Metal catalyst-free by design. The synthesis of amides from alkyl iodides, carbon monoxide and amines by a hybrid radical/ionic reaction

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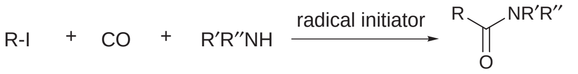
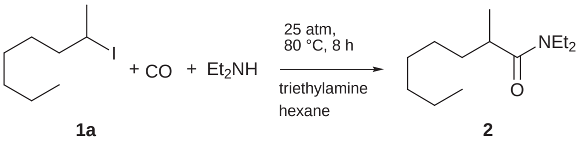
Amides can be synthesized from alkyl iodides and amines in the presence of CO (20–25 atm), without using transition metal catalyst; the radical cascade is initiated thermally using AIBN and allyltributyltin.

Transition metal catalysts facilitate many useful synthetic transformations. However, metal catalyst-free procedures, which do not require complicated techniques for recovering the expensive metals and ligands, would have a distinct advantage.[1] We recently discovered that irradiation conditions enable us to synthesize carboxylic acid esters from alkyl iodides, CO, and ROH.[2] This ester synthesis represents an intriguing example of a reaction which was previously possible only in the presence of a catalyst, but can now be carried out under metal catalyst-free conditions. The role of irradiation was unclear, especially as to whether it was generating an alkyl/iodine radical pair in a non-chain process or simply initiated a radical chain process. Here we report the synthesis of amides from alkyl iodides, CO and amines under thermal initiation conditions [eqn. (1)], expanding the utility of the metal catalyst-free approach and demonstrating the involvement of a radical *chain* transfer step in this hybrid radical/ionic reaction.



(1)

Thermally initiated conditions for the catalyst-free synthesis of amides were examined for the conversion of 2-iodooctane **1a**, diethylamine, and CO into *N*,*N*-diethyl amide **2** [eqn. (2)]. No reaction took place under thermal conditions without a radical initiator. However, the results with conventional radical initiators, such as AIBN and BPO, were disappointing, since only low yields of the desired **2** were obtained. For example, when a hexane solution of **1a** and Et_2NH was heated under 25 atm of CO at 80 °C for 8 h in the presence of AIBN (30 mol%), **2** was obtained in 10% yield. A dramatic increase in the yield of **2** up to 91% was achieved when both AIBN (25 mol%) and allyltributyltin (10 mol%) were used. The combination of AIBN and tris(trimethylsilyl)silane also gave a good result but AIBN–tributyltin hydride gave inferior results. On the other hand, in the presence of 20 mol% of galvinoxyl, the reaction was inhibited, and 81% of iodide **1a** was recovered. These results convinced us that the pathway by which amide **2** is formed includes a radical *chain* transfer.

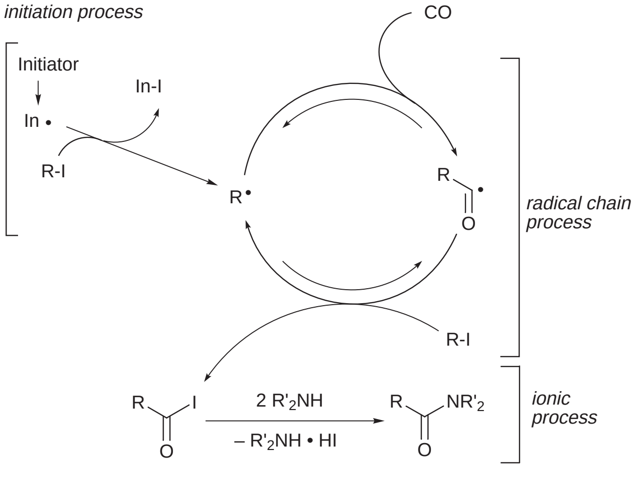


(2)

no initiator	0%
AIBN (30 mol%)	10%
BPO (20 mol%)	17%
AIBN (25 mol%), allyltributyltin (10 mol%)	91%
AIBN (25 mol%), allyltributyltin (10 mol%), galvinoxyl (20 mol%)	5%
AIBN (25 mol%), $(TMS)_3SiH$ (20 mol%)	80%
AIBN (30 mol%), Bu_3SnH (30 mol%)	43%

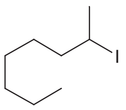
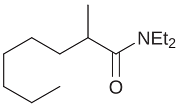
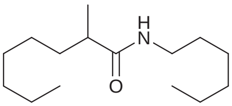
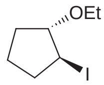
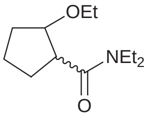
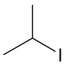
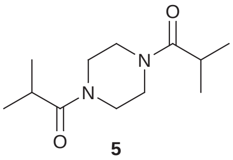
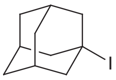
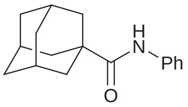
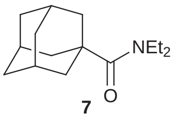
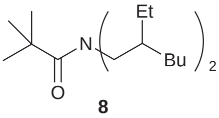
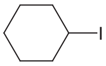
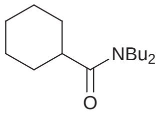
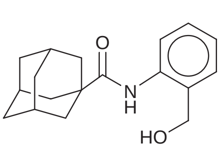
Encouraged by the above results, we then examined the generality of the amide synthesis using AIBN–allyltin as thermal initiator. Table 1 shows that amides can be successfully prepared from RI, medium pressure CO (20–25 atm) and amines.[3] In general triethylamine was added as a base to trap HI, whereas in entry 3, for convenience 2 equiv. of the amine were used as both nucleophile and base. Solvents can be varied, and even in the case where MeOH was used as the solvent, the amide was the only product of the carbonylation reaction (entry 4). Both primary and secondary amines were useful. In general carbonylation of tertiary radicals is relatively inefficient compared with secondary and primary alkyl radicals due to the facile reverse reaction.[4,5] However, the unique radical/ionic cooperation driving the carbonylation/decarbonylation equilibrium in the forward direction could provide an enormous advantage for the carbonylation of tertiary radicals. Using bis(2-ethylhexyl)amine, diamide **8** was prepared (entry 7). On the other hand, when an *o*-aminobenzyl alcohol was treated with **1d**, an *N*-acylated product **10** was obtained (entry 9). In these examples, standard flash chromatography on silica gel was used for the isolation of products, whereas in one case, Renaud's recently reported procedure for removing small amounts of tin residue was tested and found to be convenient (entry 8).[6]

It should be noted that the use of irradiation conditions, which were employed in our previous study,[2] can also be used for the amide synthesis, and are especially useful for the reaction of primary alkyl iodides.[7] Scheme 1 illustrates the three step



Scheme 1

Table 1 Amide synthesis *via* catalyst-free carbonylation of alkyl iodides[a]

Entry	Alkyl iodide	Amine (equiv.)/ solvent/conditions	Product	Yield (%)[b]
1	 **1a**	Et_2NH (0.9) Et_3N (1.3) hexane (0.5 ml) 80 °C, 8 h CO (25 atm)	 **2**	89
2	**1a**	n-$C_6H_{13}NH_2$ (1.1) Et_3N (1.1) hexane (0.5 ml) 80 °C, 8 h CO (20 atm)	 **3**	60[c]
3	 **1b**	Et_2NH (2.3) hexane (0.5 ml) 80 °C, 8 h CO (20 atm)	 **4** (*trans*:*cis* = 85:15)	82
4[d]	 **1c**	piperazine Et_3N (3.0) MeOH (1 ml) 80 °C, 10h CO (20 atm)	 **5**	57
5	 **1d**	$PhNH_2$ (1.0) Et_3N (1.3) MeCN (0.5 ml) 80 °C, 8 h CO (20 atm)	 **6**	96
6	**1d**	Et_2NH (0.9) Et_3N (1.5) hexane (0.5 ml) 80 °C, 8 h CO (20 atm)	 **7**	80
7	 **1e**	bis(2-ethylhexyl)-amine (0.5) Et_3N (1.5) hexane (0.5 ml) 80 °C, 8 h CO (20 atm)	 **8**	97
8	 **1f**	Bu_2NH (1.0) Et_3N (1.3) hexane (0.5 ml) 90 °C, 8 h CO (20 atm)	 **9**	74[e]
9	**1d**	*o*-amino benzyl-alcohol(1.0) Et_3N (1.3) MeCN (0.5 ml) 80 °C, 10 h CO (25 atm)	 **10**	52

[a] In general reactions were conducted on 1 mmol scale with AIBN (20–30 mol%)–allyltributyltin (10%) as initiator. For typical procedure: see ref. 3. [b] Yields after isolation by chromatography on silica gel. [c] *N*-Hexyl-*N*-(1-methylheptyl)amine was formed as a by-product by direct aminolysis. [d] Molar ratio: **1c**:piperazine:Et_3N = 2.5:1.0:3.0. [e] Renaud's NaOH workup (ref. 6) was performed to eliminate tin residues.

mechanism: (i) radical initiation *via* either irradiation or thermal initiator, (ii) radical chain propagation, composed of two reversible type radical reactions (carbonylation and iodine atom transfer), and (iii) ionic quenching to shift the equilibria of the reversible radical reactions.

In this study, we have achieved a new metal-free synthesis of amides from organic iodides, CO and amines using AIBN and allyltributyltin, which previously could only be accomplished in the presence of a transition metal catalyst.[8] We are now examining the applications of this approach to bifunctional substrates which hold promise for the synthesis of a variety of nitrogen heterocycles and designed polyamides.

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Notes and References

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1 For recent progress in the efficient recovery of catalysts including fluorous biphasic systems, see J. A. Gladysz, *Science*, 1994, **266**, 55; I. T. Horváth and J. Rábai, *Science*, 1994, **266**, 72; J. J. J. Juliette, I. T. Horváth and J. A. Gladysz, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1610. Also see a related review: D. P. Curran, *Angew. Chem., Int. Ed.*, 1998, **37**, 1174.

2 K. Nagahara, I. Ryu, M. Komatsu and N. Sonoda, *J. Am. Chem. Soc.*, 1997, **119**, 5465.

3 General procedure: A magnetic stirring bar, AIBN (0.3 mmol), hexane (0.5 ml), allyltributyltin (0.1 mmol), alkyl iodide **1a** (1 mmol), triethylamine (1.3 mmol) and amine (1.2 mmol) were placed in a 50 ml stainless steel autoclave with a glass liner. The autoclave was closed, purged twice with CO, pressurized with 25 atm of CO and then heated with stirring at 80 °C for 8 h. Excess CO was discharged at room temperature. Washing the crude mixture with MeCN (10 ml) followed by precipitation of ammonium salts in Et_2O (40 ml), filtration, evaporation of filtrate and column chromatography on silica gel gave pure amide **2**.

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