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Cyclen-catalyzed Henry reaction under neutral conditions

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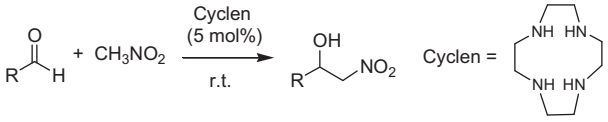
ABSTRACT

A convenient cyclen-catalyzed Henry reaction of aldehydes with nitroalkanes under mild and neutral conditions is reported. This procedure constitutes the first cyclen-catalyzed synthesis of nitroalcohols and is adapted to the condensation of both aromatic and aliphatic aldehydes with nitromethane in THF at room temperature without addition of stoichiometric amount of the base. A wide range of substrates, β-nitroalcohols, were obtained in moderate to good yields (up to 98%) using this methodology.

The Henry reaction (or nitroaldol reaction) discovered in 1895[1] is an efficient method for C–C bond construction, the result of the reaction of a nitroalkane with an electrophilic carbonyl derivative (aldehyde or ketone). This reaction became very popular because the resulting β-nitroalcohols are highly valuable synthons for the preparation of useful intermediates in synthetic organic chemistry.[2] Their preparation in high yield and selectivity following a safe and economic procedure is still challenging. The scope of this reaction depends largely on the nature of the catalyst used as well as on the reaction conditions and has already been described in several reviews.[3] Among the large variety of catalysts which are known in this reaction, alkali metal bases and alkaline alkoxides in alcoholic solution,[4] simple amines,[5] ammonium salts,[6] guanidine derivatives,[7] organo-phosphorus derivatives,[8] and lithium-aluminum hydride[9] were used successfully. Furthermore, asymmetric versions of this reaction were reported since the pioneering report of Shibasaki.[10]

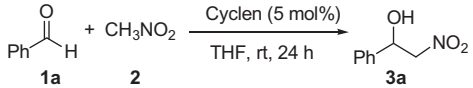
We described herein our preliminary results concerning the cyclen-catalyzed addition of nitoalkanes to aldehydes using an efficient and mild procedure (Scheme 1).

In the course of our research program on iron-catalyzed reactions,[11] and in the light of the use of a cyclen/iron system to promote direct C-arylation,[12] we decided, in an initial attempt to synthesize nitroalcohol from benzaldehyde (1 mmol) and nitromethane (2 mmol) in THF, to use a combination of $Fe_2(SO_4)_3{\cdot}xH_2O$ and cyclen as a catalyst (5 mol %) for the Henry reaction. Starting with benzaldehyde provided the desired nitroaldol product **3a** in 83% yield. While this result appeared promising, control experiments proved to be even more enlightening. In the presence of 5 mol % of $Fe_2(SO_4)_3{\cdot}xH_2O$ without the cyclen ligand no nitroaldol product **3a** was detected while cyclen alone gave a very good con-



Scheme 1. Cyclen-catalyzed Henry reaction of aldehydes with nitromethane.

Table 1
Optimization of the reaction conditions[a]



Entry	Cyclen (mol %)	CH_3NO_2 (equiv)	Yield[b] (%)
1	/	2	0
2	5	Solvent[c]	25
3	5	2	86
4	5	5	85
5	5	10	80

[a] Experimental conditions: benzaldehyde (1 mmol), nitromethane, cyclen (2–10 mol %) in 1 mL of THF for 24 h.
[b] Determined by NMR.
[c] Nitromethane was used as the solvent instead of THF.

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version, implicating cyclen as the active catalyst (Table 1, entry 3). Control experiments in the absence of cyclen (Table 1, entry 1) show no reaction and confirmed the crucial role of the tetraaza-macrocycle catalyst played in the described transformation.

A systematic study was then undertaken to define the best reaction conditions, and Table 1 lists the representative data obtained for the synthesis of 2-nitro-1-phenylethanol **3a** under various experimental conditions.

In general, 5 mol % of cyclen was applied as the catalyst in THF and the reaction mixture was stirred at room temperature for 24 h.

First of all, when cyclen was employed as the catalyst (5 mol %), in nitromethane as the solvent, low conversion was observed (25%, Table 1, entry 2). Among the different amounts of nitromethane used in THF as the solvent, the best result was achieved when the reaction was performed with 2 equiv, furnishing the 2-nitro-1-phenylethanol **3a** in 86% conversion (Table 1, entry 3). Hence, the optimized conditions found for the synthesis of 2-nitroalcohols starting from aldehyde and nitromethane are the use of 1 equiv of aldehyde, 2 equiv of nitromethane in the presence of 5 mol % of cyclen in THF at room temperature for 24 h under air.

The substrate scope was then investigated. A variety of aldehydes and nitroalkanes were tested under the optimized conditions using cyclen as the catalyst (Table 2). As shown in Table 2, β-nitroalcohols **3** are obtained in good to excellent yields; it should be underlined that the by-products resulting from typical side reactions such as the retro-aldol reaction[1] or the dehydration of the 2-nitroalcohol into nitroalkene[13] were not observed due to the mild reaction conditions.

It turned out that this cyclen-catalyzed Henry reaction could adapt to various aldehydes. For arylaldehydes bearing electron-withdrawing groups, the reaction proceeded smoothly and gave rise to the corresponding β-nitroalcohols **3b–f** in moderate to good isolated yields ranging from 75% to 98% (Table 2, entries 2–6)[14]. Interestingly, when the reaction was performed with *m*- and *o*-bromobenzaldehyde, the corresponding 2-nitroalcohols **3g–h** were obtained in 97% and 70% isolated yields, which shows that the *meta*- or *ortho*-substituents did not hamper the reaction. Arylaldehydes bearing electron-donating groups such as *p*-anisaldehyde also reacted under our general conditions, but the reaction did not go to completion, resulting in 30–75% of the corresponding nitroalcohol (Table 2, entries 9–11). In these cases, the reactions were clean and no dehydration of 2-nitroalcohols to the corresponding nitroalkenes was observed in the crude reaction mixture in ^{1}H NMR and the conversion determined by ^{1}H NMR was in the same range as the isolated yields. Furthermore, the reaction did not proceed when a free phenolic hydroxyl or a dimethylamino moiety was present on the aromatic ring.

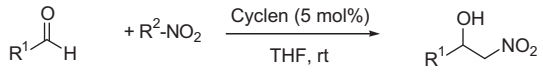
Principles of this cyclen-catalyzed Henry reaction can also be extended to heterocyclic aldehydes. Thus, 2-pyridylaldehyde could be smoothly converted into 1-pyridyl-2-nitroethanol **3l** in 62% isolated yield (Table 2, entry 12). When 2-furaldehyde, 3-furaldehyde, and 2-thiophenealdehyde were used, the corresponding 2-nitroalcohols **3m–o** were isolated in 55%, 62%, and 55% yield, respectively (Table 2, entries 13–15). It must be pointed out that to obtain cleanly these heteroarylnitroalcohols, the reaction must be conducted under argon at 5 °C. Furthermore, at the end of the reaction the reaction mixture had to be washed with a 1-M HCl solution to remove the cyclen catalyst and avoid any degradation of the nitroalcohol derivatives.

In order to prove the generality of the method, various aliphatic aldehydes were condensed with nitromethane and the results obtained are summarized in Table 2 (entries 18 and 19).

We successfully extended the procedure to include other nitroalkanes such as nitroethane (entry 16) and nitropropane (entry 17). In these cases, the reactions proceeded at room temperature for 24 h and led to the corresponding nitroalcohols in moderate isolated yields (50–51%).

In conclusion, we have developed a cyclen-catalyzed Henry reaction which involves an efficient and simple method providing in most cases the desired β-nitroalcohol in moderate to good yields. Cyclen catalyst is shown to be highly efficient especially in terms of milder reaction conditions (room temperature, with 5 mol % of cyclen and 2 equiv of nitroalkane). It should be underlined that the mild reaction conditions and the easy work up prevents typical side reactions usually observed while using amines as catalysts such as the retro-aldol reaction, the dehydration of the 2-nitro alcohol into nitroalkene even if aromatic aldehydes are used, or the formation of 1,3-dinitroalkene derivatives.

Table 2
Scope of the reaction[a]



1 2 3

Entry	R^1	R^2	Time		Isolated yield (%)
1	Ph	Me	24 h	**3a**	80
2	4-NO_2–C_6H_4	Me	22 h	**3b**	78
3	4-NC–C_6H_4	Me	24 h	**3c**	88
4	4-F_3C–C_6H_4	Me	24 h	**3d**	98
5	4-Ph–C_6H_4	Me	19 h	**3e**	90
6	4-Br–C_6H_4	Me	24 h	**3f**	75
7	3-Br–C_6H_4	Me	22 h	**3g**	97
8	2-Br–C_6H_4	Me	22 h	**3h**	70
9	4-MeO–C_6H_4	Me	21 h	**3i**	30
10	3,4,5-$(MeO)_3$–C_6H_2	Me	23 h	**3j**	62
11	3,5-$(MeO)_2$–C_6H_3	Me	24 h	**3k**	75
12	Pyrid-2-yl	Me	23 h	**3l**	62
13	Furan-2-yl	Me	24h[b]	**3m**	55
14	Furan-3-yl	Me	24 h[b]	**3n**	62
15	Thiophen-2-yl	Me	24 h[b]	**3o**	55
16	Ph	Et	24 h	**3p**	50
17	Ph	Pr	24 h	**3q**	51
18	Cyclohexyl	Me	24 h	**3r**	70
19	Propyl	Me	24 h	**3s**	71

[a] Experimental conditions: aldehyde (1 mmol), nitroalkane (2 mmol), cyclen (0.05 mmol, 5 mol %) in 1 mL of THF.
[b] The reaction was performed at 5 °C under argon.

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Supplementary data

Supplementary data (typical experimental procedures and copies of ^{1}H and ^{13}C NMR spectra of all the products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.106.

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14. *Representative experimental procedure*: In a 10-mL vial equipped with a magnetic stirring bar, 2 mmol (105 μL) of nitromethane was added to the solution of 3-bromobenzaldehyde (185 mg, 1 mmol) in tetrahydrofuran (1 mL). Cyclen (8.6 mg, 0.05 mmol, 5 mol %) was then added. The solution was stirred at room temperature for 16 h. Volatile components were then removed under reduced pressure and the product was isolated by column chromatography over silica gel with mixed solvent (pentane/diethyl ether) to give a clear yellow oil (97% isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95 (s, 1H), 4.47–4.62 (m, 2H), 5.43 (dd, 1H, J = 3.3, 9.0), 7.25–7.34 (m, 2H), 7.49 (m, 1H), 7.58 (m, 1H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 140.2, 132.0, 130.6, 129.1, 124.5, 123.1, 80.9, 70.2.