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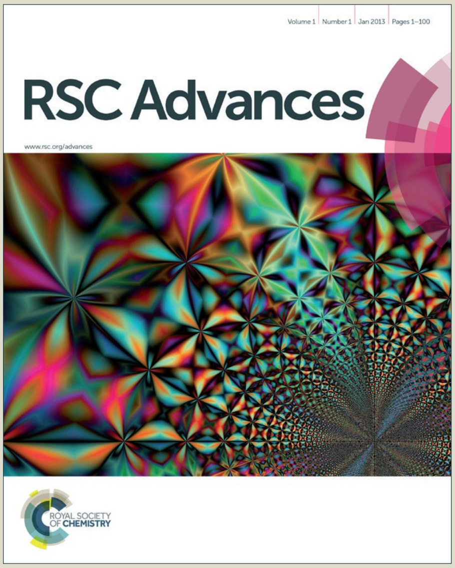

Journal Name

ARTICLE

An efficient magnetic copper ferrite nanoparticle catalysed ligand and solvent free synthesis of N-aryl amide from aldoximes and iodobenzene.

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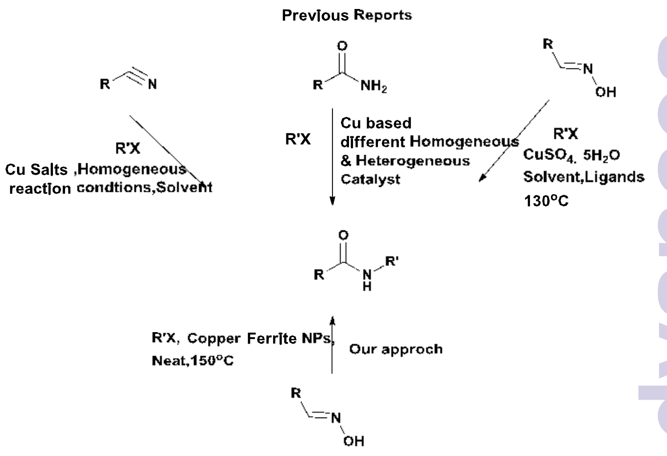
Sachin A.Sarode[a] Jeevan M. Bhojane[a] and Jayashree M.Nagarkar[a]

A simple, efficient, and environmentally benign method has been reported for the synthesis of N-aryl amides by using Aldoximes and Iodobenzene under ligand free and solvent free conditions using magnetically separable copper ferrite nanoparticles as catalyst. The catalyst was characterised by using XRD, FEG-SEM,EDAX,ICP-AES and TEM and tested recyclability up to five cycles.

Introduction

N-aryl amides are important moieties in the medicinal chemistry which are the backbone of many pharmaceutical and biologically active natural products. [1] The medicinal chemistry database discovered that, the amide bond appears in more than 25 % of known pharmaceutical active ingredients. [2] Additionally, amides are very useful building blocks in organic synthesis, and are precursors for many valuable compounds such as agrochemicals, polymers and organic materials.[3] Eventually, the amide bond formation reactions play an important role in achieving green chemistry perspective in organic synthesis.[4] However, traditional trans amide formation reactions are usually carried out by using coupling reactions between corresponding acids or acid chlorides with amines.[5] The rearrangement of ketoximes in presence of strong acids, gives the straightforward product of trans amide.[6] Both the above traditional methods have some drawbacks such as high temperature, strong acidic conditions, and hazardous waste.[7] There are various methods of synthesis of N-aryl amide using the aryl halide (Scheme 1). Aldoximes on sequential reaction of hydration and dehydration in presence of transition metals, give primary amides.[8] Recently 'Panda et al.' reported copper catalysed homogeneous coupling reaction of aldoximes and aryl halides to afford N-aryl amides directly.[9] There are many reports on formation of trans amide by using coupling reaction between primary amides and aryl halides, with various homogenous and heterogeneous catalytic systems.[10] In situ hydration of benzonitrile and coupling reactions with aryl halide was also reported.[11] Green and heterogeneous catalytic coupling reactions of amides and amines for the synthesis of N-aryl amides are also reported.[12] Most of the above reported reactions take place in solvent medium. However, the reaction in solvent free condition has great importance in the area of green chemistry.[13] Magnetically separable nanoparticles as catalysts have attracted much attention in organic reactions. [14] These nanoparticles have shown large surface to area ratio, good activity and reusability. [15] Particularly, copper ferrite nanoparticles possess good catalytic activity when employed in various organic transformations.[16] Here, we propose the solvent and ligand free, magnetically separable copper ferrite nanoparticles, as catalyst for the coupling reactions between aldoximes and aryl halides to get N-arylated amides. [17] This protocol overcomes the drawback of regioselectivity and moreover, it is the first report, on the said reaction by using heterogeneous catalyst.



Scheme 1: Various methods of N-aryl amide formation using aryl halides

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[a] *Department of Chemistry, Institute of Chemical Technology, Matunga, Mumbai – 400019, India. E-mail: jm.nagarkar@ictmumbai.edu.in; Fax: +91 22 33611020; Tel: +91 22 33611111/2222*

† Footnotes relating to the title and/or authors should appear here.

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Experimental

Catalyst was prepared by using known simple co-precipitation followed by thermal decomposition method.[15b] Copper (II) nitrate (4.1 mmol) and iron (III) nitrate (8.2 mmol) were taken in stoichiometric proportions and 100 mL of deionised water was added to produce clear solution. 1M NaOH solution was added drop wise under stirring to the above solution till the pH becomes 10.Reddish-black precipitate of copper ferrite was formed. The reaction mixture was warmed to 90°C and stirred for 2h which on cooling gave magnetic particles. The catalyst was then washed with water and ethanol and separated by using a magnet. It was kept in air oven at 80°C for 12 h. Then the catalyst was grinded in a mortar-pestle and kept in a furnace at 700°C for 5 h. It was then cooled to room temperature slowly to get the magnetic copper ferrite NPs.

Characterization of material

Synthesized catalyst was characterized by various techniques such as X-ray diffraction (XRD), Field emission gun Scanning electron microscopy (FEG-SEM) and Transmission electron microscopy (TEM). The XRD analysis was performed on Shimadzu XRD 2400 instrument using Cu Kα radiation (λ= 1.5406 A°) with scanning rate 2 degree per minute. TEM analysis was performed over PHILIPS 2200 instrument. FEG-SEM analysis was performed on 25 TESCAN MIRA Instrument. The energy dispersive X-ray spectral analysis (EDS) image was recorded with an Oxford instrument at 10 kV. Beam intensity was kept high to get good response by the detector. GC analysis is performed over PerkinElmer Clarus 480 instrument. GC-MS Spectra recorded over Shimadzu QP-2010 Instrument. 1H spectra's were recorded on Agilent 400MHz

Result and Discussion

XRD analysis showed peak at 2θ = 30.1, 35.14, 43.41, 54.601, 40 57.0671and 63.6651 which represent the Bragg reflections from the (220), (311), (400), (422), (511) and (440) planes respectively (Figure 1 A). XRD pattern of prepared copper ferrite nanoparticles shows the tetragonal structure with good crystallinity (JCPDS card No. 034-0425).[15] We found the same XRD pattern of the recycled copper ferrite nanoparticles after the fifth cycle of reaction (Figure 1 B). Elemental analysis of nano $CuFe_2O_4$ was confirmed by EDS (Figure 2 E) and ICP-AES. Elemental analysis gave the copper – Iron ratio as 1:2 approximately. ICP-AES study shows the 0.00026 mmol/g of copper and 0.00056 mmol/g of iron in the catalyst. The particle size of nano copper ferrite measured by using the TEM was found in between 11-14 nm (Figure 2 B). FEG-SEM analysis shows the crystalline nature of the copper ferrite nanoparticles. The FEG-SEM analysis shows the same morphology of the nanoparticles after the fifth cycle of the reaction (Figure 2 A-C). The FEG-SEM analysis of the reaction mass clearly shows the homogenisation of the catalyst (Figure2 D).

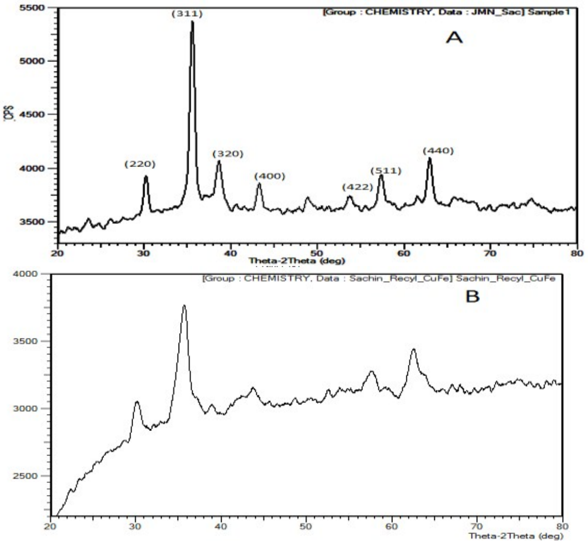


Figure 1: X-ray diffraction spectrum of fresh copper ferrite nanoparticles (A) and after the fifth cycle (B)

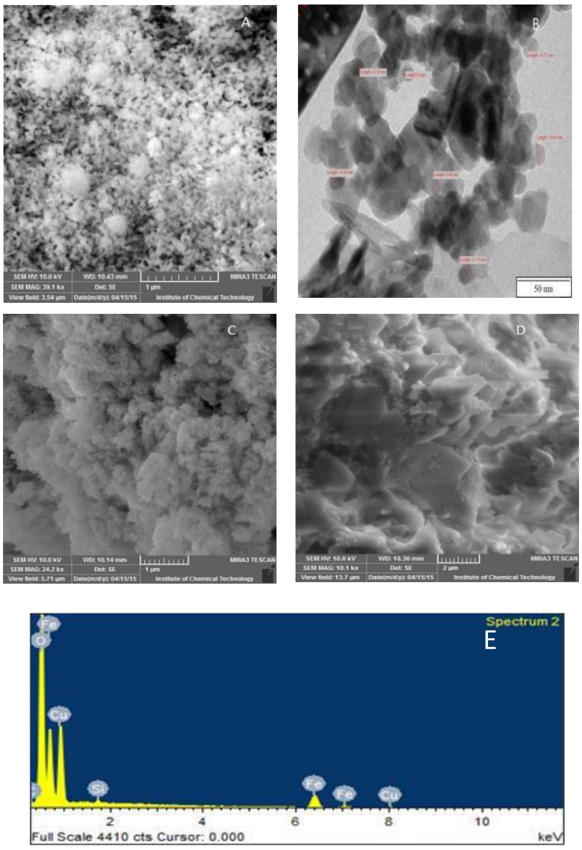


Figure 2: Scanning electron microscopy images of copper ferrite nanoparticles before (A),after Five cycles (C) and after the reaction without washing of organic compounds (D).Transmission electron microscopy of cooper ferrite nanoparticles (B). EDAX of copper ferrite nanoparticles (E)

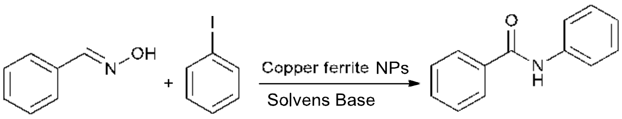
We started the optimisation of reaction parameters by considering the reaction between benzaldoxime and iodobenzene. It is treated as a model reaction. Initially we have carried out the reaction without using the catalyst which gave benzamide as the major product instead of desired product (Table 2Entry 7). Various copper and iron based catalysts were employed to get the best catalytic system (Table 1). Copper ferrite NPs were found to be the most effective catalyst for the model reaction in presence of K_2CO_3 under solvent free condition (Table 1 Entry 8). We also tried model reaction with various bases. Triethylamine and Na-tert-butoxide did not even initiate the reaction and starting materials remain unchanged (Table2 Entry 2-3). The model reaction carried out by using sodium carbonate, KOH and potassium phosphate afforded moderate yield, where as K_2CO_3 gave 88% yield of N-phenyl benzamide (Table 2 Entry 4-6). Hence K_2CO_3 was used as a base throughout the optimisation of reaction conditions (Table 2 Entry 1). The reaction was also carried out in various solvents, where in more amount of benzamide was obtained decreasing the yield of coupling product N-phenyl benzamide (Table 2 Entry 11-15). When the reaction was carried out at 100 °C, it afforded only 40% yield. The reaction carried out at 160°C did not show any significant increase in the product yield. The optimised catalyst concentration was found to be 10 mol %. The model reaction carried out by using 5 and 7.5 mol% of the catalyst, offered 48% and 65% yield respectively whereas 12% catalyst loading did not show significant increase in the product yield (Table 2 entry 7-9).

Table 1 Synthesis of N-aryl amides by using different Cu and Fe based catalysts[a]

Entry	Catalyst	Yield[b]
1	CuI	43
2	CuO (Bulk)	45
3	$CuSO_4$	ND
4	Cu_2O (Nano)	68
5	$FeCl_3.6H_2O$	53
6	Fe_3O_4	55
7	$FeSO_4$	ND
8	Copper ferrite NPs	88

Reaction Conditions: A mixture of iodobenzene (1mmol), benzaldoxime (2mmol.), 10 mol% catalyst and K_2CO_3 (2 eq.) at 150 °C for 12 h. Isolated yield[b].

Table 2 Optimisation of reaction conditions[a]



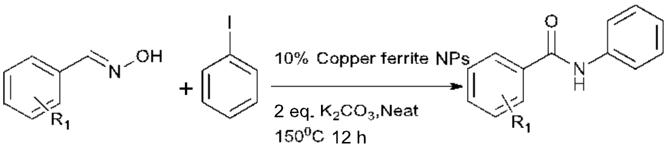
Entry	Solvent	Base	Mol %	Yield[b]
1	Neat	K_2CO_3	10	88
2	Neat	TEA	10	ND
3	Neat	Na-tertbutoxide	10	ND
4	Neat	KOH	10	68
5	Neat	Na_2CO_3	10	73
6	Neat	K_3PO_4	10	56
7	Neat	K_2CO_3	-	ND[d]
8	Neat	K_2CO_3	5	48
9	Neat	K_2CO_3	7.5	65
10	Neat	K_2CO_3	12	90
11	Toluene	K_2CO_3	10	54[c]
12	DMF	K_2CO_3	10	45[c]
13	NMP	K_2CO_3	10	43[c]
14	H_2O	K_2CO_3	10	36[c]

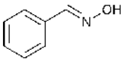
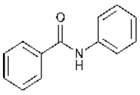
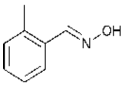
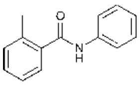
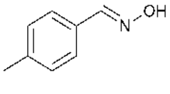
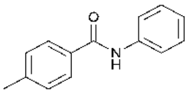
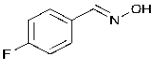
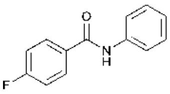
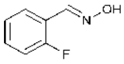
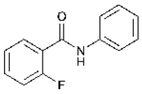
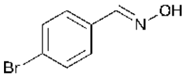
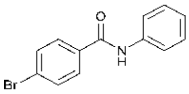
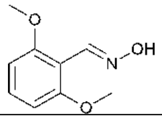
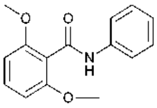
15	Ethanol	K_2CO_3	10	30[c]

[a]**Reaction Conditions:** Iodobenzene (1mmol), benzaldoxime (2 mmol.), copper ferrite NPs, base (2 eq.), Neat, 150 °C for 12 h. [b] Isolated yield. [c] solvent as medium [d] without catalyst

We applied these optimised reaction conditions to various derivatives of the aldoximes and iodobenzene to explore and to check the stability of functional group. We have used different substrates having electron donating groups as well as bulkier groups at various positions. We observed that the compound containing electron donating group on aldoximes gave good yield of the product (Table 3). The bulkier group also gave moderate yield of the desired product (Table 3 entry 7). Aryl halides bearing flouride, methyl, methoxy ,chloride, bromide and -CF_3 groups gave moderate to good yield of the respective products (Table 4). We observed that reaction of benzaldoximes with 2-bromoiodobenzene gave the mixture of 2-phenyl benzaoxazole and 2 bromo-N-phenylbenzamide products (Table 4 Entry 10). Reaction of chlorobenzene and bromobenzene with the benzaldoximes did not give the desired product under the present reaction conditions.

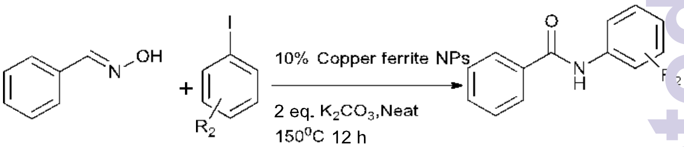
Table 3 Reactions of Aldoximes with Iodobenzene[a]

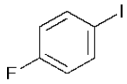
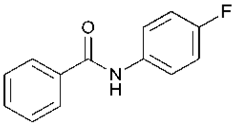
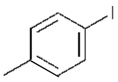
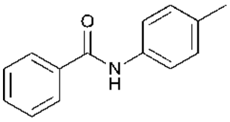
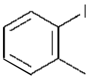
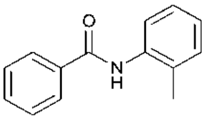
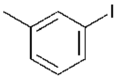
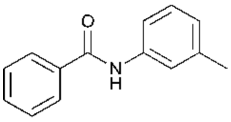
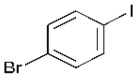
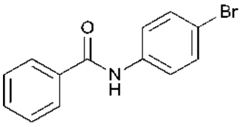


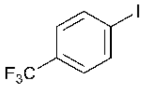
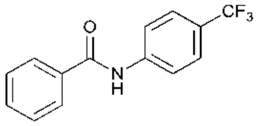
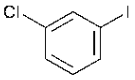
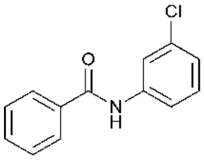
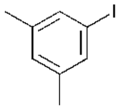
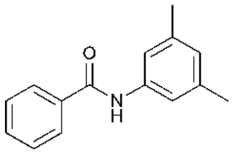
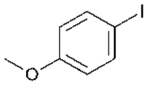
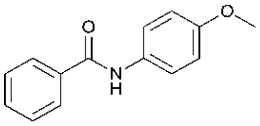
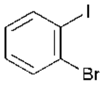
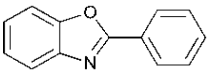
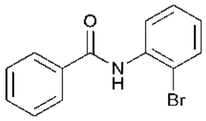
Sr.No	Aldoxime R1	Product	Yield[b]
1			88
2			76
3			86
4			84
5			82
6			**83**
7			**73**

[a]**Reaction Conditions:** Iodobenzene (1mmol),aldoxime (2mmol.), copper ferrite NPs (10mol %), K_2CO_3 (2 eq.) Neat, 150 °C for 12 h. [b] Isolated yield.

Table 4 Reactions of Aryl halides with benzaldoximes[a]



Sr no.	Aryl halide R2	Product	Yield[b]
1			85
2			84
3			80
4			73
5			79

6			86
7			83
8			77
9			85
10			35
			45

[a]**Reaction Conditions:** Aryl halides (1mmol), benzaldoxime (2 mmol.), copper ferrite NPs catalyst (10mol %) and K_2CO_3 (2 eq.) neat, 150 °C for 12 h.[b]Isolated yield

Based on literature reports[8] and our present experimental results a plausible reaction mechanism has been proposed. We carried out the control reaction to check the mechanism. In absence of iodobenzene and optimised reaction conditions the benzaldoximes get converted to benzamide and benzonitrile. We carried out the reaction with benzonitrile and iodobenzene under same reaction conditions but we did not obtain the desired product. It was confirmed that the dehydration and hydration of benzaldoxime take place in presence of copper ferrite nanoparticles. Here, in situ formed benzamide then coupled with iodobenzene on surface of copper ferrite NPs to give N-arylated amides (Figure 3).

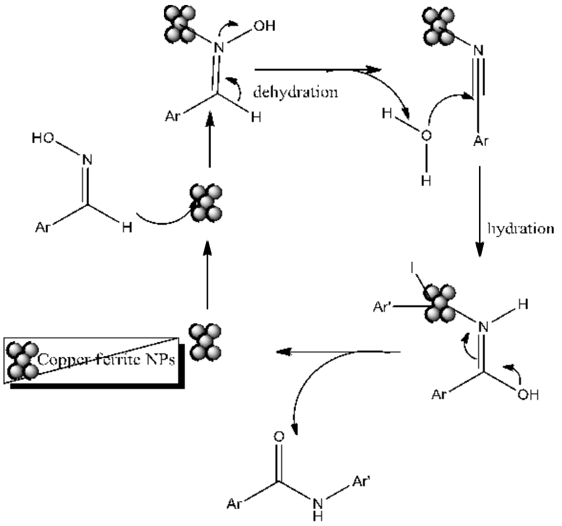


Figure 3: Plausible reaction mechanism.

In leaching test, it is very difficult to remove the catalyst from in between the reaction to study the leaching of copper and iron. We did the ICP-AES study of the filtrate of reaction mass after the completion of reaction. ICP-AES study revealed leaching of 0.029 ppm copper and 0.021 ppm iron in the filtrate which is negligible It confirms the heterogeneous nature of nanoparticles. At the end of the reaction, the catalyst was seperated by using the magnet from the crude reaction mixture, washed with ethyl acetate and water, dried at 100°C, and reused as such for succeeding experiments (up to fifth cycle) under similar reaction conditions. Slight decrease in the product yield indicates that the catalyst can be reused up to five cycles (Figure 4).

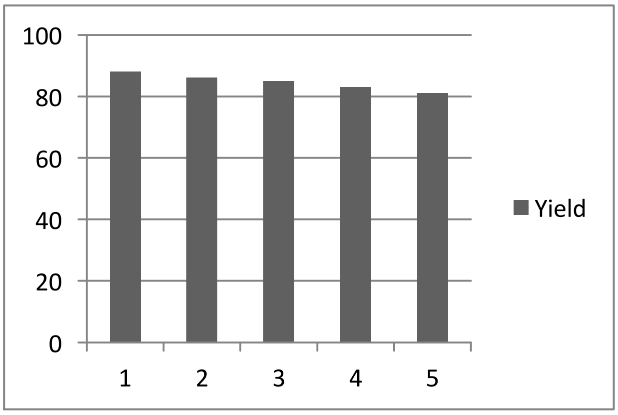


Figure 4: Recyclability study of copper ferrite NPs catalyst

Conclusions

In conclusion, we have developed the simple and green protocol for the one pot synthesis of N-aryl amide by using aldoxime and Iodobenzene as starting material and nano copper ferrite as a catalyst. The protocol is applicable to various substrates and afforded moderate to good yields.

Solvent free reaction and reusable as well as magnetically separable heterogeneous catalyst are the main advantages of the protocol.

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Notes and references

‡Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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etc.

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17 General procedure for N- Arylation of amide
An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with benzaldoxime (2 mmol), iodobenzene (1 mmol), Copper ferrite NPs (10mol%), and K_2CO_3 (2 mmol). Reaction mixture was heated in an oil bath at 150°C and was stirred for 12 h. The reaction was monitored by GC and TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and the reaction mass was diluted with ethyl acetate. Catalyst separated by using magnet.The resulting filtrate was washed with water and 20% brine solutions. The organic layer was separated and dried over anhydrous sodium sulphate. The solvent was removed under vacuum to get the crude product, which was purified by column chromatography on silica gel eluting with the mixture of pet ether / EtOAc (80: 20) mixture to afford the pure product. The purity and identity of known products are conformed by ^{1}H NMR and GC-MS Spectroscopic techniques.

Graphical abstract:

An efficient magnetic copper ferrite nanoparticle catalysed ligand and solvent free synthesis of N-aryl amide from aldoximes and iodobenzene.

Sachin A.Sarode[a],Jeevan M. Bhojane[a] and Jayashree M.Nagarkar[a]

One pot dehydration, hydration and coupling reaction protocol for N-substituted amide formation.