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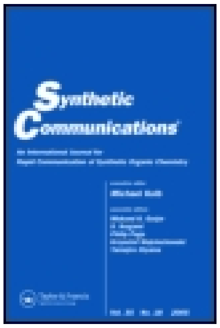

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Sono-Transition-Metal-Catalysis of One Pot Three-Step Synthesis of Glycosyl-1,2,3-Triazoles

Mohsine Driowya [a] [b] , Khalid Bougrin [a] & Rachid Benhida [b]

[a] Laboratoire de Chimie des Plantes et de Synthèse Organique et Bioorganique, Université Mohammed V-Agdal, Faculté des Sciences B.P., Rabat, Maroc

[b] Laboratoire de chimie des molécules bioactives et des arômes UMR-CNRS, Université de Nice-Sophia Antipolis, Parc Valrose, 06108 Nice Cedex, France

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Sono-Transition-Metal-Catalysis of One pot Three-stepSynthesis of glycosyl-1,2,3-triazoles

Mohsine Driowya[1,2], Khalid Bougrin[1], Rachid Benhida[2]

[1]Laboratoire de Chimie des Plantes et de Synthèse Organique et Bioorganique, Université Mohammed V-Agdal, Faculté des Sciences B.P., Rabat, Maroc, [2]Laboratoire de chimie des molécules bioactives et des arômes UMR-CNRS, Université de Nice-Sophia Antipolis, Parc Valrose, 06108 Nice Cedex, France.

E-mail: kbougrin@yahoo.fr

Abstract

As a continuation of our studies directed at the development of straightforward and sustainable methodologies, we describe herein a first and original example of cooperative effect of ultrasonic activation and iron-copper dual catalysis that allows an efficient and eco-friendly one pot three-step route to new series of nucleosides substituted triazoles. The reactions were carried out under both conventional and ultrasonic irradiation conditions.

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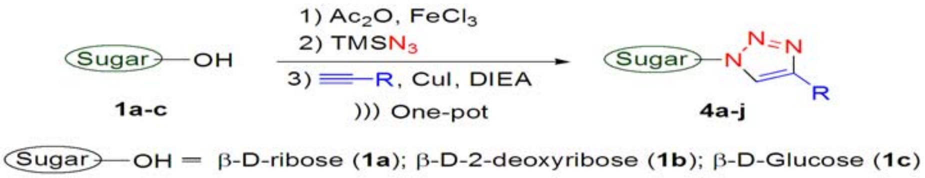

KEYWORDS: Nucleosides, 1,2,3-triazoles, acetylation, azidation, 1,3-dipolar cycloaddition, one-pot, ultrasound, iron-copper catalysis

INTRODUCTION

The Huisgen cycloaddition using azides and alkynes is an important method for the synthesis of 1,2,3-triazoles.[1] It's the highest possible atom economy and simple purification has led to various applications for pharmaceuticals, agrochemicals, polymers, biochemicals, and functional materials.[2] In general, this cycloaddition reaction requires harsh conditions and usually leads to a mixture of 1,4- and 1,5-regioisomers.[3] In 2002, K. B. Sharpless and M. Meldal improved the regioselectivity of the cycloaddition by Cu(I)-catalyzed ligation (click chemistry) of organic azides and terminal alkynes.[4] Recently, several examples of Cu(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition under mild conditions have been described.[5] Most recently, Then, Kacprzak developed an efficient one-pot method for the synthesis of 1,4-disubstituted-1,2,3-triazoles from benzyl or alkyl halides, sodium azide, and alkynes in the presence of Cu(I) in DMF.[6]

The glycosylazide derivatives serve as important synthetic precursors in the preparation of numerous natural and synthetic compounds with significant biological activities.[7] In addition, these products can be converted to antiviral and anticancer analogues with nucleosides-based triazole moiety by employing click chemistry,[8] i.e., copper(I)-catalyzed azide-alkyne [3+2] cycloaddition.[9] Since 1,2,3-triazole nucleosides have become increasingly useful and important in drugs and pharmaceuticals, the development of improved methods for their synthesis with structural diversity is highly desirable. Though there are reports on the synthesis of triazoles from azide via click reaction, the synthesis of nucleosides-based triazoles still remains a challenge. In addition, analogues of the purine and pyrimidine nucleosides have been studied extensively as antiviral agents[10] and a triazole moiety has been used as surrogate of the pyrimidine (or purine) ring to give compounds (e.g., **A**; Fig. 1) which were reported to have both antiviral and cytotoxic properties.[11] Similar analogues, bearing a good leaving group (**B**) (Fig. 1), were synthesized to be used as alkylating agents in cancer chemotherapy.[12]

Thus, Ribavirin (**C**) (Fig.1) is a synthetic nucleoside endowed with a broad-spectrum of antiviral activity against many RNA and DNA viruses.[13] It is the unique small molecule drug currently used for the treatment against hepatitis C virus, in combination with interferon-□-peg. Therefore, the search for more suitable preparation of triazolyl-nucleosides analogues of ribavirin continues today.

The chemical applications of ultrasound, ‘‘sonochemistry”, have become an exciting field of research during the past two decades.[14] Compared with conventional methods, the procedure is more convenient. A large number of organic reactions can be carried out in higher yield, shorter reaction time and milder conditions under ultrasound irradiation than at classical conditions.[15] The sonochemical methods are potentially useful in carbohydrate chemistry.[16] First, the mechanical effect of the acoustic waves improves heterogeneous reactions of liquid-liquid or liquid-solid systems, e.g., of simple or polymeric sugars, in terms of smoother experimental conditions reducing the need of expensive or polluting solvents. Second, due to the easy formation of transient reactive species (radicals), new transformations can be designed. Earlier data clearly show that ultrasound irradiation can activate the surface of metal powder and reduce the particle size, and brings about an effective surface modification. Many metal-involved organic reactions have been accelerated under ultrasound.[17]

Sonochemical one-pot multistep (MSP) reactions, present significant advantages over conventional linear step synthesis by reducing reaction time period and saving money, energy, and raw materials, thus resulting in both economical and environmental benefits. One-pot MSP sequential synthetic methods, in which a number of synthetic steps involving two or more reactants are carried out in the same flask without the isolation of any intermediate, feature a high degree of reaction mass efficiency and are especially suitable in diversity oriented synthetic programs. Methods based on ultrasound assisted multicomponent reactions have proved quite efficient for the construction of different arrays of heterocyclic compounds. Sonochemical one-pot MSP, indoles via Sonogashira reaction,[18] carbohydrates chemistry,[16] and others heterocyclic reactions.[19] In our knowledge, the ultrasound-assisted synthesis of triazolyl-nucleosides has not yet been reported.[20]

In continuation of our investigations for the development of original methods to heterocycles,[21] we wish to report an efficient and practical procedure for the synthesis of nucleosides-1,2,3-triaroles with sugar, Lewis acid, acetic anhydride, $TMSN_3$, copper iodide and alkyne via one-pot regioselective method (Scheme 1).

RESULTS AND DISCUSSION

Many recent papers describing the use of ultrasound in carbohydrate transformations pointed out that its use due to enhance the reaction rates, formation of purer products in high yields, easier manipulation and considered a processing aid in terms of energy conservation and waste minimization which compared with traditional methods [15g, 17e-g, 22]. In continuation of our work to develop new and efficient synthetic methodologies [11a, 23], we envisioned that by fine-tuning the reaction conditions, both sugar-acyl and azide partners can be generated in situ, which thereafter may undergo Huisgen's cycloaddition under the same Lewis acidic condition to make it practically a four-component reaction. During the course of our investigations on the catalytic activation of acylation reaction (i), we first attempted the coupling of □-D-glucose (**1a**) with acetic anhydride in the presence of 10 mol% of various Lewis acids under ultrasonic irradiation at ambient temperature (Scheme 2) and (Table 1, entries 1-10).

Preliminary results showed that an intense short ultrasonication of the anhydrous $FeCl_3$ powder (10%)[24] sufficed to accelerate the reaction at room temperature under solvent-free conditions in comparison to magnetically stirring (Table 1, entry 2). The reaction proceeded efficiently to afford the acylated□-D-glucose product **2a** in 95% yield. The best results were also obtained using $ZnCl_2$, $FeCl_2$, $SnCl_2$ and BF_3OMe_2 (Table 1, entries 1, 3-5), but our reason-based choice of $FeCl_3$ catalyst as an inexpensive, stability and environmentally friendly Lewis acid. In all the reactions including acylation (entries 1-5) the yields were very good (> 86%); the nature of metal cation of the catalyst had negligible effect on the rate as well as the regioselectivity of the reaction (entries 1-4). The relative proportion of the reactants and the reaction time were also tested and the best result was obtained by using 5.5 equiv of acetic anhydride, witch plays the dual role of reagent and solvent in this reaction. Under these mild conditions, the reaction was very rapid (15 min) and the acylated □-D-glucose was obtained in high yield (95%). A larger excess of $FeCl_3$ was not required and did not change the results. Other iron(III) salts such as $Fe(acac)_3$ and $Fe(NO_3)_3$ were not so effective for conversions. In contrast, for the others catalysts (entries 6-10), the conversion rate of the starting sugar is low and therefore the reaction is incomplete even after several hours of ultrasonication.

In the second step, the ultrasonication was continued until acylated □-D-glucose (**2a**) had disappeared as indicated by TLC, and transformed to acylated □-D-glucose azide (**3a**) by addition of $TMSN_3$ under iron catalyst used in the first step with ultrasound irradiation. In this case, we also observe an evident acceleration of the reaction under ultrasonic irradiation in comparison to conventional method, and the best results were obtained with iron ($FeCl_2$ and $FeCl_3$) as catalysts for the azidation (entries 1 and 2). We noticed that a larger excess of $FeCl_3$ was not required and did not change the results. During the course of azidation (ii), we have tried to optimise the reaction conditions. When the molar ratio of acylated □-D-glucose and $TMSN_3$ was 1:1, the acylated □-D-glucose azide was obtained in a lower yield. By increasing the molar ratio to 1:2, the yield of product was increased to 95% (Table 2, entry 2). The second step necessitated an addition of a solvent in small amount. So, the reaction was carried out in various solvents such as ether, cyclohexane, toluene and THF and gave only the best results with CH_2Cl_2. The best result obtained in CH_2Cl_2 as hydrophobic solvent; and the mechanical effect of the acoustic waves improves heterogeneous reactions. The cavitation also accelerates mass transport and the much easier contact between immiscible or poorly soluble reactants such as □-D-glucose non soluble in the beginning of reaction. Second, due to the easy formation of transient reactive species (radicals), we have considered the possible contribution of the acetyl radical can be produced by ultrasound excitation of acetic anhydride.

The 1,3-dipolar cycloaddition step was carried out using the azido-sugar **3a** and the ethyl propiolate as a model reaction. After optimization of the reaction conditions, the best results were obtained using alkyne/CuI/DIEA in 2/2/3 molar ratio. Under these conditions, the cycloadduct **4a** [9b] was obtained in high yield under ultrasonication (84%, 20 min) compared to conventional activation (75% after 120 min, Scheme 3 and Table 3).

Considering the efficiency of the procedure described above with iron and copper catalysts, the scope of these transformations was examined with a range of sugars and alkynes under ultrasound activation (Table 3). Furthermore, to avoid storage and manipulation of organic azide known for their low stability a one-pot process was explored. The results are summarized in Table 3.

As shown in the Table 3, all experiments were performed in relatively short global times (50-190 min) and in good global yields (50-86%). However, some cycloaddition reactions require a mild heating at 35 °C with ultrasound assisted to complete (entries 3, 5, 7, 9), due to the poor reactivity of the dipolarophiles (alkynes) used. The best results are obtained with the use of ethyl propiolate as alkyne (entries 1 and 4) for the global times and yields of 55 min, 84% (entry 1) and 50 min, 86% (entry 4) respectively. Indeed, the presence of an electron-withdrawing group (CO_2Et) facilitates the dipolar cycloaddition between the azido-sugar and the alkyne. In contrast, the presence of electron-donating or bulky groups, such as *p*-Pr-phenyl and bi-phenyl (entries 3, 5, 7), reduces partially the efficiency of the click chemistry step and therefore the reactions times and yields for these tests are between 120-190 min (35°C) and 50-65% respectively.

Furthermore, no epimerization of the anomeric stereocenter was observed since the anomeric stereochemistry of all products remained unchanged during this one-pot three-step process, as attested by ^{1}H NMR and ^{13}C NMR data.

All results clearly show that ultrasonic irradiation accelerates the reactions compared to the magnetic stirring. Indeed, by classical method the yields are lower to moderate after two hours of stirring, except for the reactions carried out with ethyl propiolate (entries 1,4). Therefore, the ultrasound can activate the surface of the iron and copper powders catalysts by reducing the particle size resulting in an efficient modification of the surface, which enables the catalysts and thus accelerate the reaction. Many metal-involved organic reactions have been accelerated under ultrasound. In the absence of catalyst, the reaction failed to give the desired product.

General Procedure For The Synthesis Of Products (4a-J)

To a 1 mmol of sugar **1a-c**, 0.1 mmol (16.2 mg) of $FeCl_3$ and 5.5 mmol (0.52 mL) of Ac_2O were added. The reaction mixture was irradiated with ultrasound irradiation at 25 °C for 15 minutes (the reaction mixture became a clear solution), then 2 mmol (0.26 mL) of $TMSN_3$ and 5 ml of CH_2Cl_2 were added to continue the irradiation for 20 minutes. When the azidation was finished (indicated by TLC), 2 mmol of alkyne, 2 mmol (0.38 g) of CuI and 3 mmol (0.52 mL) of DIEA were added and the mixture was sonicated further at room temperature, except for the compounds (**4c, 4e, 4g, 4i**) in which the ultrasonication is accompanied by a moderate heating of the ultrasonic bath at 35°C. The termination of the reaction was monitored by TLC using cyclohexane:AcOEt (1:1) as eluent. Finally, the reaction was quenched by the addition of CH_2Cl_2 (50 mL) and sat. aq NH_4Cl (20 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). After that the organic layer was washed with water (20 mL) and an aqueous solution of saturated brine (20 mL) before dried over $MgSO_4$ and concentrated in vacuum to give the crude product, which was purified by flash silica gel chromatography (cyclohexane-EtOAc : 70/30) to afford the pure desired adducts **4a-j**.

Complete experimental details are available online in the Supplementary Information.

CONCLUSION

In this work, we have developed a clean, efficient and rapid protocol for the synthesis of triazolyl-4-substituted nucleosides which may have important biological activities. This new methodology is based on a one-pot procedure that involves a cooperative effect of iron-copper catalysis and ultrasound activation starting from available starting materials. The evaluation of the potential antileukemic effect of these analogues towards the chronic myelogenous leukemia (CML) K562 cell line, is under investigation.

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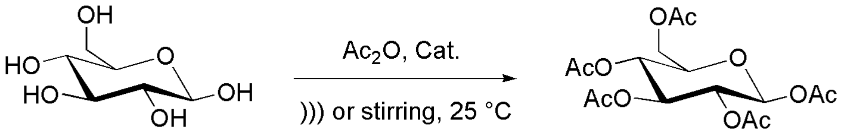
Table 1. The effect of catalysts and ultrasound in the acetylation reaction.

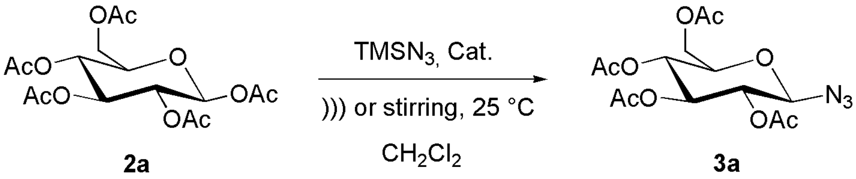


1a **2a**

Entry [a,c]	Catalyst	Time		Yield (%)[b]	
		Stirring (h)	))) (min)	Stirring	))) (min)
1	$FeCl_2$	1.5	15	93	94
2	$FeCl_3$	1	15	93	95
3	$SnCl_2$	1.5	20	87	86
4	$ZnCl_2$	1.5	15	95	95
5	BF_3OMe_2	1	15	94	93
6	$CuCl_2$	24	30	43	68
7	$Cu(OAc)_2$	48	45	21	40
8	$CoCl_2$	48	60	17	29
9	$NiCl_2$	24	45	25	38
10	$NiSO_4$	24	45	26	38

[a] catalyst (10 mol%), Ac_2O (5.5 equiv.). [b] yields based on the isolated product. [c] entries 6-10 : incomplete reactions.

Table 2. The effect of catalysts and ultrasound in the azidation reaction.

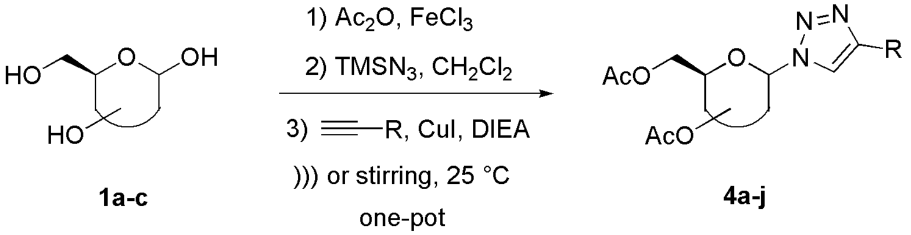


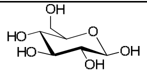
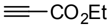
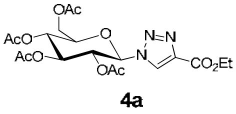
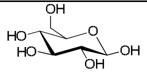
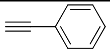
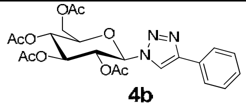
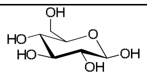
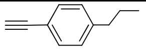
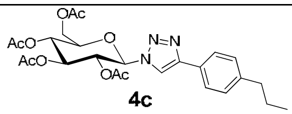
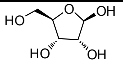
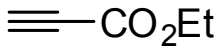
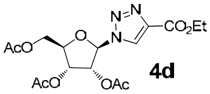
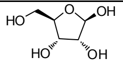
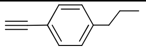
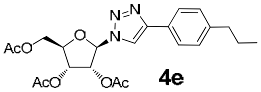
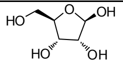
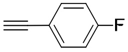
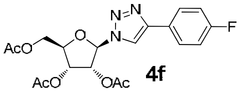
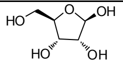
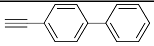
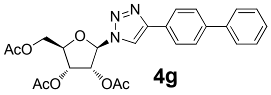
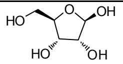
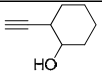
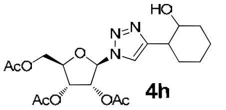
Entry [a]	Catalyst	Time		Yield (%)[b]	
		Siirring(h)	))) (min)	Siirring(h)	))) (min)
1	$FeCl_2$	3	25	76	92
2	$FeCl_3$	2.5	20	78	95
3	$SnCl_2$	3	25	70	72
4	$ZnCl_2$	3	25	74	78
5	BF_3OMe_2	2	20	88	87

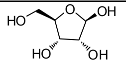
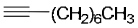
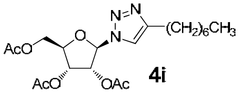
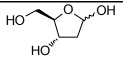
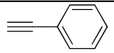
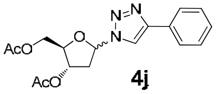
[a] catalyst (10 mol%), $TMSN_3$ (2 equiv.).

[b] yields based on the isolated product.

Table 3. Extension of the one-pot three-step reaction by ultrasonication.

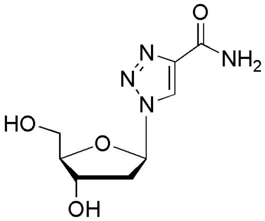


Entry[a]	Sugar	Alkyne	Product	Time (min)[b]	Yield (%)[b]
1			 **4a**	55	84[9b]
2			 **4b**	80	77[9b]
3[c]			 **4c**	120	56
4			 **4d**	50	86
5[c]			 **4e**	120	53
6			 **4f**	70	76
7[c]			 **4g**	190	50
8			 **4h**	100	64

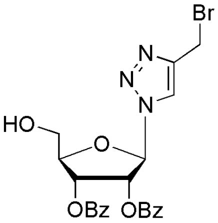
9[c]			 **4i**	120	65
10[d]			 **4j**	75	78

[a] Ac_2O (5.5 equiv.), $FeCl_3$ (10 mol%), $TMSN_3$ (2 equiv.), Alcyne/CuI/DIEA (2:2:3). [b] global times and yields (yields based on the isolated product). [c] heating of click chemistry step (35 °C). [d] □/□̤ □̃ □̣̃.

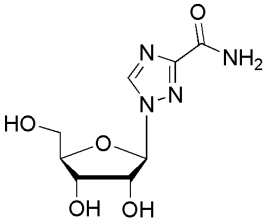
Figure 1.



A



B

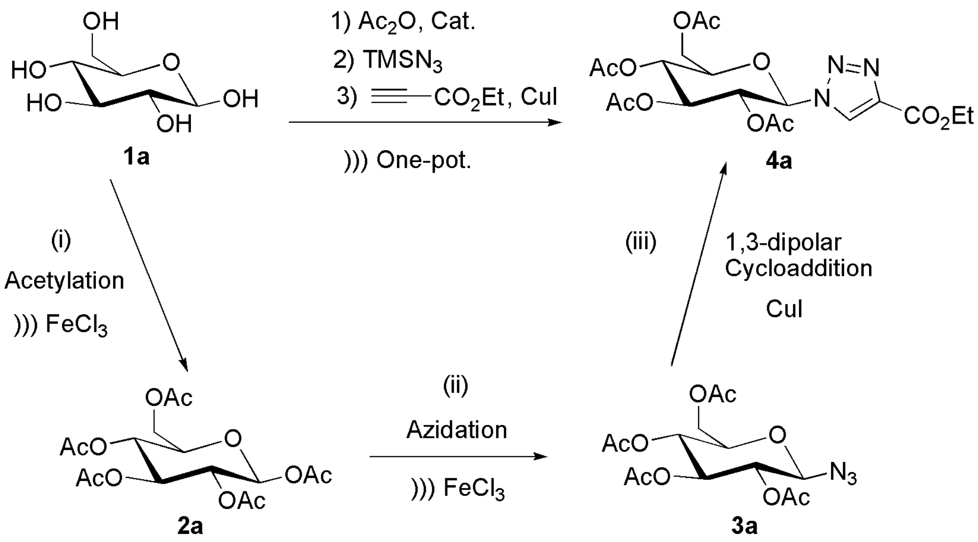


C

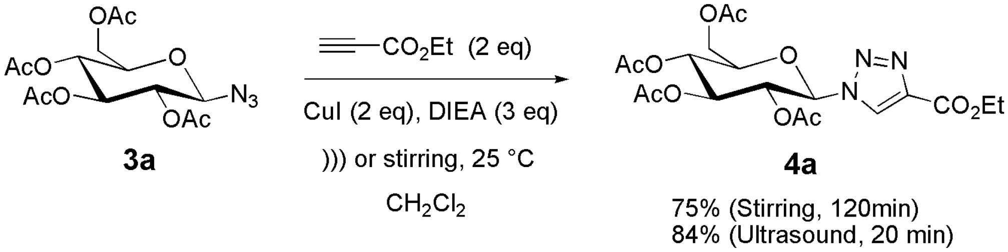
Scheme 1.


1) Ac2O, FeCl3
2) TMSN3
3) ≡—R, CuI, DIEA
))) One-pot
Sugar
OH
1a-c
Sugar
N
N
N
R
4a-j
Sugar
OH = β-D-ribose (1a); β-D-2-deoxyribose (1b); β-D-Glucose (1c)

Scheme 2.


1a
2a
3a
4a
1) Ac_2O, Cat.
2) $TMSN_3$
3) $\equiv$—CO_2Et, CuI
))) One-pot.
(i)
Acetylation
))) $FeCl_3$
(ii)
Azidation
))) $FeCl_3$
(iii)
1,3-dipolar Cycloaddition
CuI

Scheme 3.


OAc
AcO
AcO
O
N$_3$
OAc
3a
CO$_2$Et (2 eq)
CuI (2 eq), DIEA (3 eq)
))) or stirring, 25 °C
CH$_2$Cl$_2$
OAc
AcO
AcO
O
N=N
N
CO$_2$Et
OAc
4a
75% (Stirring, 120min)
84% (Ultrasound, 20 min)