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Graphene oxide (GO) catalyzed transamidation of aliphatic amides: An efficient metal-free procedure

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ABSTRACT

Transamidation involves direct interconversion of an amide with amine, and represents an alternative to the common method of amide formation from the reaction of carboxylic acid with an amine. While the carboxamides have huge potential in biological systems and polymer industries, their formation from carboxylic acids requires activation by a suitable catalyst. A metal-free transamidation of aliphatic amide with aromatic amine catalyzed by graphene oxide (GO) has been developed and established as a general, synthetically useful and selective procedure. Graphene oxide bearing several carboxylic acids on the edges and having large surface area acts as an efficient and recyclable catalyst for transamidation.

Introduction

The carboxamide function is present in numerous molecules of proteins, pharmaceuticals, polymers and small organic molecules.[1] Synthesis of amides is therefore an extremely important organic reaction. The condensation of carboxylic acid with an amine is considered by far as the most common synthetic procedure.[2,3] Since amide formation results in the generation of one molecule of water, a suitable catalyst is required to activate the carboxylic acid function.[4] Without the presence of any catalyst, the acid and the amine usually undergo salt formation or require high temperature.[5] As a result, several metal-based catalytic systems have been developed to achieve this reaction.[6,7] Another alternative strategy avoiding direct use of carboxylic function is the interconversion of amides, commonly known as transamidation.[3,7] Although transamidation is relatively uncommon due to the fact that the amide function is a poor electrophile, suitable catalytic systems could activate and exchange with amines resulting in the formation of new carboxamide derivatives.[8] The catalytic system and reaction conditions remain the key factors for transamidation of primary, secondary or tertiary amides to establish a synthetically useful procedure. Among different catalytic systems, metal-free catalysts like boronic acid,[9,10] hypervalent iodosobenzene diacetate,[11] hydroxylamine hydrochloride,[12] L-proline,[13] Et_3N,[14] and $K_2S_2O_8$[15] are noteworthy, while metal-based catalysts like $Cu(OAc)_2$, CeO_2 and Cp_2ZrCl_2 showed better activation of the amide group to undergo transamidation.[16–20]

Harnessing the catalytic efficiency of sustainable nanomaterials like graphene oxide (GO) in diverse synthetic reactions is an intriguing area of research.[21,22] GO possesses a rich oxygenated chemical functionality, is somewhat acidic (pH 4.5 at 0.1 mg mL^{-1} in aqueous suspension),[23] and is recognized as having strong oxidizing properties.[24]

In connection with our interests in utilizing catalytic function of GO,[23,25] we disclose herein our studies on the transamidation reaction under solvent-free conditions, which finally constitute a complete metal-free, general and useful protocol to prepare a variety of carboxamides (Scheme 1).

Results and discussion

We began our experiment taking aniline and acetamide (equimolar and 1 mmol scale) with GO (50 mg) in toluene. Monitoring the reaction by TLC reveal multiple spots and after isolation by chromatography, a moderate yield of the desired amide is obtained (Table 1, entry 1). Changing the reaction medium with more polar and low to high-boiling solvents like acetonitrile, DMSO or even water gave moderate to poor yields of the acetanilide (entries 2–4). Considering that solvent might not have much desired influence towards improving the yield, we perform the reaction under solvent–less i.e., in neat conditions at varying temperatures (80–150 °C). In Table 1, entries 5–7 show that the best results are obtained when we take a mixture of aniline, acetamide

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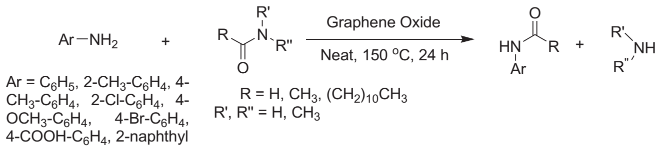


Scheme 1. Transamidation reaction using graphene oxide (GO) as a heterogeneous catalyst.

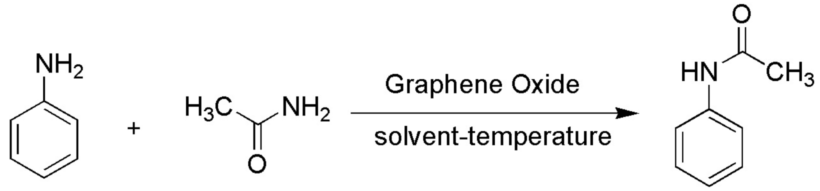
and GO and heated at 150 °C affording the desired amide in 76% yield after purification (entry 7). Further optimization of reaction is conducted by varying the catalyst (GO) quantity, as shown in entries 7–9. While doubling the catalyst quantity does not have significant effect (entry 8), lowering its (GO) quantity afforded considerably poor yield (entry 9). In the absence of GO, there was no conversion indicating that GO has definite role in catalyzing the process (Table 1, entry 10). We also performed two experiments taking reacting partners in 1:2 ratios (entries 11 and 12), which however did not give any significant increase in yield of the transamidation product. In order to check any effect of atmospheric air, we conducted the reaction under blanket of N_2 and ended up with 70% isolated yield (Table 1, entry 13). Hence, it can be concluded that there is no such effect of the atmospheric oxygen in the reaction. We therefore considered the optimized reaction condition as in entry 7, i.e.: amine (1 mmol), amide (1 mmol), GO (50 mg), 150 °C, 24 h.

After optimization, we extended the method for various amine components and amides (Table 2). Diverse functionalities on the amine moiety including electron donating and withdrawing groups e.g., CH_3, OCH_3, Cl, Br, COOH and also naphthyl system gave products in the range of 60–79% yields. Changing the amide from acetamide to formamide produced *N*-formylated products (Table 2, entries 4–7). In these cases, a mixture of rotamers was achieved as evident from NMR data and also supported by literature reports.[13,26] However, 2-chloroaniline afforded the single compound, which can be attributed to the presence of a halogen in *ortho* position (Table 2, entry 7). *N*-Substituted aliphatic amides like *N*-methylacetamide, *N*,*N*-dimethylacetamide also worked efficiently affording the desired products (Table 2, entries 8–10). In the case of aromatic amides (Table 2, entries 11 and 12) however no product was formed. This could be attributed to the additional conjugation of the amide carbonyl with the benzene ring, which also reduces the electrophilicity of the centre. We have performed one reaction using a long carbon chain amide (Table 2, entry 13) and obtained the corresponding carboxamide in 70% isolated yield. On the other hand, aliphatic amine (Table 2, entry 18) in spite of being more nucleophilic in nature no reaction was observed. This could be attributed to possible attachment of aliphatic amines on the surface of graphene oxide, as reported previously,[27,28] and also discussed in the mechanism section.

Mechanism

The carbonyl carbon of amide is unreactive and should be activated for further reaction. It is believed that the –COOH groups present on the edges of GO initially form H-bonding with the amide and the epoxide oxygen with the amine hydrogen **(1)** as shown in the Scheme 2. Then the nucleophile, the $-NH_2$ function attacks at the carbonyl centre to form the intermediate **2**. Finally elimination of the primary/secondary amine (deamination) generates the product **3** (Scheme 2). Activation of the amide group is important for the transamidation, which is corroborated by the fact that aromatic amide bond being sufficiently stable through conjugation could not be activated by the GO (Table 2, entries 11 and 12). From the literature reports, the reason behind unreactive nature of aliphatic amines in the presence of GO is assumed to be (a) amine forms H-bond with the oxygen functionalities present on GO, (b) it may attack the epoxide ring before it attacks the amide carbonyl, (c) some sort of ionic bonding is also described by forming $-COO^{-}\ {}^{+}NH_3R$.[27,28]

Table 1
Optimization of reaction conditions.



Entry	Catalyst amount (mg)	Solvent	Temperature (°C)	Yield (%)[a]
1	50	Toluene	100	55
2	50	DMSO	120	Trace
3	50	CH_3CN	80	43
4	50	Water	90	Trace
5	50	Neat	80	50
6	50	Neat	120	64
7[b]	**50**	**Neat**	**150**	**76**
8	100	Neat	150	78
9	20	Neat	150	39
10	–	Neat	150	NR
11[c]	50	Neat	150	77
12[d]	50	Neat	150	70
13[e]	50	Neat	150	70

[a] Isolated yield of product by column chromatography.
[b] Optimized condition.
[c] Aniline (1 mmol), acetamide (2 mmol).
[d] Aniline (2 mmol), acetamide (1 mmol).
[e] Reaction was done under N_2 in a sealed tube. All reactions were carried out up to 24 h and 1 mmol of each reactant were used unless mentioned.