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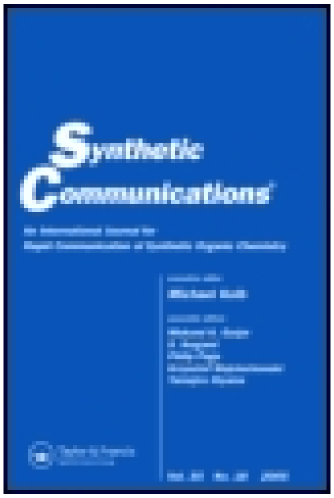

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NaOH/Et_3N-Promoted Stereoselective One-Pot Synthesis of α-Diazo Oxime Ethers via Diazo Transfer Reaction

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NaOH/Et_3N–Promoted Stereoselective One-Pot Synthesis of *α*-Diazo Oxime Ethers via Diazo Transfer Reaction

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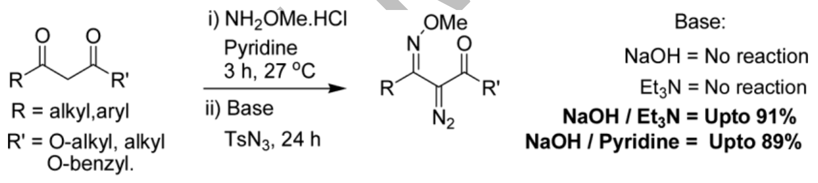
Abstract

For the first time, we have observed a combined effect of two bases NaOH/Et_3N to promote the diazo transfer reaction of *β*-oximino esters. This unusual synergistic effect has been employed to obtain *α*-diazo oxime ethers directly from *β*-keto esters by one-pot process. This method is simple, cost effective and the reagents are readily available.



One - Pot Process

KEYWORDS: *α*-diazo imines, diazo transfer reaction, one-pot process, synergistic effect.

Diazo compounds have a long history of useful applications in the organic synthesis.[1] They are versatile intermediates and undergo a variety of organic transformations including insertion, rearrangement, cycloaddition, etc.[2] After the first synthesis of ethyl diazoacetate *via* diazotization of glycine, several attempts had been made to achieve this useful functional group.[3] Among them, dehydrogenation or oxygenation of hydrazones,[4] decomposition of organic azide in the presence of phosphine,[5] etc. are a few to be acknowledged. The major breakthrough came with the discovery of diazo transfer reaction by Regitz,[6] which make use of sulfonyl azides as the nitrogen source and gave promising results with the active methylene compounds. Hitherto, the diazo transfer reaction is identified as the simplest protocol that makes use of easy to handle reagents, involves simple work up and purification. Chemical modification of ethyl diazoacetate *via* aldol type reaction,[7] Pd-catalyzed reaction,[8] etc., have also helped to get diversity in diazo compounds.

Even though several methods are available for *α*-diazo ketones, its nitrogen analogs *i.e.*, *α*-diazo oxime ethers, have rarely been studied. Shimon Shatzmiller *et al*. carried out diazo transfer reaction of acetophenone oxime ether using *n*-BuLi at -78 ^{o}C.[9] Recently, we have developed[10] a methodology for the stereoselective synthesis of α-diazo imines *via* diazo transfer reaction using 4-nitrobenzenesulfonyl azide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base at -20 ^{o}C (condition 1, Scheme 1). Even though, both the geometrical isomers of the oxime ethers were employed for the reaction, *cis* diazo imine was obtained exclusively. The limitation of this method includes use of expensive, non-readily available reagents and requirement of very low temperature. In this communication, we report a modified one-pot procedure for the synthesis of diazo imines from *β*-keto ester *via* diazo transfer reaction, which makes use of the synergistic effect between NaOH/Et_3N.

During our study on diazo compounds,[11] we found that the diazo transfer reaction of imines also proceeds with readily available 4-toluenesulfonyl azide (TsN_3) when a mixture of bases, *i.e.*, NaOH/Et_3N was employed. Accordingly, oxime ether **1b** reacts with TsN_3 in the presence of NaOH/Et_3N in CH_3CN to give diazo compound **2b** at ambient conditions (condition 2, Scheme 1).

It is noteworthy to observe that the reaction proceeds at room temperature with higher reaction rate in the presence of NaOH/Et_3N to give comparable yield of the compound **2b**. But, the reaction failed to give the desired product when NaOH or Et_3N was employed as the only base (Entry 1 & 2, Table 1). Hence, the use of two bases is mandatory and the need for two bases is not well understood. For the first time we have come across such a peculiar observation with diazo transfer reaction. To our understanding, Et_3N surrounds the metal cations (**A** & **B**) formed in the presence of metal hydroxide and fine-tune its nucleophilicity to attack the TsN_3 to give the diazo compounds. When NaOH is employed as the base, such increase in nucleophilicity is not possible whereas, Et_3N due to its poor basicity is not able to generate the anion (Fig. 1).

We also tried this reaction with combination of different bases, of which one is strong inorganic base and the other is organic amine. For instance, KOH/Et_3N, K_2CO_3/Et_3N, NaOH/DMAP, NaOH/DIPEA, NaOH/pyridine, were screened and the results are given in the Table 1. Both NaOH and KOH gave comparable yields of the diazo compound while K_2CO_3 failed to give the product. Among the amines, Hunig's base, pyridine, diisopropyl amine gave moderate yield after three hours and the reaction rate was found to be considerably slow. Among the solvents, acetonitrile gave the better yield while THF, dioxane, diethyl ether and halogenated solvents gave moderate to poor yields. There was not much increase in the yield of the diazo compounds when the reaction was carried out at 0 ^{o}C.

In order to understand the scope of the reaction, we screened a few active methylene oxime ethers and the results are given in the Table 2. The oxime ethers were prepared from the corresponding keto esters by reacting with methoxylamine hydrochloride in pyridine as solvent and were used without purification after work up. Even though both *cis* and *trans* oxime ethers were employed only *cis* diazo oxime ethers were obtained in consistence to our earlier method. All the yields obtained are comparable with our earlier method.

Since the oxime ethers are prepared in pyridine as solvent and diazo transfer reaction proceeds smoothly in NaOH/ Pyridine condition (Entry 6, Table 1), we attempted to synthesize α-diazo oxime ethers directly from β-keto esters by one-pot process. Accordingly, β-keto esters **3** were converted to the corresponding oxime ethers **4** by reacting with methoxylamine hydrochloride in the presence of pyridine for 3 h. Subsequent addition of NaOH and TsN_3 to the reaction mixture facilitated the diazo transfer reaction with *in situ* generated oxime ethers to give α-diazo oxime ethers **5** (Scheme 2). Even though the reaction rate was comparatively slow, good yields were obtained after 24 h. In consistence with our earlier observation, only *cis* isomer was obtained with comparable yields. Interestingly, 1,3-diones such as, 1,3-pentadione, cyclohexadione, dimedone were successfully subjected to this reaction to obtain corresponding *α*-diazo mono oxime ethers in good yields (Entry c, d, and f Table 3).

In conclusion, we have developed a simple and cost effective protocol for the synthesis of diazo oxime ethers *via* diazo transfer reaction using NaOH/Et_3N mixture as base. The reaction is carried out at ambient conditions and is fast enough to reach completion in 30 minutes. We have also developed a one-pot process for the synthesis of *α*-diazo oxime ethers from *β*-keto esters. Further, this methodology could be extended for non-active methylene compounds and the need for the two bases can be studied.

EXPERIMENTAL

All reagents and solvents were obtained from Merck and Aldrich is used without any purification. ^{1}H- and ^{13}C- NMR spectra were recorded on Bruker FT- 500 or 400 using tetramethyl silane (TMS) as an internal standard. The IR spectra were recorded on Shimadzu FTIR spectrophotometer (in KBr).The compounds were purified by column chromatography using silica gel (100-200 mesh) and pet ether:ethyl acetate. TLC was performed using silica gel 60 F_{254} precoated on aluminium sheets, obtained from Merck. Visualization of spots on TLC plate was done with uv light (254 nm).

TYPICAL PROCEDURE

Procedure For One-Pot Synthesis Of *A*-Diazo Oxime Ethers

To a solution of *β*-keto ester (1 eq.) in pyridine at room temperature was added methoxylamine hydrochloride (1.1 eq.) in one portion and the reaction mixture was stirred for 3 h. Sodium hydroxide (2 eq.) and 4-toluenesulfonyl azide (1.1 eq.) were then added to the same reaction mixture and stirred for 24 h. After the completion of the reaction as indicated by the TLC, the mixture was washed with water, brine, and extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to get crude product which was purified by column chromatography using pet ether:ethyl acetate (19:1) to obtain pure α-diazo oxime ethers.

(*Z*)-Ethyl 2-diazo-3-(methoxyimino) butyrate: (5a & 2c) Yield: 65% (Yield: 0.240 gm); IR (cm^{-1}) 2125, 1708, 1470, 1373, 1320; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 (q, 2H, *J* = 14.0 & 7.0 Hz), 3.84 (s, 3H), 1.60 (s, 3H), 1.3 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 146.1, 61.7, 61.1, 52.1, 19.2, 14.3; MS (EI) m/z $[M+H]^+$: Calcd for $C_7H_{11}N_3O_3$: 185.1805, Found: 185.1825.

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SUPPLEMENTAL MATERIAL

Full experimental detail, and ^{1}H and ^{13}C NMR spectra for this article can be accessed on the publisher's website.

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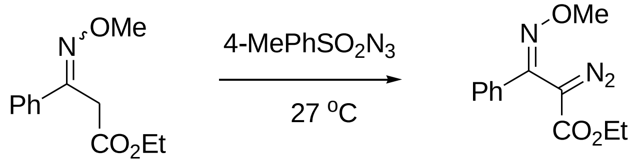
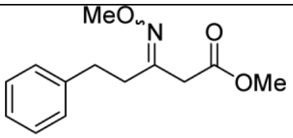
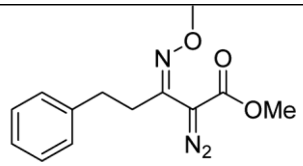
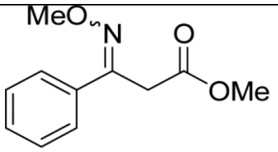
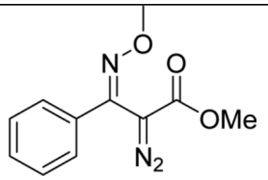
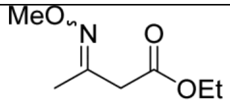
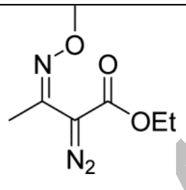
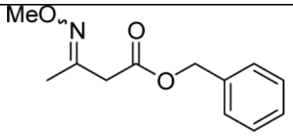
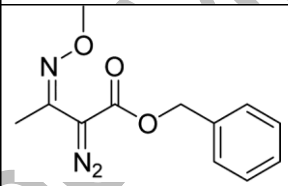
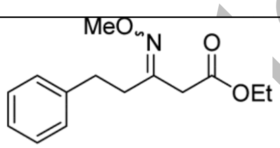
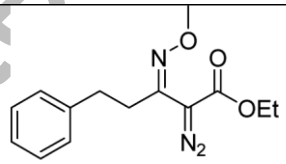
Table 1 Screening of base and solvent for the diazo transfer reaction[a]



Entry	Base	Solvent	Time (min)	Yield[b]
1	NaOH	CH_3CN	180	No reaction
2	Et_3N	CH_3CN	180	No reaction
3	NaOH/ Et_3N	CH_3CN	30	91
4	KOH/ Et_3N	CH_3CN	30	88
5	NaOH/ *i*Pr_2NEt	CH_3CN	180	62
6	NaOH/ Pyridine	CH_3CN	180	65 (89)[c]
7	NaOH/ *i*Pr_2NH	CH_3CN	180	52
8	NaOH/ DMAP	CH_3CN	180	45
9	K_2CO_3/ Et_3N	CH_3CN	180	-
10	NaOH/ Et_3N	1,4-dioxane	180	30
11	NaOH/ Et_3N	THF	180	25
12	NaOH/ Et_3N	Et_2O	180	10
13	NaOH/ Et_3N	$CHCl_3$	180	Trace[d]

[a] oxime ether (2 mmol), tosyl azide (2 mmol), mixture of base (Inorganic/organic, 2 mmol/2 mmol), solvent (6 mL), RT. [b] yield corresponds to the isolated yield by column chromatography. [c] Yield after 24 h. [d] observed by HPLC.

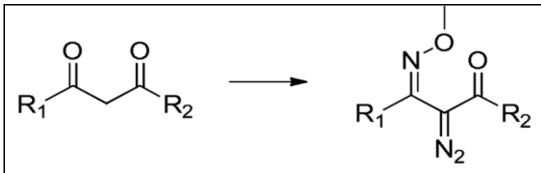
Table 2 Synthesis of α-diazo oxime ethers using TsN_3 and $NaOH/Et_3N$[a]

Entry	Reactant[b] (**1**)	Product (**2**)	Yield[c]	Reference
A	 (64:36)		77	10
B	 (82:18)		89	10
C	 (50:50)		65	-
D	 (60:40)		68	-
E	 (65:35)		75	-

[a] oxime ether (2 mmol), tosyl azide (2 mmol), $NaOH/Et_3N$ (2 mmol/ 6 mmol), CH_3CN (6 mL), 30 min, 27 °C.

[b] *cis trans* ratio has been given in the parenthesis. [c] Yield corresponds to the isolated yield by column chromatography.

Table 3 Synthesis of α-diazo mono oxime ethers using TsN_3 and $NaOH/Et_3N$[a]



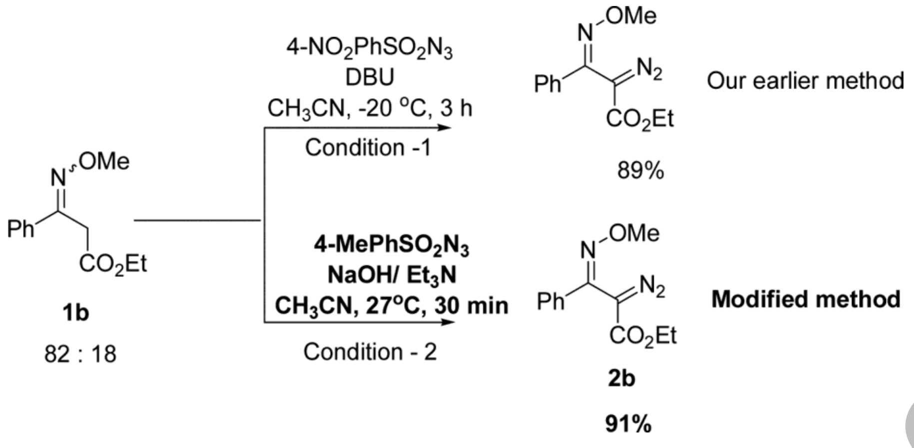
3 5

Entry	R_1	R_2	Yield[b]	Reference
a	CH_3	OEt	65	-
B	$PhCH_2CH_2$-	OEt	75	-
C	$-CH_2-CH_2-CH_2-$		70	-
D	$-CH_2-C(CH_3)_2–CH_2-$		66	-
E	CH_3	$PhCH_2O$-	68	-
F	CH_3	CH_3	63	-
G	CH_3	OMe	65	10
H	4-NO_2Ph	OMe	80	10
I	$CH{\equiv}C-CH_2$	OMe	70	10
J	$PhCH_2CH_2$-	OMe	77	10

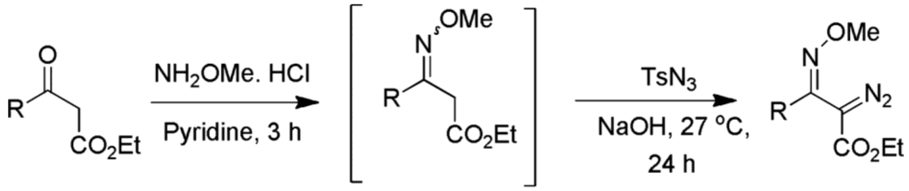
[a] NH_2OMe (2.2 mmol), pyridine (6 ml), 3 h then tosyl azide (2 mmol), NaOH (2 mmol), 24 h, 27 °C.

[b] Yield corresponds to the isolated yield by column chromatography.

Scheme 1.


4-NO2PhSO2N3
DBU
CH3CN, -20 °C, 3 h
Condition -1
Our earlier method
89%
1b
82 : 18
4-MePhSO2N3
NaOH/ Et3N
CH3CN, 27°C, 30 min
Condition - 2
Modified method
2b
91%
OMe
N
Ph
N2
CO2Et

Scheme 2. One-pot synthesis of α-diazo oxime ethers

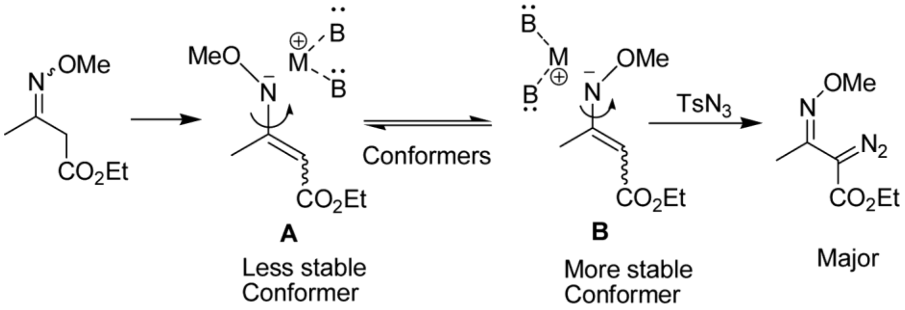


3

4

5

Figure 1.


OMe
N
CO2Et
MeO
N
M
B
B
CO2Et
A
Less stable Conformer
Conformers
B
M
B
N
OMe
CO2Et
B
More stable Conformer
TsN3
N
OMe
N2
CO2Et
Major