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Research Article

MICHAEL-TYPE ADDITION OF NITROALKANES TO NITROALKENES IN WATER: SYNTHESIS OF 1,3-DINITRO COMPOUNDS

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ABSTRACT

Michael-type addition of nitroalkanes with nitroalkenes to afford 1,3-dinitro compounds in good yields (60-86%) under very mild conditions is described using 1M solution of sodium bicarbonate.

Keywords: Michael-type addition, 1,3 dinitro compounds, water, sodium bicarbonate.

INTRODUCTON

The development of more environment friendly chemical processes using water as a reaction medium have received considerable interest because water has unique features over organic solvents as it is environmentally clean, safe, and cheap.[1] The use of water or aqueous media in catalytic organic reactions is a further challenge due to the fact that it tends to inhibit the catalyst activity by interrupting ionic interaction and hydrogen bonds which are critical for stabilizing the transition state of the reaction. However, water due to its small size, high polarity and three dimensional hydrogen bonded network, provides some unique properties which include large cohesive energy density, a high surface tension and hydrophobic effect.[2] Therefore a great deal of effort has been given to the development of organic reactions in water with a main focus on the process promoted by a simple catalyst.[3]

The conjugative addition of stabilized carbanions to electron-deficient unsaturated systems, the so called Michael addition, is one of the important and reliable tool for the construction of C-C bonds in organic syntheisis.[4] Among the various candidates for this bond forming process, nitroalkanes are particularly attractive because of the stabilized carbanion and their versatility into various functionalities.[5] The use of nitroalkenes as Michael acceptors for the C-C bond formation has proven to be a challenging task despite the fact that nitroalkenes are more active than unsaturated carbonyls. In particular, 1,3-dinitroalkanes, an addition product of nitroalkanes to nitroalkenes, are the precursors of a variety of 1,3-difunctionalized compounds such as 1,3-dicarbonyl compounds, heterocycles derived there from and 1,3-diamines which are versatile building blocks from synthetic as well as pharmaceutical view point.[6]

Earlier reports on Michael-type addition of nitroalkanes to nitroalkenes, either isolated or generated in situ, for the synthesis of 1,3-dinitro compounds,[7] have limitation(s) in one way or other thereby restricting their wide-spread applicability. Thus, strong basic conditions, a large excess of nitroalkanes, the formation of by-products due to poly-addition and tedious work up are unfavorable factors. Moreover, no attempt has been made to use water, thereby making the process more eco-friendly. In this communication, we wish to describe the results of diastereo selective Michael-type addition reaction of aliphatic nitroalkanes to nitroalkenes to afford synthetically useful 1,3-dinitro compounds using environmentally compatible solvent.

MATERIALS AND METHODS

All the chemicals used for synthesis were purchased from Sigma Aldrich (Bangalore, India) in LR grade. ^{1}H NMR and ^{13}C NMR were recorded on 300 MHz Brucker Avance DRX-300 using $CDCl_3$ with TMS as internal standard. Mass spectrometry spectra (GCMS) were obtained from a Shimadzu's GCMS-QP2010. The homogeneity of the compounds was monitored by thin layer chromatography (TLC) Silica-G (Merck) coated glass plates, visualized by iodine vapor.

General experimental procedure

A mixture of nitroalkane (1.5 mmol), nitroalkene (1 mmol), and 1M $NaHCO_3$ (1 mL) was stirred at room temperature for the required time. After completion of the reaction (monitored by TLC), the product was extracted with ethyl acetate (5 mL x 3). The combined organic phase was dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography using silica gel (eluent: hexane-EtOAc) to afford the pure product.

RESULTS AND DISCUSSION

The reaction of 1-nitropropane with trans-β-nitro styrene was used as a model reaction for screening different bases in water and the results are presented in Table 1. It was observed that in a 1M K_2HPO_4 solution, nitro styrene **(1a)** reacts with 1-nitropropane **(2a)** to afford the addition product **3a** in 38% yield with moderate diastereoselectivity (4.6:1) (Table 1, entry 1). Accordingly various inorganic and organic bases were tested for the addition reaction of **1a** with **2a** and **3a** was isolated up to 86% yield (Table 1, entries 1-9). The nature of inorganic base has a pronounced effect on the yield and diastereoselectivity of the reaction. The product yield varies in the order of $NaHCO_3$ > NaOH > K_2CO_3 > $(NH_4)_2HPO_4$ > K_2HPO_4. Organic bases were also examined and found inactive in this addition reaction (Table1, entry 6-9). Alcohols such as methanol, ethanol and isopropanol with water in different ratios were also studied for this reaction and found that the diastereoselectivity was slightly improved when methanol was employed in combination with water. Thus the reaction of **1a** with **2a** in water/methanol system (9:1) afforded **3a** in 84% with highest diastereoselectivity *syn*: *anti* (6.7:1) (Table 1, entry 10).

After optimizing the conditions for the reaction of 1-nitropropane with trans-β-nitro styrene using 1 M $NaHCO_3$ solution at room temperature, the scope of the Michael-type addition reaction was extended to other nitroalkanes to nitroalkenes and the results obtained are summarized in Table 2. Thus the reaction of the aromatic nitroalkenes bearing electron-donating substituents (Table 2, entries 2-5 and entries 9-11) proceeds well with nitroalkanes in the 1M $NaHCO_3$ solution and the addition products are isolated in high to good yields with moderate diastereoselectivity. The substrates containing electron-withdrawing groups exhibited relatively low reactivity patterns (Table 2, entries 6 and 12).

In case of **1b** with **2a**, a similar solvent effect was noticed on the improvement of yield and diastereoselectivity of the reaction when methanol was employed in combination with water, H_2O: MeOH (9:1) (Table 1, entry 10 *vs* Table 2, entry 3). The steric effect also plays an important role in governing the diastereoselectivity of the addition product and shows high diastereoselectivity ratio (Table 2, entries 5 and 11). Michael addition was successfully extended to the hetero aromatic nitroalkenes to afford the corresponding products in good yields (Table 2, entries 7 and 13). The addition of nitromethane to nitrostyrene afforded 1, 3-dinitro-2-phenylpropane with 83% yield. No addition product was observed using 2-nitropropane as a Michael donor which may be attributed by the steric bulk of the secondary carbon. All the products were characterized by NMR, Mass-spectroscopy and GC analysis and showed two diastereoisomers (*syn*/*anti*), the major Michael adduct was assigned to be *syn* according to the literature.[8]

CONCLUSION

In conclusion, we have developed the Michael-type addition reactions of nitroalkanes to nitroalkenes in water using a simple and cheap inorganic base. Thus, the procedure appears to be attractive from environmental standpoint and can be safely applied for the Michael-type addition of various to nitroalkenes to obtained 1,3-dinitroalkanes in good to high yields.

ACKNOWLEDGEMENT

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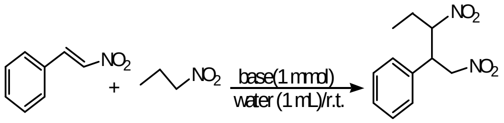
Scheme 1:



1a 2a 3a

Table 1: Screening of bases for the Michael-type addition reaction of 1-nitropropane to trans-β-nitrostyrene[a]

Entry	Base	t/h	Yield **3a** (%)[b]	dr[c] (*syn:anti*)
1	K_2HPO_4	14	38	4.6:1
2	$(NH_4)_2HPO_4$	14	58	4.6:1
3	K_2CO_3	14	60	1.3:1
4	NaOH	14	61	4.6:1
5	$NaHCO_3$	14	86	4.9:1
6	Pyridine	14	32	1.9:1
7	Et_3	14	~2	-
8	DABCO	14	~3	-
9	DPEA	14	~3	-
10[d]	$NaHCO_3$	24	84	6.7:1
11[e]	$NaHCO_3$	24	82	5.3:1
12[f]	$NaHCO_3$	24	80	5.3:1

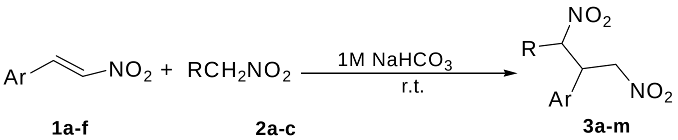
[a] Reaction conditions: trans–β- nitro styrene (1 mmol), 1-nitropropane (1.5 mmol), base (1 mmol) in water (1 mL) at room temperature.;

[b] Isolated yields.;

[c] Determined by ^{1}H NMR spectroscopy and GC.;

[d] In H_2O:MeOH (9:1).; [e] In H_2O:EtOH (9:1).; [f] In H_2O:iPrOH (9:1).

Scheme 2:



1a: Ar = C_6H_5
1b: Ar = 4-Me-C_6H_4
1c: Ar = 4-OMe-C_6H_4
1d: Ar = 2-OMe-C_6H_4
1e: Ar = 4-Cl-C_6H_4
1f: Ar = furyl

2a: R= Et
2b: R= Me
2c: R= H

3a: Ar= C_6H_4; R= Et
3b: Ar= 4-Me-C_6H_4; R= Et
3c: Ar= 4-OMe-C_6H_4; R= Et
3d: Ar= 2-OMe-C_6H_4; R= Et
3e: Ar= 4-Cl-C_6H_4; R= Et
3f: Ar= furyl; R= Et
3g: Ar= C_6H_5; R= Me
3h: Ar= 4-Me-C_6H_4; R= Me
3i: Ar= 4-OMe-C_6H_4; R= Me
3j: Ar= 2-OMe-C_6H_4; R= Me
3k: Ar= 4-Cl-C_6H_4; R= Me
3l: Ar= furyl; R= Me
3m: Ar= C_6H_5; R= H

Table 2: Michael-type addition reaction of nitroalkanes to nitroalkenes[a]

Entry	Ar	R	t/h	Yield (%)[b]	dr[c] (*syn:anti*)
1	**1a**	**2a**	24	**3a** (86)	4.9:1
2	**1b**	**2a**	24	**3b** (60)	3.2:1
3	**1b**	**2a**	13	**3b** (82)[d]	5.3:1
4	**1c**	**2a**	24	**3c** (80)	2.3:1
5	**1d**	**2a**	24	**3d** (84)	5.3:1
6	**1e**	**2a**	48	**3e** (72)	1.7:1
7	**1f**	**2a**	14	**3f** (83)	1.9:1
8	**1a**	**2b**	14	**3g** (78)	2.2:1
9	**1b**	**2b**	24	**3h** (66)	2.5:1
10	**1c**	**2b**	24	**3i** (68)	1.3:1
11	**1d**	**2b**	24	**3j** (80)	4.9:1
12	**1e**	**2b**	48	**3k** (60)	1.9:1
13	**1f**	**2b**	10	**3l**(72)	1.9:1
14	**1a**	**2c**	24	**3m**(83)	--

[a] Reaction conditions: nitro alkene (1 mmol), nitro alkane (1.5 mmol), 1 M $NaHCO_3$ (1 mL), at room temperature. ;

[b] Isolated yields.;

[c] Determined by ^{1}H NMR spectroscopy and GC.; [d] In H_2O:MeOH (9:1) (1mL).

REFERENCES

1. Roberto Ballini, Luciano Barboni and Francesco Fringuelli. Recent developments on the chemistry of aliphatic nitro compounds under aqueous medium. Green Chem. 2007;9:823-838.
2. Chao-Jun Li and Liang Chen .Organic chemistry in water .Chem Soc Rev. 2006;35:68-82.
3. Roberto Ballini P and Giovanna Bosica .The Michael reaction of nitroalkanes with conjugated enones in aqueous media .Tetrahedron Letters. 37(44):8027-8030.
4. Sibi Shankar Manyem. Enantioselective Conjugate Additions. Tetrahedron. 56(41): 8033-8061.
5. Constantin Czekelius and Erick M. Carreira .Convenient Transformation of Optically Active Nitroalkanes into Chiral Aldoximes and Nitriles.Angew. Chem. Int Ed. 2005;44: 612 –615.
6. Heterocycle formation from 1,3-dinitroalkanes. A novel pyrazole synthesis. Tetrahedron Letters. 1988;29(46):6001.
7. Alcántara, María-Paz Derri, Escribano, Francisca Cabrera, Gómez-Sánchez Antonio, Diánez M. Jesús, Estrada M Dolores, López-Castro, Amparo Pérez-Garrido and Simeón. Synthesis of Aliphatic 1,3-Dinitro Compounds.Synthesis 1996;(1):64-70.
8. Jian Wang,a Hao Li,a Liansuo Zu and Wanga b. Organocatalytic,.Enantioselective Conjugate Addition of Nitroalkanesto Nitroolefins.Adv. Synth. Catal. 2006;348:2047 – 2050.
9. Chao-Jun Li .Organic Reactions in Aqueous Media with a Focus on Carbon-Carbon Bond Formations: A Decade Update. Chem Rev. 2005;105:3095-3165.
10. Francesco Fringuelli and Giosanna Pani .Condensation reactions in water of active methylene compounds with arylaldehydes. One-pot synthesis of flavonols. Tetrahedron. 1994;50(39):11499-11508.
11. Jens Christoffers and Angelika Baro. Construction of Quaternary Stereocenters: NewPerspectives through Enantioselective Michael Reactions.Angew. Chem Int Ed. 2003;42:1688 – 1690.
12. Peter I, Dalko and Lionel Moisan .Enantioselective Organocatalysis.Angew. Chem Int Ed. 2001;40:3726 -3748.
13. Peter I, Dalko and Lionel Moisan. In the Golden Age of Organocatalysis.Angew. Chem Int Ed. 2004;43:5138 – 5175.
14. Duy-Phong Pham-Huu and Mária Petrušová. The first synthesis of a nitromethylene-linked C-(1→2)-disaccharide.Tetrahedron Letters. 1999;40(15):3053-3056.
15. Marek M Kabat Radical reaction of Williams' glycinate auxiliaries with α-amidoacrylates: synthesis of orthogonally functionalized (2R,4R)- and (2R,4S)-diaminoglutamic acids. Tetrahedron Letters. 2001;42(42):7521-7524.
16. Frederick Cohen and Larry E. Overman .Enantioselective Total Synthesis of Batzelladine F:Structural Revision and Stereo chemical Definition. J Am Chem Soc. 2001;123:10782-10783.
17. Ballini, Roberto, Bosica, Giovanna, Fiorini Dennis and Palmieri Alessandro. One-Pot Synthesis of 1,3-Dinitroalkanes under Heterogeneous Catalysis. Synthesis 2004;(12):1938-1940.
18. Takashi Ooi, Saki Takada, Kanae Doda and Keiji Maruoka. Highly Diastereo- and Enantioselective Formal Conjugate Addition of Nitroalkanes to Nitroalkenes by Chiral Ammonium Bifluoride Catalysis. Angew Chem Int Ed. 2006;45:7606 – 7608.
19. Shao-Feng Lu, Da-Ming Du, Jiaxi Xu, and Shi-Wei Zhang. Asymmetric Michael Addition of Nitroalkanes to Nitroalkenes Catalyzed byC2-Symmetric Tridentate Bis(oxazoline) and Bis(thiazoline) Zinc Complexes. J Am Chem Soc. 2006;128:7418-7419.