-unsaturated amide (eq 7) and of aromatic amides (Table 4) can also be achieved under identical reaction conditions; in the case of aromatic amides, the C−N couplings were conducted with alkyl iodides, since the relatively low solubility of many of these amides in CH_3CN/DMF led to lower yields with alkyl bromides.[23] Electron-rich, electron-poor, and naphthyl amides are suitable reaction partners with unactivated cyclic and acyclic secondary iodides (entries 3−9). An array of heteroaromatic primary amides can be utilized as nucleophiles, including furyl-, thienyl-, and pyridyl-containing substrates (entries 10−13). These examples also illustrate the compatibility of the coupling conditions with an aryl amine, ether, fluoride, and nitrile.



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Blanco-Pillado has reported that amide **2**, which was prepared in six steps, serves as an opioid receptor antagonist (Figure 1).[24] Using photoinduced, copper-catalyzed N-alkylation of

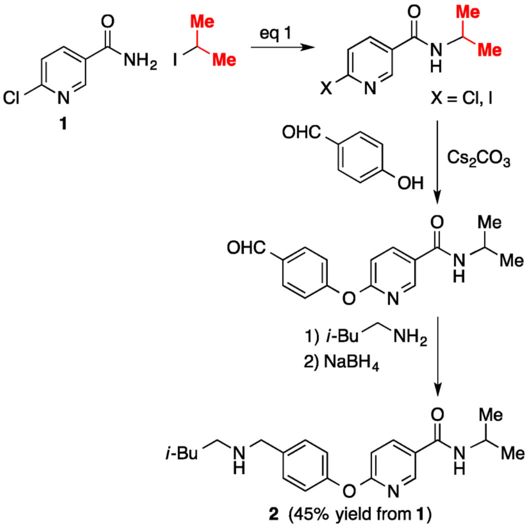


Figure 1. Application of photoinduced, copper-catalyzed N-alkylation to the synthesis of an opioid receptor antagonist (**2**).

an unactivated secondary alkyl halide as a key step, we have synthesized amide **2** in four steps from commercially available pyridyl amide **1**.[25]

We have begun to investigate the mechanism of photoinduced, copper-catalyzed N-alkylations of amides; an outline of one possible pathway (more complex mechanisms are also under consideration) is depicted in Figure 2.[26,27] We postulate that a copper(I)−amidate complex, $[L_nCu(Nu)]$ (**3**),[28] may be a critical intermediate in the catalytic cycle, undergoing excitation and then electron transfer. Although we have not been able to crystallographically characterize a relevant copper complex of a primary amide, we were able to generate X-ray-quality crystals of a Cu(I)−oxazolidinyl tetramer (**4**) through treatment of mesitylcopper(I) with 2-oxazolidinone (Figure 3).

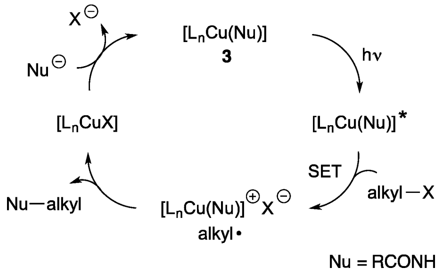


Figure 2. Outline of one of the possible pathways for photoinduced, copper-catalyzed N-alkylations of amides.

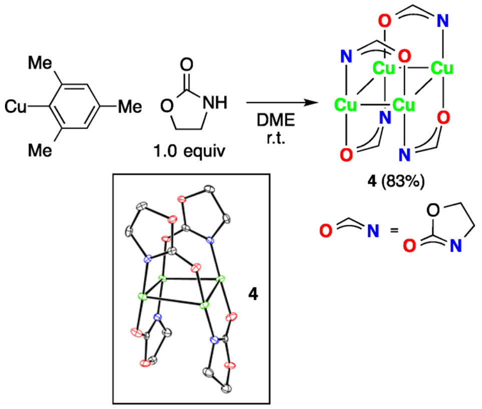
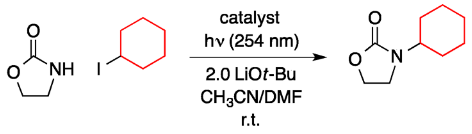


Figure 3. Synthesis and crystal structure of copper complex **4** (thermal ellipsoids drawn at 50% probability and hydrogens omitted for clarity).

Each oxazolidinyl group bridges two copper centers through a nitrogen and an oxygen, affording a structure with D_2 symmetry.

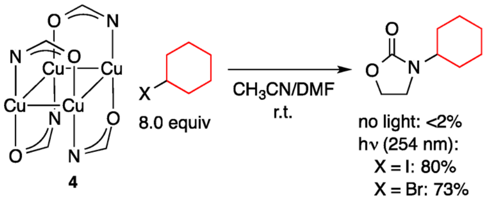
Copper complex **4** can be used in place of CuI in a photoinduced, copper-catalyzed N-alkylation of an amide (eq 8).[29] Furthermore, whereas tetramer **4** does not react with cyclohexyl iodide or bromide at room temperature in the absence of light, C−N bond formation proceeds upon irradiation (eq 9). Thus, a copper−oxazolidinyl adduct is chemically competent in an N-alkylation reaction with an alkyl halide.

To gain insight into the possible intermediacy of an alkyl radical in these photoinduced couplings, electrophiles that bear pendant olefins were subjected to the standard N-alkylation conditions, resulting in the formation of a cis-fused [3.3.0] bicyclic product in good yield, via cyclization and then C−N bond formation (eq 10). The endo:exo ratio of each coupling product is similar to that observed for the respective radical cyclizations of these alkyl bromides,[30] as would be expected if there is a common intermediate in the ring-forming step.

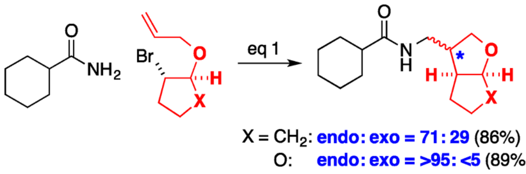


(8)

catalyst	yield (%)
CuI (10%)	85%
Complex **4** (2.5%)	83%

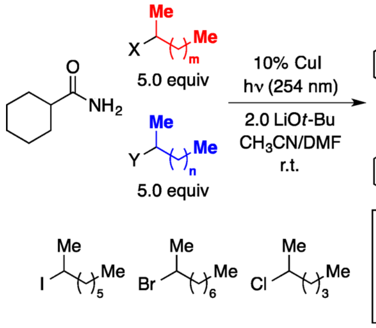


(9)



(10)

Through competition experiments between alkyl halides, we have established that selective N-alkylation can be achieved according to the following reactivity order: I > Br > Cl (eq 11).

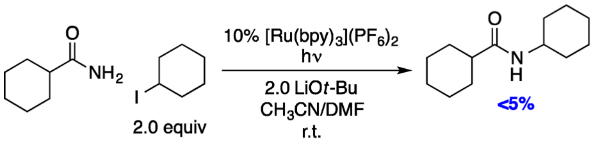


(11)

X, Y	A : B
I, Cl	>50 : 1
I, Br	10 : 1
Br, Cl	>50 : 1

This preference is consistent with the expectations for a process in which selectivity is determined by the relative propensity of the alkyl halide to participate in an electron-transfer reaction.[31]

Finally, we have established that a photoredox catalyst does not effect amide N-alkylation under a variety of conditions (eq 12).[32] As suggested in Figure 2, we postulate that, for the photoinduced process described herein, it is not only a copper complex that undergoes excitation but also a copper complex that participates in the key bond-forming step of the catalytic cycle.



(12)

Conditions
254 nm
compact fluorescent light bulb
compact fluorescent light bulb; 10% CuI

■ CONCLUSION

We have developed, to our knowledge, the first method for the transition-metal-catalyzed N-alkylation of amides with unactivated secondary alkyl halides: specifically, a photoinduced, copper-catalyzed coupling of primary amides with secondary (and hindered primary) alkyl bromides and iodides. Under a single set of relatively simple, mild conditions, a wide variety of aliphatic and aromatic primary amides, as well as a lactam and a 2-oxazolidinone, are alkylated in generally good yield with a range of alkyl halides. An array of functional groups, including an acetal, olefin, carbamate, thiophene, and pyridine, are compatible with the method. We hypothesize that the reaction mechanism includes photoexcitation of a copper−amidate complex (demonstrating for the first time that the nucleophile need not include an aromatic ring), followed by electron transfer to form an alkyl radical. We have crystallographically characterized a tetrameric copper−oxazolidinyl complex and established that, upon irradiation, it reacts with alkyl electrophiles to generate a new C−N bond. Stereochemical and relative reactivity studies are consistent with the proposed electron-transfer/radical pathway. Our current efforts are directed at expanding the scope of these photoinduced, copper-catalyzed processes and improving our understanding of the reaction mechanism.

■ EXPERIMENTAL SECTION

General Procedure for the Photoinduced, Copper-Catalyzed N-Alkylation of Amides. CuI (19.5 mg, 0.10 mmol), the amide (1.00 mmol), and LiO-*t*-Bu (160 mg, 2.00 mmol) were added to an oven-dried 10 mL quartz test tube that contained a stir bar (3 × 13 mm). The test tube was fitted with a rubber septum, the joint was wrapped with electrical tape, and the test tube was evacuated and back-filled with nitrogen (3 cycles). A solution of the alkyl bromide (2.00 mmol) in CH_3CN (5.4 mL) and then DMF (0.8 mL) were added in turn by syringe. The test tube was detached from the nitrogen line, and the puncture holes of the septum were covered with vacuum grease. The resulting mixture was stirred vigorously for 5 min, and then the quartz test tube was placed in a Luzchem photoreactor. The stirred mixture was irradiated with UVC lamps centered at 254 nm for 24 h (during the first 12 h, the reaction tube was shaken vertically every ∼2−3 h to ensure good mixing of the entire reaction mixture). Next, the reaction mixture was purified by flash column chromatography.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, tables, and a CIF file giving experimental procedures, compound characterization data, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(22) (a) This is not yet a general method. For example, under our standard conditions, a six-membered lactam undergoes N-alkylation with cyclohexyl bromide in relatively low yield (~25%). (b) A preliminary attempt to alkylate a relatively unhindered (N-methyl) secondary amide was not successful.

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