Res Chem Intermed
DOI 10.1007/s11164-015-2156-5

Synthesis, modeling and optimization of cyanide antidote (3-methylbutyl) nitrite using response surface methodology

Vahid Khakyzadeh[1] · Hadi Rezaei Vahidian[2] · Amir Ahmad Salarian[3] · Mohammad Ali Zolfigol[2]

Received: 30 December 2014 / Accepted: 27 June 2015
© Springer Science+Business Media Dordrecht 2015

Abstract In this research, synthesis of cyanide antidote (3-methylbutyl) nitrite has been designed and performed by response surface methodology. The antidote was prepared by the reaction of 3-methyl-1-butanol with sodium nitrite, which is the nitrosonium (NO^+) source, in the presence of sulfonic acid-functionalized Fe_3O_4 ($Fe_3O_4@SO_3H$) as a nanomagnetic solid acid catalyst and triethylammonium hydrogen sulfate as ionic liquid in aqueous media. Optimization of the reaction conditions was investigated using the response surface method (central composite design). In accordance with analysis of variance, a quadratic polynomial model was able to predict the response. Predicted response values by the obtained model was in good agreement with the experimental results. A clean reaction, easy workup procedure, reusability of the catalyst and a high yield are some advantages of this method.

Keywords Cyanide antidote · Nitrosonium · Experimental design · Functionalized sulfonic acid ($Fe_3O_4@SO_3H$)

✉ Vahid Khakyzadeh
v.khakyzadeh@gmail.com; mr.khakyzadeh@yahoo.com

[1] Institut fur Organische Chemie, Albert-Ludwigs-Universitat Freiburg, Albertstrasse 21, 79104 Freiburg, Germany

[2] Faculty of Chemistry, Bu-Ali Sina University, 6517838683 Hamedan, Iran

[3] Department of Toxicology, School of Pharmacy, Shahid Beheshti University of Medical Science, Tehran, Iran

Published online: 03 July 2015

Introduction

Cyanide poisoning may be observed in a wide variety of settings. Hydrocyanic acid and cyanide are used in most common industrial processes such as metal cleaning, electroplating, precious metal extraction, laboratory examinations, jewelry production and photography [1–4]. Moreover, one of the chemical intermediates in the manufacture of plastics, synthetic fibers and nitriles is hydrogen cyanide [5]. Also, fire smoke inhalation in enclosed spaces may result in cyanide poisoning [6, 7].

By binding with the Fe^{3+} of mitochondrial cytochrome oxidase, cyanide produces histotoxic hypoxia and disrupts the ability of cells to utilize O_2 in oxidative phosphorylation and in the normal functioning of the electron transport chain [1]. (3-methylbutyl) nitrite is one of the important cyanide antidotes [8].

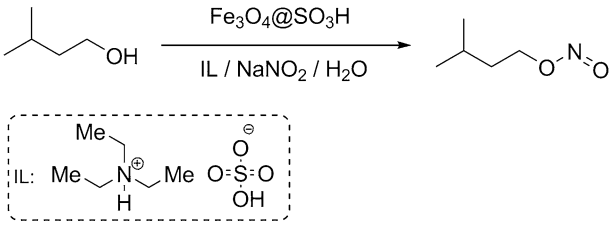
In cyanide poisoning, (3-methylbutyl) nitrite produces methemoglobinemia and vasodilation. In this case, vasodilation may contribute to adverse effects and require therapy [9].

Considering the above points and toxicity of cyanide, finding new improvement paths for synthesis of cyanide antidotes is still of importance.

Since the late 90s, green chemistry research has been a strategy of removing waste from chemical processes, thereby contributing to environmental protection [10, 11]. One aspect of green chemistry involves using ionic liquids as helpful substitutes for the conventional organic solvents. In fact, room temperature ionic liquids have various unique properties such as high thermal stability, wide liquid range, controllable polarity, negligible vapour pressure and excellent solubility for a wide range of substances [12].

High specific surface area of the active component is an important property of nanocatalysts, in which the contact between reactants and catalyst enhances reactions [13, 14]. To reuse nanomaterials, they must be separated from the reaction media, a difficult undertaking. This problem could be solved by application of magnetic nanoparticles (MNPs) as a catalyst. MNPs have large specific surface area and can be easily collected by a magnet for reuse to prevent loss of the catalyst [15–20]. The relationship between a phenomenon and the response of natural process and the factors which affect them can be categorized in three levels: top level, slightly low-level and lower level. The top level is deterministic phenomena, and the second and third levels are stochastic phenomena [21]. Synthesis processes are in the lower level. This area of knowledge is based on experimental results. A mathematical model can be used to interpret the experimental results. Modelling and optimization of the synthesis processes can be done using design of experiment (DOE) [22].

Having the above facts in mind, we report a clean, facile and efficient method for synthesis of cyanide antidote (3-methylbutyl) nitrite from 3-methyl-1-butanol and nitrosonium (NO^+) which is generated in situ using sulfonic acid-functionalized Fe_3O_4 ($Fe_3O_4@SO_3H$) as a nanomagnetic solid acid catalyst and triethylammonium hydrogen sulfate (TEAHS) as ionic liquid in aqueous media (Scheme 1). The synthesis was modelled and optimized by experimental design.



Scheme 1 Synthesis of cyanide antidote (3-methylbutyl) nitrite

Experimental

Chemicals and characterization methods

All chemicals were purchased from Merck, Fluka and Dae-Jung Chemical Companies. The product was characterized by a gas-chromatography (GC) system, Shimadzu model CLASS-GC14B with a flame ionization detector (FID).

General procedure for the synthesis of cyanide antidote

To a mixture of 3-methyl-1-butanol (0.1 mL, 1 mmol), H_2O (3 mL), $NaNO_2$ (0.142 g, 2.09 mmol) and $Fe_3O_4@SO_3H$ [23, 24] (0.005 g) in a test tube at 0 °C, TEAHS (1.06 mL) was added at a rate of 0.15 mL/s, and the resulting mixture was stirred for 6 h at 0 °C. The reaction conversion was investigated by GC. After completion of the reaction, two phases were formed. The product was accumulated in the upper phase (yellow liquid). The organic layer was separated and washed with saline solution, then dried with $MgSO_4$ to give the product with a conversion of 87 %.

Table 1 Effect of various solvents and temperatures on the reaction of 3-methyl-1-butanol (1 mmol) with $NaNO_2$ (1.5 mmol), TEAHS (0.5 mL)

Entry[a]	Solvent	Conversion (%)		
		−10 °C	0 °C	25 °C
1	–	–	Trace	Trace
2	H_2O	20	50	15
3	EtOH	Trace	Trace	Trace
4	EtOAc	–	Trace	–
5	$CHCl_3$	–	Trace	Trace
6	THF	Trace	–	–
7	*n*-Hexane	–	Trace	–
8	Acetonitrile	Trace	–	Trace

All reactions were carried out with a constant catalyst amount (0.01 g)

[a] Reaction time: 6 h

Results and discussions

Quick screening of the variables

At first, to find the general reaction conditions and the range of variables for the synthesis of the cyanide antidote before design of experiments, a number of pre-tests were performed. To this end, the reaction of 3-methyl-1-butanol with different amounts of $NaNO_2$ in the presence of TEAHS as an ionic liquid and $Fe_3O_4@SO_3H$ as a catalyst was tested in two general conditions. To compare the efficiency of the solvent-free versus solvent conditions as well as the suitable reaction temperature, the reaction was examined in various solvents and solvent-free conditions in a range of −10 to 25 °C (Table 1). As it is clear from Table 1, trace conversions of the reaction were obtained in the organic solvents and also in solvent-free conditions within the investigated temperature range. The best results were observed in aqueous media at 0 °C (Table 1, entry 2). Thus, selection of aqueous media and temperature of zero were two general results of variable screening before design of the experiment.

In continuation, the effect of different amounts of the nanomagnetic catalyst on the reaction was investigated at 0 °C in water (Table 2). As shown in Table 2, higher conversion was obtained when the reaction was carried out using 0.017 g of $Fe_3O_4@SO_3H$.

Experimental design and statistical analysis

The central composite design (CCD) of the response surface method, with nine replicates at the central point was employed for design of the experiment. Variables, such as temperature (A), catalyst amount (B), amount of $NaNO_2$ (C), amount of H_2O (D), amount of ionic liquid (E), rate of adding the compounds (F) and rate of mixing the compounds (G) were used as effective parameters of the process. The levels of the variables are shown in Table 3.

Table 2 Effect of different amounts of nano magnetic catalyst on the reaction of 3-methyl-1-butanol (1 mmol) with $NaNO_2$ (1.5 mmol) and TEAHS (0.5 mL)

Entry[a]	Catalyst amount (g)	Conversion (%)
1	0.017	52
2	0.015	50
3	0.01	50
4	0.007	48
5	0.005	45
6	0.001	<20

All reactions were carried out at 0 °C

[a] Reaction time: 6 h

Table 3 Levels of the experimental variables of the CCD

Variables	Units	−α	Low actual	0	High actual	+α
A	°C	−15	−7.5	0.000	7.5	15
B	g × 1000	1	3.25	5.500	7.75	10
C	eq.	1	1.5	2.000	2.5	3
D	mL	1	2	3.000	4	5
E	mL × 100	50	75	100.000	125	150
F	(mL/s) × 10	1	1.25	1.500	1.75	2
G	rpm	800	900	1000.000	1100	1200

Table 4 Analysis of variance for the response surface quadratic model for conversion

Source	Sum of squares	df	Mean square	*F* value	*p* value prob > *F*
Model	33,041.91	16	2065.12	98.03	<0.0001
A	420.01	1	420.01	19.94	<0.0001
B	210.01	1	210.01	9.97	0.002
C	958.24	1	958.24	45.49	<0.0001
E	1012.07	1	1012.07	48.04	<0.0001
G	748.24	1	748.24	35.52	<0.0001
AC	223.13	1	223.13	10.59	0.0014
AD	110.63	1	110.63	5.25	0.0235
AF	118.2	1	118.2	5.61	0.0193
AG	134.07	1	134.07	6.36	0.0128
A^2	9176.75	1	9176.75	435.63	<0.0001
B^2	871.18	1	871.18	41.36	<0.0001
C^2	1766.96	1	1766.96	83.88	<0.0001
D^2	1645.3	1	1645.3	78.1	<0.0001
E^2	1053.75	1	1053.75	50.02	<0.0001
F^2	871.18	1	871.18	41.36	<0.0001
G^2	828.25	1	828.25	39.32	<0.0001

Based on the CCD methodology, there were 151 runs, with different operational conditions, for deriving the objective function for conversion. Table 4 shows the analysis of variance (ANOVA) for the response surface reduced quadratic model.

In accordance with regression analysis, the quadratic polynomial model based on significant levels was fitted with the data as follows.

$$\begin{aligned} Y = {} & +89.02 - 1.76A + 1.24B + 2.65C + 2.73E + 2.35G - 1.32AC \\ & + 0.93AD + 0.96AF - 1.02AG - 16.26A^2 - 5.01B^2 \\ & - 7.13C^2 - 6.88D^2 - 5.51E^2 - 5.01F^2 - 4.88G^2 \end{aligned} \quad (1)$$

where Y is the response value and A, B, C, D, E, F and G are the coded variables, and the coefficients of them show their effects on the response and interaction between them [25].

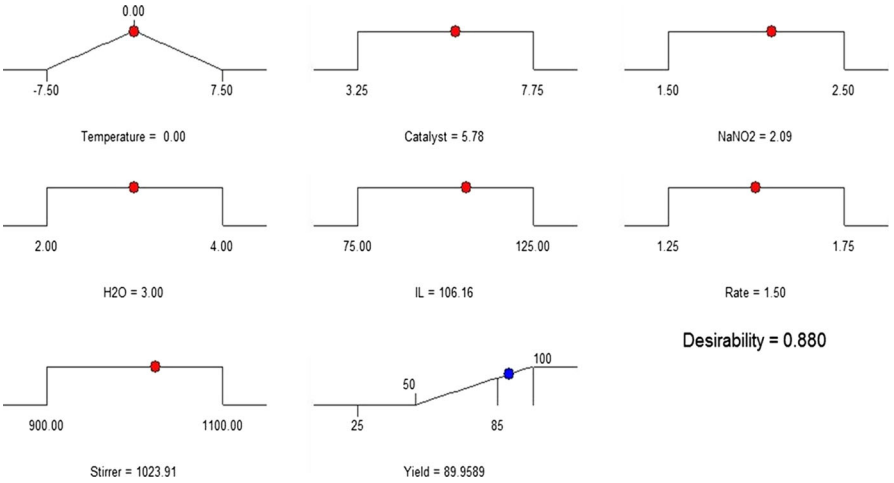


Fig. 1 Introduced optimal point of variables

Totally, the value of terms show the amount of their effect; plus or minus signs indicate a positive or negative effect on Y, respectively. For checking the significance of each model term, the p value was used as a tool (p values ≤ 0.05 indicate that the model terms are significant). The statistical parameter of correlation coefficient (R^2) of 0.92, R^2-predicted of 0.82, adjusted R^2 of 0.91, lack of fit F value of 44.74 and adequate precision of 44.52 (>4 is desirable) reveal that the predicted values are in good agreement with the experimental values. The Model F value and p value are 98.3 and <0.0001, respectively, which imply the model is significant.

Optimization of operational condition

In this work, the purpose of reaction optimization is to determine the optimal variable values at which the reaction conversion is maximized. For this aim, the desired goal for each variable was chosen within the range except temperature which was set in the target of 0 °C because of easier operation.

The range of variables and associated optimum values were demonstrated in Fig. 1. In the optimum condition ($A = 0$ °C, $B = 0.00578$ g, $C = 2.09$ eq., $D = 3$ mL, $E = 1.06$ mL, $F = 0.15$ mL, $G = 1023$ rpm), the value of predicted conversion is 89.95 %, which is a high conversion rate for this reaction.

Validation of the model

Finally, the validity of the obtained model to predict response values was tested in the optimum condition. A conversion value of 87 % was obtained from experimental results which is in good agreement with the predicted response (89 %). Thus, the model is valid for results prediction.

Conclusions

In conclusion, we have introduced a new protocol for the synthesis of cyanide antidote (3-methylbutyl) nitrite.[1] Using $Fe_3O_4@SO_3H$ as a nanomagnetic solid acid catalyst in aqueous media wherein the influence of various factors on the process was investigated. In accordance with regression analysis, a quadratic polynomial model can be fitted to the process. Statistical parameters showed that theoretical values were in good agreement with the experimental values. The promising points for the presented protocol were efficiency, high conversion, a cleaner reaction profile and simplicity.

Acknowledgments The authors gratefully acknowledge partial support of this work by the Research Affairs Office of Bu-Ali Sina University (Grant number 32-1716 entitled development of chemical methods, reagents and molecules), the Center of Excellence in Development of Chemical Method (CEDCM), Hamedan, I. R. Iran, Shahid Beheshti University of Medical Science, Tehran, Iran and AJJ-A University of Medical Science, Tehran, Iran.

References

1. A.H. Hall, B.H. Rumack, Ann. Emerg. Med. **15**, 1067 (1986)
2. P. Blance, M. Hogan, K. Mallin, D. Hryhorczuk, S. Hessl, B. Bernard, J. Am. Med. Assoc. **253**, 367 (1985)
3. R. Hartung, Cyanides and nitriles, in *Patty's Industrial Hygiene and Toxicology*, 4th edn., ed. by G.D. Clayton, F.E. Clayton (Wiley, New York, 1994)
4. A. Krieg, K. Saxena, Ann. Emerg. Med. **16**, 582 (1987)
5. G.J. Hathaway, N.H. Proctor, J.P. Hughers, Hydrogen cyanide. In *Proctor and Hughers' Chemical Hazards of the Workplace*, 4th edn. (Van Nostrand-Reinhold, New York 1996)
6. G.D. Hart, M.B. Strauss, P.A. Lennon, D.D. Whitcraft, J. Emerg. Med. **3**, 211 (1985)
7. F.J. Baud, P. Barriot, V. Toffis, B. Riou, E. Vicaut, Y. Lecarpentier, R. Bourdon, A. Astier, C. Bismuth, N. Engl. J. Med. **325**, 1761 (1991)
8. K.K. Chen, C. Rose, G. Clowes, JAMA **100**, 1921 (1933)
9. J.M. Marraffa, V. Cohen, M.A. Howland, Am. J. Health Syst. Pharm. **69**(3), 199 (2012)
10. J.H. Clark, Green chemistry: challenges and opportunities. Green Chem. **1**, 1–8 (1999)
11. L. Xuehui, Z. Dongbin, F. Zhaofu, W. Lefu, Sci. China Ser. B Chem. **49**, 385 (2006)
12. H. Liu, G.-H. Tao, D.G. Evans, Y. Kou, Carbon **43**, 1782 (2005)
13. V. Polshettiwar, R.S. Varma, Green Chem. **12**, 743 (2010)
14. M.A. Zolfigol, V. Khakyzadeh, A.R. Moosavi-Zare, A. Zare, P. Arghavani-Hadi, Z. Mohammadi, M.H. Beyzavi, S. Afr, J. Chem. **65**, 280 (2012)
15. Y. Zhu, L.P. Stubbs, F. Ho, R. Liu, C.P. Ship, J.A. Maguire, N.S. Hosmane, Chem. Cat. Chem. **2**, 365 (2010)
16. V. Polshettiwar, R.S. Varma, Org. Biomol. Chem. **7**, 37 (2009)
17. K.S. Lee, M.H. Woo, H.S. Kim, E.Y. Lee, I.S. Lee, Chem. Commun. **25**, 3780 (2009)
18. V. Polshettiwar, Á. Molnár. Tetrahedron, **63**, 6949 (2007)
19. L.M. Rossi, I.M. Nangoi, N.J.S. Costa, Inorg. Chem. **48**, 4640 (2009)
20. M. Ma, Q. Zhang, D. Yin, J. Dou, H. Zhang, H. Xu, Catal. Commun. **17**, 168 (2012)
21. Z.R. Lazic, *Design of Experiments in Chemical Engineering* (Wiley-VCH Verlag GmbH and Co. KGaA, Weinheim, 2004)

[1] Spectral data of (3-methylbutyl) nitrite: boiling point: 99 °C, ^{1}H NMR (300 MHz, chloroform-d) δ ppm 0.91–0.98 (m, 7 H) 1.59–1.74 (m, 2 H) 4.70–4.74 (*t*, $J = 6.60$ Hz, 2 H). ^{13}C NMR (101 MHz, chloroform-d) δ ppm 24.99 (s, 1 C) 26.02 (s, 1 C) 37.66 (s, 1 C) 66.73 (s, 1 C). MS: m/z = 117 (M^+).

22. R. Leardi, Anal. Chim. Acta **652**, 161 (2009)
23. M.B. Gawande, A.K. Rathi, I.D. Nogueira, R.S. Varma, P.S. Branco, Green Chem. **15**, 1895 (2013)
24. M.A. Zolfigol, V. Khakyzadeh, A.R. Moosavi-Zare, A. Rostami, A. Zare, N. Iranpoor, M.H. Beyzavi, R. Luque, Green Chem. **15**, 2132 (2013)
25. T.F. Edgar, D.M. Himmelblau, L.S. Lasdon, Optimization of Chemical Processes, (McGraw-Hill, New York, 2001)