Tetrahedron Letters 52 (2011) 2629–2632

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Straightforward synthesis of nitroolefins by microwave- or ultrasound-assisted Henry reaction

Jose M. Rodríguez, M. Dolors Pujol *

Laboratori de Química Farmacèutica (Unitat Associada al CSIC), Facultat de Farmàcia, Universitat de Barcelona, Av. Diagonal 643, E-08028 Barcelona, Spain

ARTICLE INFO

Article history:
Received 16 November 2010
Revised 1 March 2011
Accepted 7 March 2011
Available online 21 March 2011

Keywords:
Henry condensation
Aldol reaction
Microwave
Ultrasound
Aryl nitroolefins

ABSTRACT

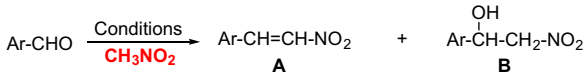
β-Nitroalcohol or nitroethylene derivatives can be obtained from aryl aldehydes and nitromethane under Henry condensation conditions. We present a new modification using microwave irradiation or ultrasound as the energy source. Microwave irradiation allowed a novel one-pot synthesis of nitroolefins from aryl aldehydes using ammonium acetate as a catalyst without solvent. Different reaction conditions, such as base, solvent, and reaction time were studied. Only small amounts of β-hydroxyl nitro compounds were isolated, using microwave irradiation for less than 25 min. In contrast, the use of ultrasound increased the yield of the nitroalcohols.

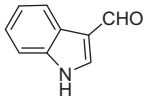
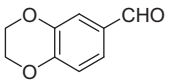
Nitroalcohols and nitroethylenes are synthetic intermediates in the preparation of a variety of organic compounds of medicinal interest.[1–5]

The nitroaldol or Henry reaction is a classic aldol-type reaction between an aldehyde and a nitroalkane.[6] The nucleophilic addition step is base catalyzed, and may be followed by an elimination reaction with the removal of water when an acidic α proton is available.[7] The reaction product is a β-nitroalcohol compound, which undergoes dehydration affording the conjugated nitroethylene derivative. Under mildly basic conditions, the intermediate nitroalcohol can be obtained. Varma et al.[8] reported the synthesis of conjugated nitroalkenes using microwaves, in which only substituted phenylcarbaldehydes were used as starting material. Whereas microwaves have been used for several organic syntheses and compared with an alternative classical procedure,[9] the comparison with ultrasound without solvent for this reaction has not been reported to date. The ultrasound-catalyzed Henry reaction in acetic acid was reported by Wolf and co-workers.[10] In the present study the Henry reaction on a range of heteroaromatic carbaldehydes is described for the first time, under two different conditions: application of microwaves and ultrasound-assisted reaction. These two methodologies have been studied for individual compounds, but to our knowledge no attempt has been made to compare them or to ascertain the most generally useful procedure.

Our study began with the preparation of 3-indolylethylamines and 1,4-benzodioxin-6-ylethylamines from indole-3-carbaldehyde and 1,4-benzodioxan-6-carbaldehyde, respectively. We first used LDA or *t*-BuLi as a base in the aldol-condensation reaction (Table 1). However, in view of its low availability and high cost in large-scale preparation, other bases were tested. It was essential to use a slight excess of nitromethane to achieve a good conversion. In several cases two molecules of nitromethane were incorpo-

Table 1
Aryl aldehyde reaction with nitromethane



Aldehyde	Conditions	**A** (yield %)	**B** (yield %)
	CH_3ONa/−5 °C	––	––
	LDA/THF/−78 °C/5 h	––	23
	t-Buli/−78 °C/5 h	––	63
	NH_4AcO/24 h	72	––
	TBAF/24 h	62	––
	CH_3ONa/−5 °C/3 h	25	––
	LDA/THF/−78 °C/5 h	––	46
	t-BuLi/−78 °C/5 h	––	79
	NH_4AcO/24 h	83	––
	TBAF/24 h	71	––

* Corresponding author.
E-mail address: mdpujol@ub.edu (M. Dolors Pujol).

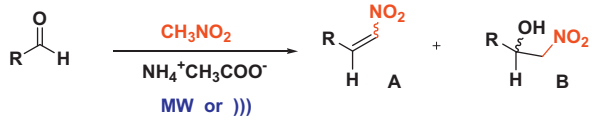
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.03.037

rated and polymerization occurred, which made it more difficult to isolate the desired compounds. A mixture of alcohol and olefin was obtained and we were unable to reduce to the corresponding aryl ethylamine. Notably, the nitroalcohol was gradually converted to the nitroolefin by dehydration. The use of CH_3ONa was completely unsuccessful under the conditions tested. When TBAF (Bu_4NF) catalyzed the aldol condensation, the olefins were obtained in acceptable yield (see Table 1). The most satisfactory conditions were found to be the use of ammonium acetate without solvent with a long heating time. With ammonium acetate, neither addition of a second molecule of nitromethane nor polymerization was observed.

In order to reduce the time of reaction we tested the effects of microwaves and ultrasound, and compared the results. Since the reactions were run for a fixed time, the isolated yields are more indicative of the reaction characteristics.

The optimum conditions were aryl aldehyde and nitromethane as reagents and a catalytic amount of ammonium acetate (0.30 mmol/mmol of aldehyde used) as a base; the reaction time was 25 (microwave) or 45 min (ultrasound) (Scheme 1). In order to generalize this procedure, several aryl nitroolefins were prepared from substituted benzaldehydes and heterocyclic aldehydes. The conventional conditions applied to indole-3-carbaldehyde and 1,4-benzodioxan-6-carbaldehyde gave the corresponding nitroolefins only after 24 h of the reaction. No reaction occurred under these conditions (short times) at room temperature until microwaves or ultrasound was applied. The results showed that microwaves and ultrasound contributed directly to the reaction, and the effect was not only thermal.[11] The products obtained were identified using a combination of analytical spectroscopic techniques. The results obtained in the reaction of various substituted aryl carbaldehydes with nitromethane are summarized in Table 2.

Under the same conditions conjugated nitroalkenes may be isolated in variable yields depending on the starting aldehyde. Electron-rich aromatic aldehydes (Table 2, entries 7, 8, and 9) led exclusively to the desired nitroalkenes in high yield under microwave irradiation. In contrast, under application of ultrasound only the 1,4-benzodioxan-5-carbaldehyde[12] (Table 2, entry 8) gave the corresponding alkene in 93% yield. Other compounds (Table 2, entries 7 and 9) afforded a mixture of aryl alkene and aryl nitroalcohol in low yields. The presence of only one methoxy group (Table 2, entry 4) led to a mixture of nitroalkene and nitroalcohol, and the nitroalkene was formed in greater yield under microwave irradiation. Under ultrasound conditions the nitroalkene was generally obtained in moderate yield (Table 2, entry 4). Withdrawing substituents (Table 2, entries 2 and 3) led to the mixture of nitroalcohol and nitroalkene for trifluoromethylbenzaldehyde (Table 2, entry 2) and a high yield of nitroalkene for the corresponding nitrobenzaldehyde (Table 2, entry 3). In this latter reaction, the microwave application gave only *trans* alkene, whereas ultrasound gave a mixture of cis/trans isomers. For conjugated aldehydes such as cinnamic aldehyde, only the nitroalkene was obtained in high yields in both methods (Table 2, entry 17). We, therefore, tested the Henry reaction on various heterocycle aldehydes under the same conditions. Indole-3-carbaldehyde gave the conjugated nitroalkene in quantitative yield under ultrasound, and a mixture of nitroalcohol and nitroalkene when microwaves were applied (Table 2, entry 10). The methylated indole (Table 2, entry 11) gave



Scheme 1. General reaction of aryl aldehydes with nitromethane.

different yields than the indole attributable to its lower solubility. Pyridine-3-carbaldehyde (Table 2, entry 12) and the chromone (Table 2, entry 16) generally gave the nitroalcohol when the microwave system was used. *N*-Methylpyrrole-3-carbaldehyde and thiophene-2-carbaldehyde led to corresponding nitroalkenes under microwave conditions in moderate yield (Table 2, entries 15 and 14, respectively). Surprisingly, furan-3-carbaldehyde gave a mixture of nitroalcohol and nitroalkene both in microwave and in ultrasound systems (Table 2, entry 13). In the chromenone aldehyde ultrasound promoted secondary reactions to yield a mixture of compounds (Table 2, entry 16). The reaction was time-dependent. Attempts to synthesize the conjugated nitroolefins after 1 h under microwave irradiation (method **c**) or after 24 h at reflux under classical conditions led to the desired products in acceptable yields without side products. Conversion of aldehyde to nitroalcohol or nitroolefins was observed by TLC within 10 min, through the disappearance of the starting material. The reaction was rapid and found to be complete in 60 min, to give nitroolefins in good yields. Since the reactions were run for a fixed time (microwave 25 min or under ultrasound 45 min) and a fixed temperature (microwave 90 °C or ultrasound 60 °C) the yields are more indicative of the rate of the reaction. Surprisingly, the effects of variation of the substituents of aldehydes compared with the benzaldehyde (Table 2, entry 1) are modest, whereas the ketones did not react under these conditions. The most satisfactory result was obtained when the same conditions were applied to the condensation of 4-methoxybenzaldehyde with nitroethane and nitropropane, and the corresponding nitroolefins were obtained in good yields under microwave (Table 2, entries 5 and 6). In contrast, the second experiment using ultrasound, furnished a mixture of nitroolefins and nitroalcohols in lower yields. The behavior of nitroalkanes was similar, but we must stress that increasing the length of the nitroalkane decreases the solubility, and the yields are low.

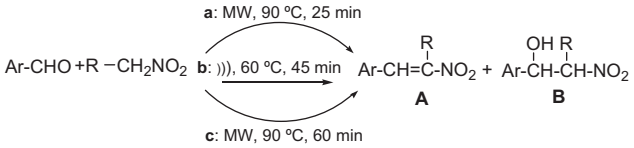
In summary, the current protocol for the synthesis of nitroolefins from the corresponding aldehydes is easy, rapid, and environmentally acceptable employing milder reaction conditions under ultrasonic or microwave conditions. This is a general method which could be used for the condensation of aryl aldehydes and nitroalkanes. We have compared the effectiveness of microwave or ultrasound.

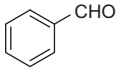
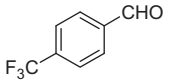
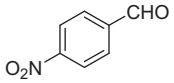
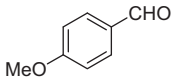
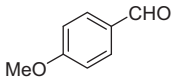
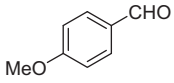
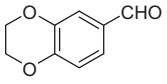
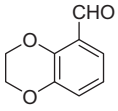
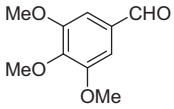
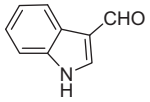
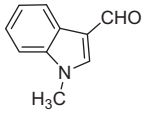
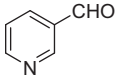
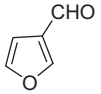
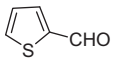
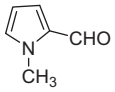
In general, the microwave method gave better yields of conjugated nitroolefins, particularly in reactions of heterocyclic aldehydes. The time required for this nitroaldol reaction with microwave or ultrasound was much shorter than that under classical conditions, and side products such as the dimers of nitrostyrenes or dinitro compounds were not observed.

General procedure: (a) Microwave: a mixture of aryl aldehyde (1 mmol) and nitromethane (3 mL) was introduced into a glass microwave tube (tube of 4 mL); a catalytic amount of ammonium acetate (0.3 mmol) was added and the tube was introduced into the microwave system (CEM-Discover) and initially irradiated at 250 W and 90 °C for 25 min. The reaction mixture was then cooled and the nitromethane was evaporated in a Büchi microdistillation apparatus. The nitrostyrenes were purified by silica-gel column chromatography, and eluted with a mixture of hexane and ethyl acetate.

(b) Ultrasound: a mixture of aryl aldehyde (1 mmol) and nitromethane (3 mL) was introduced into a glass microwave tube; a catalytic amount of ammonium acetate (0.2 mmol) was added and the tube was placed inside an ultrasound apparatus (Ultrasounds Medi II, Selecta, Spain) preheated at 60 °C. It was exposed for 45 min at 100 W and 18 kHz. The reaction mixture was then cooled and the nitromethane was evaporated on a Büchi microdistillation apparatus. The compounds obtained after isolation and purification showed analytical data in accordance with the assigned structures.[25]

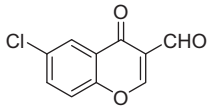
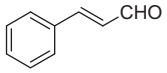
Table 2
Experimental data of Henry reaction using microwave or ultrasound



Entry	Aldehyde/ketone	R	Method	**A** (yield %)	**B** (yield %)	Mp (°C) (Lit.) of **A**
1		H	**a**	71	12	58–60 (58–59)[13]
			b	21	57	
			c	95	––	
2		H	**a**	63	32	92–95 (89–91)[14,15]
			b	25	50	
			c	91	––	
3		H	**a**	83	––	202–204 (201–202)[13]
			b	*cis* 43	––	
				trans 35		
4		H	**a**	59	35	84–86 (86–87)[13]
			b	66	5	
			c	96	––	
5		Me	**a**	54	23	46–48 (44–45)[13]
			b	18	50	
			c	86	––	
6		Et	**a**	48	19	58–60 (55–56)[13]
			b	10	29	
			c	72	––	
7		H	**a**	92	––	148–150 (147–149)[16]
			b	24	18	
8		H	**a**	85	––	112–114 (hexane/ethyl acetate)
			b	93	––	
9		H	**a**	94	––	121–123 (120–121)[17]
			b	18	18	
10		H	**a**	23	40	173–175 (172)[18]
			b	96	––	
			c	93	––	
11		H	**a**	50	10	169–171 (165–167)[19]
			b	20	––	
			c	67	––	
12		H	**a**	––	54	139–142 (141)[20]
			b	*cis* 19	16	
				trans 14		
			c	56	Trace	
13		H	**a**	17	59	72–74 (68–70)[21]
			b	52	16	
			c	83	Trace	
14		H	**a**	65	9	80–82 (79–80)[22]
			b	58	12	
			c	89	––	
15		H	**a**	88	7	99–100 (102)[23]
			b	17	––	
			c	94	––	

(*continued on next page*)

Table 2 (*continued*)

Entry	Aldehyde/ketone	R	Method	**A** (yield %)	**B** (yield %)	Mp (°C) (Lit.) of **A**
16		H	**a**	––	84	122–124 (hexane/ethyl acetate)
			b	––*	<5	
			c	––	Trace	
17		H	**a**	81	––	46–48 (45–46)[24]
			b	90	––	

Method **a**: microwave, 90 °C, 25 min; Method **b**: ultrasound, 60 °C, 45 min. Method **c**: microwave, 90 °C, 60 min. ** Starting material.
* Side products of Michael reaction.

Acknowledgments

We are grateful to the Minister of Science and Technology (CTQ2007-60614/BQU), for the financial support. One of us (J.R.) thanks the Minister of Education and Science (Government of Spain) for a fellowship.

References and notes

1. Perrone, M. G.; Santandrea, E.; Bleve, L.; Vitale, P.; Colabufo, N. A.; Jockers, R.; Milazzo, F. M.; Sciarroni, A. F.; Scilimati, A. *Bioorg. Med. Chem.* **2008**, *16*, 2473–2488.
2. Czekelius, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 4575–4577.
3. Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452–6455.
4. Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621–2623.
5. Dwivedi, A. P.; Kumar, S.; Varshney, V.; Singh, A. B.; Srivastava, A. K.; Sahu, D. P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2301–2305.
6. (a) Ballini, R.; Castagnani, R.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 2160–2164; Bauer, H. H.; Urbas, L. In *The Chemistry of the Nitro and Nitroso Group*; Feuer, H., Ed.; Interscience: New York, 1970; pp 75–200. Chapter 2; (c) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. Chapter 3, p 30; (d) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1996. Vol 2, pp 321-340; (e) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945.
7. Andrew, R. G.; Raphael, R. A. *Tetrahedron* **1987**, *43*, 4803–4812.
8. (a) Varma, R. S.; Dahiya, R.; Kumar, S. *Tetrahedron Lett.* **1997**, *38*, 5131–5134; (b) Abdallah-El Ayoubi, S.; Texier-Boullet, F.; Hamelin, J. *Synthesis* **1994**, 258–260.
9. (a) Chetia, A.; Longchar, M.; Lekhok, K. C.; Boruah, R. C. *Synlett* **2004**, 1309–1311; (b) Gan, C.; Chen, X.; Lai, G.; Wang, Z. *Synlett* **2006**, 387–390.
10. Mc Nulty, J.; Steere, J. A.; Wolf, S. *Tetrahedron Lett.* **1998**, *39*, 8013–8016.
11. Raner, K. D.; Strauss, C. R.; Vyskoc, F.; Mokbel, L. *J. Org. Chem.* **1993**, *58*, 950–958.
12. 1,4-Benzodioxan-5-carbaldehyde was obtained from the 2,3-dihydroxybenzaldehyde by treatment with 1,2-dibromethane and K_2CO_3 in DMF at 80 °C in a 92% of yield.
13. Gairaud, C. B.; Lappin, G. R. *J. Org. Chem.* **1953**, *18*, 1–3.
14. (a) Dingwalla, J. G.; Ehrenfreund, J.; Hall, R. G. *Tetrahedron* **1989**, *45*, 3787–3808; (b) Popp, B. V.; Thorman, J. L.; Morales, C. M.; Landis, C. R.; Shahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 14832–14842.
15. Tinsley, S. W. *J. Org. Chem.* **1961**, *26*, 4723–4724.
16. Dauksas, V.; Milvydiene, G. D. I. *Mendeleeva* **1966**, *11*, 474–475 (CAN 65:99316).
17. Dauzonne, D.; Royer, R. *Chem. Pharm. Bull.* **1986**, *34*, 1628–1633.
18. Büchi, G.; Mak, C.-P. *J. Org. Chem.* **1977**, *42*, 1784–1786.
19. Canoira, L.; Gonzalo Rodríguez, J.; Subirats, J. B.; Escario, J. A.; Jiménez, I.; Martínez-Fernández, A. R. *Eur. J. Med. Chem.* **1989**, *24*, 39–42.
20. Dornow, A.; Boberg, F. *Just. Lieb. Ann. Chem.* **1952**, *578*, 101–112.
21. Masayuki, F. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4029–4035.
22. King, W. J.; Nord, F. F. *J. Org. Chem.* **1949**, *14*, 405–410.
23. Bourguignon, J.; Le Nard, G.; Queguiner, G. *Can. J. Chem.* **1985**, *63*, 2354–2361.
24. Gawley, R. E.; Chemburkar, S. R. *Heterocycles* **1989**, *29*, 1283–1292.
25. All compounds gave satisfactory spectroscopic and analytical data. Analytical data given only for the new compounds: 5-(2-nitrovinyl)-2,3-dihydro-1,4-benzodioxane. Yellow solid, mp 112–114 °C (hexane/ethyl acetate). R_f = 0.6 (hexane/ethyl acetate 5:5). NMR ($CDCl_3$, 300 MHz) δ (ppm), 4.41 (m, 2H, CH_2O–); 4.42 (m, 2H, CH_2O–); 6.98 (d, J = 7.5 Hz, 1H, H-8); 7.02–7.04 (m, 2H, H-6 and H-7); 7.85 (d, J = 13.7 Hz, 1H, CH=); 8.07 (d, J = 13.7 Hz, 1H, CH=). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm), 64,0 and 64.5 (CH_2, CH_2O–); 112.9 (CH, C-8); 114.7 (C, C-5); 117.0 (CH, C-6); 122.7 (CH, C-7); 132.0 (CH, CH-NO_2); 137.4 (CH, CH-C-5); 145.2 (C, C-4a); 146.2 (C, C-8a). 6-Chloro-3-(1-hydroxy-2-nitroethyl)-4*H*-chromen-4-one. Yellow solid, mp 122–124 °C (hexane/ethyl acetate). R_f = 0.19 (hexane/ethyl acetate 5:5). NMR ^1H ($CDCl_3$, 300 MHz) δ (ppm), 1.56 (bs, 1H, OH); 4.13 (m, 1H, CHO–); 4.89 (d, J = 6 Hz, 1H, CH-NO_2); 5.02 (d, J = 6 Hz, 1H, CH-NO_2); 7.42 (d, J = 8.5 Hz, 1H, H-8); 7.69 (d, J = 8.5 Hz, 1H, H-7); 7.97 (s, 1H, H-2); 8.16 (s, 1H, H-5). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm), 62.4 (CH, CHOH); 79.6 (CH_2, CH_2-NO_2); 113.5 (C, C-8); 117.8 (C, C-3); 123.8 (C, C-4a); 127.4 (C, C-6); 132.4 (CH, C-5); 133.2 (CH, C-7); 145.2 (CH, C-2); 153.1 (C, C-8a); 182.9 (C, C=O).