

A green and highly effective protocol for the synthesis of *N,N'*-alkylidene bisamides using saccharin-*N*-sulfonic acid

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Received: 3 February 2019, Accepted: 13 May 2019, Published: 1 January 2020

Abstract

A green and highly effective solvent-free protocol has been reported for the synthesis of *N,N'*-alkylidene bisamides *via* the reaction of arylaldehydes (1 eq.) with primary amides (2 eq.) in the presence of saccharin-*N*-sulfonic acid (SaSA) as a solid-acid catalyst. The mentioned compounds have been obtained in high yields and short reaction times.

Keywords: *N,N'*-Alkylidene bisamide; arylaldehyde; primary amide; saccharin-*N*-sulfonic acid (SaSA); solid acid; solvent-free.

Introduction

Amide functional group is of importance since it is present as a crucial component in a wide range of compounds which are applicable in chemistry, industry and medicinal chemistry [1-9]. For instance, bisamides are key moieties for introducing *gem*-diaminoalkyl components in retro-inverse pseudopeptide derivatives [5,6]. Their application in the preparation of peptidomimetic molecules have been also reported [7,8]. Additionally, bisamides have been applied as ligands in the synthesis of potentially drugs *via* Ullmann reaction [9]. A practical method for the synthesis *N,N'*-alkylidene bisamides consists of the reaction of arylaldehydes (1 eq.) with primary amides (2 eq.) promoted by a catalyst; e.g. $\text{CF}_3\text{SO}_3\text{H}$ [10],

$\text{NiFe}_2\text{O}_4@\text{KIT-6}@\text{ZnO}$ [11], montmorillonite K10 [12], silica-bonded S-sulfonic acid nanoparticles [13], $\text{NiFe}_2\text{O}_4@\text{SiO}_2\text{-PPA}$ [14], sulfonated carbon/nano-titania composites [15], hydroxyapatite [16], Silzic [17], $\text{H}_{14}[\text{NaP}_5\text{W}_{29}\text{MoO}_{110}]$ [18], and $\text{B}(\text{HSO}_4)_3$ [19]. Nevertheless, many of the reported methods for preparation of *N,N'*-alkylidene bisamides are associated with one or more disadvantages such as high reaction temperature [12,13,15,19], moderate yield [12,14,17-19], long reaction time [10,12-16,18], difficult procedure for preparation of catalyst [11,13-15], the use of volatile and toxic organic solvents as reaction media [10,13,14,16,18], and poor agreement with green chemistry protocols [10,13,14,16,18]. So, introducing

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catalysts to solve the mentioned problems is highly desirable.

Solid acids are a significant class of catalysts which have attracted much attention to perform organic transformations [20-28]. These catalysts have several benefits; *e.g.* catalytic effectuality, suitable thermal and chemical stability, simple operation, easy isolation from reaction media, good compliance with green chemistry protocols, high selectivity, need of milder conditions, and minimizing waste/by-product formation [20-28].

“Solvent-free conditions” in organic synthesis compared to “classical solution conditions” has often advantages such as decreasing or avoiding production of waste/by-products, environmentally benign nature, maximum conversion of reactants to aim product, higher yield, shorter reaction time, avoiding application of volatile and harmful organic solvents as reaction media, higher selectivity, easier work-up and purification of product and fewer energy requirement to carry out reaction [29-32].

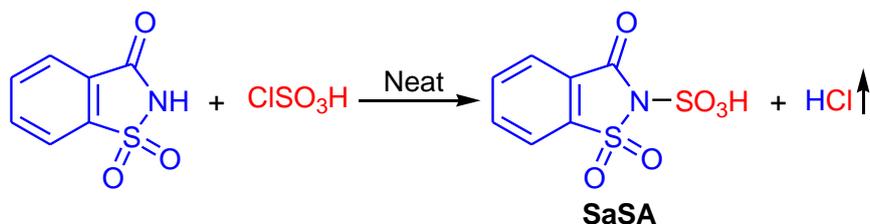
Collecting the advantages of “solid-acid catalyst” and “solvent-free conditions” in a synthetic protocol can be attractive and valuable. For this reason herein we have introduced a highly effective solvent-free protocol for the synthesis of *N,N'*-alkylidene bisamides *via* the reaction of arylaldehydes with primary amides in the presence of saccharin-*N*-sulfonic acid (SaSA) as a solid-acid catalyst.

Experimental

All starting materials and solvents were purchased from Merck, Fluka or Iranian Chemical Companies (Razi and Arman Sina). All known compounds were identified by comparison of their melting points and/or spectral data with those reported in the literature. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. The ¹H NMR (500 MHz) and ¹³C NMR (125 MHz) were run on Bruker Avance DPX, FT-NMR spectrometers (δ in ppm). Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

Procedure for the preparation of saccharin-*N*-sulfonic acid

“A flask (500 mL) charged with saccharin (17.1 g, 0.1 mol) was equipped with a constant pressure dropping funnel containing chlorosulfonic acid (11.65 g, 0.1 mol) and a gas outlet tube which was dipped into water to dissolve the generated HCl gas during the reaction. The flask was put into an ice bath and chlorosulfonic acid was added dropwise over a period of 10 min and the resulting mixture was stirred slowly for another 10 min. The temperature of the mixture was brought up to the room temperature and was stirred for an additional 30 min. The mixture was triturated with *n*-hexane (10 mL) and then filtered. The solid residue was washed with *n*-hexane (10 mL) and dried under vacuum to give saccharin-*N*-sulfonic acid as a white powder”; m.p. 109-111 °C (lit. 110-112 °C) [21,22] (Scheme 1).



Scheme 1. The preparation of saccharin-*N*-sulfonic acid (SaSA)

General procedure for the production of *N,N'*-alkylidene bisamides using SaSA

A mixture of arylaldehyde (1 mmol), primary amide (2 mmol) and SaSA (0.032 g, 0.12 mmol) was vigorously stirred by a small rod at 90 °C. After completion the reaction (as observed by TLC), the reaction mixture was cooled to room temperature, and the resulting solid was recrystallized from EtOH (96%) to give the pure bisamide.

Selected spectroscopic data of the synthesized *N,N'*-alkylidene bisamides

***N,N'*-(4-Nitrophenyl)methylene)dibenzamide (B)**

¹H NMR (500 MHz, DMSO-*d*₆): δ (ppm) 7.15 (t, *J* = 7.5 Hz, 1H, CH), 7.50 (t, *J* = 7.4 Hz, 4H, ArH), 7.57 (t, *J* = 7.3 Hz, 2H, ArH), 7.78 (d, *J* = 8.6 Hz, 2H, ArH), 7.96 (d, *J* = 7.4 Hz, 4H, ArH), 8.28 (d, *J* = 8.6 Hz, 2H, ArH), 9.00 (d, *J* = 5.1 Hz, 2H, 2NH); ¹³C NMR (125 MHz, DMSO-*d*₆): δ (ppm) 59.0, 124.0, 128.0, 128.5, 128.8, 132.2, 134.0, 147.5, 148.0, 166.4.

***N,N'*-(4-Methylphenyl)methylene)dibenzamide (F)**

¹H NMR (500 MHz, DMSO-*d*₆): δ (ppm) 2.31 (s, 1H, CH₃), 7.01 (t, *J* = 7.7 Hz, 1H, CH), 7.20 (d, *J* = 8.0 Hz, 2H, ArH), 7.36 (d, *J* = 8.0 Hz, 2H, ArH), 7.48-7.51 (m, 4H, ArH), 7.55-7.59 (m, 2H, ArH), 7.91 (d, *J* = 7.1 Hz, 4H, ArH), 9.00 (d, *J* = 7.7 Hz, 2H, 2NH); ¹³C NMR (125 MHz, DMSO-*d*₆): δ

(ppm) 21.3, 59.1, 127.0, 128.1, 129.0, 129.4, 132.1, 134.5, 137.4, 138.1, 166.1.

***N,N'*-(4-Chlorophenyl)methylene)diacetamide (H)**

¹H NMR (500 MHz, DMSO-*d*₆): δ (ppm) 1.87 (s, 6H, 2CH₃), 6.48 (t, *J* = 7.7 Hz, 1H, CH), 7.33 (d, *J* = 8.4 Hz, 2H, ArH), 7.44 (d, *J* = 8.4 Hz, 2H, ArH), 8.57 (d, *J* = 7.8 Hz, 2H, 2NH); ¹³C NMR (125 MHz, DMSO-*d*₆): δ (ppm) 23.0, 57.4, 128.8, 128.9, 132.7, 140.1, 169.2.

***N,N'*-(2-Bromophenyl)methylene)diacetamide (I)**

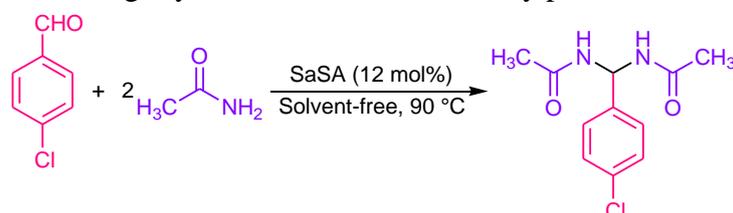
IR (KBr): 3303, 3099, 2928, 1653, 1551, 1467 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ (ppm) 1.84 (s, 6H, 2CH₃), 6.58 (t, *J* = 7.2 Hz, 1H, CH), 7.27 (t, *J* = 7.5 Hz, 1H, ArH), 7.41 (t, *J* = 7.4 Hz, 1H, ArH), 7.49 (d, *J* = 7.6 Hz, 1H, ArH), 7.62 (d, *J* = 7.9 Hz, 1H, ArH), 8.53 (d, *J* = 7.1 Hz, 2H, 2NH); ¹³C NMR (125 MHz, DMSO-*d*₆): δ (ppm) 22.8, 58.4, 123.2, 128.1, 128.5, 130.2, 133.2, 139.8, 168.9. Mass (EI, 70 ev): *m/z* 285 (M⁺).

Results and discussion

Initially, the condensation of 4-chlorobenzaldehyde (1 mmol) with acetamide (2 mmol) was chosen as a model reaction (Scheme 2), and influence of the catalyst amount and temperature was investigated under solvent-free conditions; for this purpose, the reaction was examined using 10-15 mol% of saccharin-*N*-

sulfonic acid (SaSA) at range of 80-100 °C; the results are summarized in Table 1. As it is shown in Table 1, the best results were acquired when the reaction was carried out in the presence of 12 mol% of the catalyst at 90 °C (Table 1, Entry 2). Increasing the catalyst amount or the temperature slightly decreased

the reaction times (Table 1, Entries 3 and 5). Nevertheless, 12 mol% and 90 °C were selected as the optimal conditions, respectively, because performing reactions using fewer amount of catalyst at lower temperature is more compliance with green chemistry protocols.



Scheme 2. The model reaction

Table 1. Effect of the catalyst amount and temperature on the model reaction

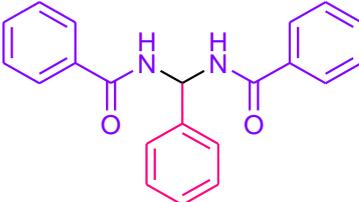
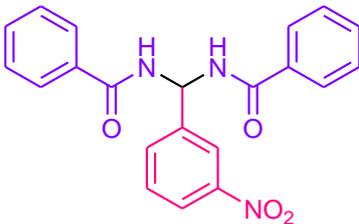
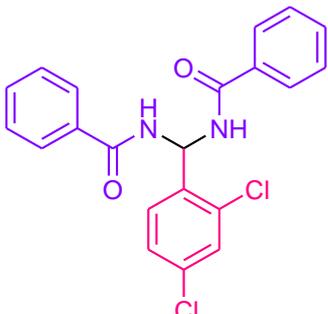
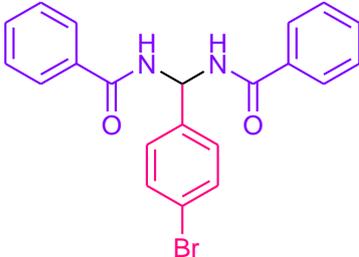
Entry	Amount of SaSA (mol%)	Temp. (°C)	Time (min)	Yield (%) ^a
1	10	90	15	83
2	12	90	13	87
3	15	90	15	87
4	12	80	20	79
5	12	100	12	87

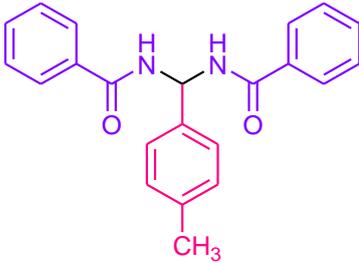
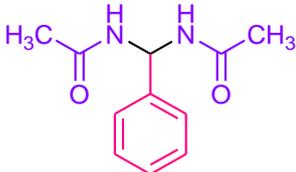
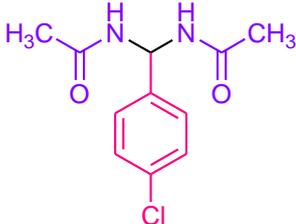
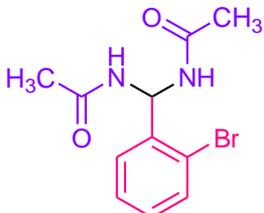
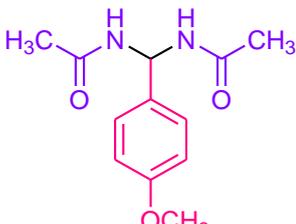
^aIsolated yield

After optimization of the reaction conditions, effectuality and generality of the protocol were appraised by examining the reaction of various aromatic aldehydes with benzamide (or acetamide); the corresponding results are illustrated in Table 2. As Table 2 indicates, high yields of the desired products were obtained in short reaction times when benzaldehyde, and also arylaldehydes bearing electron-withdrawing, halogen and electron-releasing substituents (on para, meta

and ortho positions) were utilized in the reaction. The synthesis of *N,N'*-alkylidene bisamides using both aromatic and aliphatic amides (benzamide and acetamide) was successful; nevertheless, benzamide afforded higher yields in comparison with acetamide. According to the obtained results, our method was highly effective and general for the preparation of *N,N'*-alkylidene bisamide derivatives.

Table 2. The solvent-free production of *N,N'*-alkylidene bisamides using SaSA (12 mol%) at 90 °C

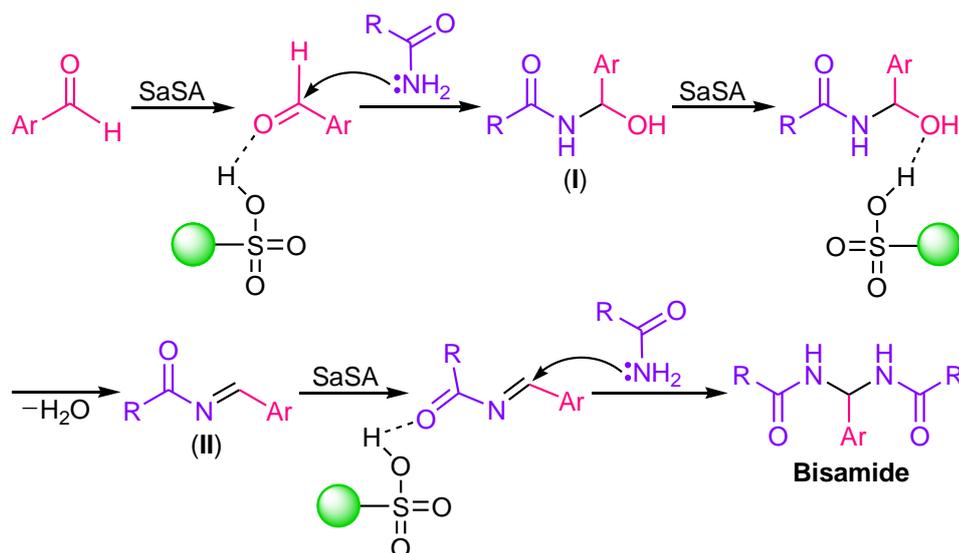
Compd. No.	Product	Time (min)	Yield (%) ^a	M.p. °C (Lit.)
A		15	96	222-224 (220-221) [11]
B		15	96	263-265 (265-267) [13]
C		10	95	227-229 (226-228) [14]
D		20	92	202-204 199-200 [18]
E		15	96	262-264 (259-260) [13]

F		15	95	240-242 (242-244) [14]
G		25	85	248-250 (251-252) [19]
H		15	87	265-267 (260-262) [16]
I		25	81	235-237
J		25	92	224-226 (222-224) [16]

^aIsolated yield

Considering to the literature [14], a plausible mechanism was proposed for the reaction (Scheme 3). Firstly, the acidic hydrogen of SaSA activates the aldehyde carbonyl, followed by the nucleophilic addition of amide to the activated aldehyde to afford **I**.

Removing a H₂O molecule from intermediate **I** by assistance of the catalyst provides **II**. After activation of **II** by saccharin-*N*-sulfonic acid, second molecule of amide add to the imine group, and *N,N'*-alkylidene bisamide produces.



Scheme 3. The proposed mechanism for the synthesis of *N,N'*-alkylidene bisamides

The comparison of the catalytic performance of SaSA with the previously reported catalysts for the preparation of *N,N'*-alkylidene bisamide **A** has been illustrated in Table 3. As it

is clear from Table 3, SaSA was superior than the other catalysts in terms of the reaction media, yield, time or temperature.

Table 3. Comparing SaSA with the reported catalysts for the production of compound **A**

Catalyst	Conditions	Time (min)	Yield (%)	Reference
SaSA	Solvent-free, 90 °C	15	96	-
CF ₃ SO ₃ H	CH ₂ Cl ₂ , reflux	720	92	[10]
NiFe ₂ O ₄ @KIT-6@ZnO	Solvent-free, 60 °C	10	90	[11]
Montmorillonite K10	Solvent-free, 100 °C	80	85	[12]
Silica-bonded S-sulfonic acid nanoparticles	Toluene, reflux	240	93	[13]
NiFe ₂ O ₄ @SiO ₂ -PPA	CH ₃ OH, reflux	80	86	[14]
Sulfonated carbon/nano-titania composites	Solvent-free, 100 °C	90	93	[15]
Hydroxyapatite	CH ₃ CN, reflux	180	95	[16]
Silzic	Solvent-free, 80 °C	35	83	[17]
H ₁₄ [NaP ₅ W ₂₉ MoO ₁₁₀]	CH ₃ OH, reflux	90	86	[18]
B(HSO ₄) ₃	Solvent-free, 100 °C	45 s	85	[19]

Conclusion

In conclusion, we have introduced a solid-acid catalyst namely saccharin-*N*-sulfonic acid for the synthesis of *N,N'*-

alkylidene bisamides from arylaldehydes and primary amides. This protocol has solved many drawbacks of the reported methods, and has the

following merits: easy workup procedure and purification of the products, effectiveness, generality, short reaction times, high yields, carrying out the synthesis in the absence of solvent, simple preparation of the catalyst, and good agreement with the green chemistry protocols. Moreover, in our work, the products have been prepared in milder conditions in comparison to many of the previous reports.

Acknowledgements

We thank Research Council of Payame Noor University for providing necessary research facilities and financial support of this work.

References

- [1] S.A. Ramachandran, P.S. Jadhavar, S.K. Miglani, M.P. Singh, D.P. Kalane, A.K. Agarwal, B.D. Sathe, K. Mukherjee, A. Gupta, S. Haldar, M. Raja, S. Singh, S.M. Pham, S. Chakravarty, K. Quinn, S. Belmar, I.E. Alfaro, C. Higgs, S. Bernales, F.J. Herrera, R. Rai, *Bioorg. Med. Chem. Lett.*, **2017**, 27, 2153-2160.
- [2] X.-L. Wang, X.-T. Sha, G.-C. Liu, N.-L. Chen, Y. Tian, *CrystEngComm*, **2015**, 17, 7290-7299.
- [3] R.S. Mulla, M.S. Beecroft, R. Pal, J.A. Aguilar, J. Pitarch-Jarque, E. García-España, E. Lurie-Luke, G.J. Sharples, J.A.G. Williams, *Chem. Eur. J.*, **2018**, 24, 7137-7148.
- [4] M.-N. Chang, X.-K. Yang, P. M. Chhetri, J.-D. Chen, *Polymers*, **2017**, 9, 691; doi:10.3390/polym9120691.
- [5] M. Rodriguez, P. Dubreuil, J. P. Bali, J. Martinez, *J. Med. Chem.*, **1987**, 30, 758-763.
- [6] J.W. Bode, *Curr. Opin. Drug Discovery*, **2006**, 9, 765-775.
- [7] M. Goodman, H. Shao, *Pure Appl. Chem.*, **1996**, 68, 1303-1308.
- [8] T. Yamazaki, K.I. Nunami, M. Goodman, *Biopolymers*, **1991**, 31, 1513-1528.
- [9] J.P. Wan, Y.F. Chai, J.M. Wu, Y.J. Pan, *Synlett*, **2008**, 19, 3068-3072.
- [10] A.H. Fernandez, R.M. Alvarez, T.M. Abajo, *Synthesis*, **1996**, 1299-1301.
- [11] H.R. Saadati-Moshtaghin, F.M. Zonoz, M.M. Amini, *J. Solid State Chem.*, **2018**, 260, 16-22.
- [12] T.L. Lambat, S.S. Deo, F.S. Inam, T.B. Deshmukh, A.R. Bhat, *Karbala Int. J. Modern Sci.*, **2016**, 2, 63-68.
- [13] M. Tajbakhsh, R. Hosseinzadeh, H. Alinezhad, P. Rezaee, *Synth. Commun.*, **2013**, 43, 2370-2379.
- [14] B. Maleki, M. Baghayeri, *RSC Adv.*, **2015**, 5, 79746-79758.
- [15] M. Kour, S. Paul, *New J. Chem.*, **2015**, 39, 6338-6350.
- [16] G. Ramachandran, R. Saraswathi, M. Kumarraja, P. Govindaraj, T. Subramanian, *Synth. Commun.*, **2018**, 48, 216-222.
- [17] H.A. Soliman, A.Y. Mubarak, S.S. Elmorsy, *Chin. Chem. Lett.*, **2016**, 27, 353-356.
- [18] B. Maleki, F. Mohammadi Zonoz, H.A. Akhlaghi, *Org. Prep. Proced. Int.*, **2015**, 47, 361-367.
- [19] Z. Karimi-Jaberi, B. Pooladian, *Monatsh. Chem.*, **2013**, 144, 659-663.
- [20] E. Noroozizadeh, A.R. Moosavi-Zare, M.A. Zolfigol, M. Zarei, R. Karamian, M. Asadbegy, S. Yari, S.H. Moazzami Farida, *J. Iran. Chem. Soc.*, **2018**, 15, 471-481.
- [21] F. Shirini, M.A. Zolfigol, M. Abedini, *Monatsh. Chem.*, **2009**, 140, 1495-1498.
- [22] F. Shirini, M.A. Zolfigol, M. Abedini, *J. Iran. Chem. Soc.*, **2010**, 7, 603-607.
- [23] M.A. Zolfigol, M. Navazeni, M. Yarie, R. Ayazi-Nasrabadi, *Res. Chem. Intermed.*, **2018**, 44, 191-200.

- [24] A. Nakhaei, A. Davoodnia, S. Yadegarian, *Iran. Chem. Commun.*, **2018**, *6*, 334-345.
- [25] A. Khazaei, N. Sarmasti, J. Yousefi Seyf, *Appl. Organomet. Chem.*, **2018**, *32*, e4308.
- [26] A. Zare, H. Asvar, F. Zarei, M. Khalili, Z. Kordrostami, A.R. Moosavi-Zare, V. Khakyzadeh, *J. Appl. Chem. Res.*, **2016**, *10*, 59-67.
- [27] A. Zare, J. Sanjideh, *Iran. Chem. Commun.*, **2018**, *6*, 416-422.
- [28] A. Zare, M. Maghsoudi, B. Gholami, A.R. Moosavi-Zare, *J. Appl. Chem. Res.*, **2016**, *10*, 31-39.
- [29] A. Zare, A. Kohzadiana, Z. Abshirini, S.S. Sajadikhah, J. Phipps, M. Benamara, M.H. Beyzavi, *New J. Chem.*, **2019**, *43*, 2247-2257.
- [30] S. Sajjadifar, G. Mansouri, S. Miraninezhad, *Asian J. Nano. Mat.*, **2018**, *1*, 11-18.
- [31] N. Noroozi Pesyan, A. Gharib, A. Monfared, *Iran. Chem. Commun.*, **2018**, *6*, 346-358.
- [32] N. Irannejad-Gheshlaghchaei, A. Zare, S.S. Sajadikhah, A. Banaei, *Res. Chem. Intermed.*, **2018**, *44*, 6253-6266.

How to cite this manuscript: Abdolkarim Zare, Manije Dianat, Nasrin Pishahang, Roghayyeh Khanivar, Soheila Kaman-Torki, Fatemeh Fakhraei, Zahra Kordrostami, Masoud Sadeghi-Takallo. A green and highly effective protocol for the synthesis of *N,N'*-alkylidene bisamides using saccharin-*N*-sulfonic acid. *Iranian Chemical Communication*, 2020, 8(1), 58-66.