Novel and Highly Efficient Synthesis of 3-(Alkyl/benzylthio)-9b-hydroxy-1*H*-imidazo[5,1-*a*]isoindole-1,5(9b*H*)-dione Derivatives

Azar Jamaleddini, Mohammad Reza Mohammadizadeh

PII: S0040-4039(16)31600-8
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.11.109
Reference: TETL 48395

To appear in: *Tetrahedron Letters*

Received Date: 26 September 2016
Revised Date: 21 November 2016
Accepted Date: 25 November 2016

Please cite this article as: Jamaleddini, A., Reza Mohammadizadeh, M., Novel and Highly Efficient Synthesis of 3-(Alkyl/benzylthio)-9b-hydroxy-1*H*-imidazo[5,1-*a*]isoindole-1,5(9b*H*)-dione Derivatives, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.11.109

Novel and Highly Efficient Synthesis of 3-(Alkyl/benzylthio)-9b-hydroxy-1*H*-imidazo[5,1-*a*]isoindole-1,5(9b*H*)-dione Derivatives

Azar Jamaleddini,[a] Mohammad Reza Mohammadizadeh[a,*]

[a]Department of Chemistry, Faculty of sciences, Persian Gulf University, Bushehr 75169, Iran

[*]Corresponding author. Tel./fax: +98 77334541494. E-mail addresses: mrmohamadizadeh@pgu.ac.ir.

Abstract: The oxidation of 3a,8a-dihydroxy-2-(alkyl/benzylthio)indeno[1,2-*d*]imidazol-8(3*H*)-ones to give the corresponding 3-(alkyl/benzylthio)-9b-hydroxy-1*H*-imidazo[5,1-*a*]isoindole-1,5(9b*H*)-dione derivatives in good to excellent yields at room temperature using two oxidants, periodic acid in aqueous ethanol and lead(IV) acetate in acetic acid, has been reported.

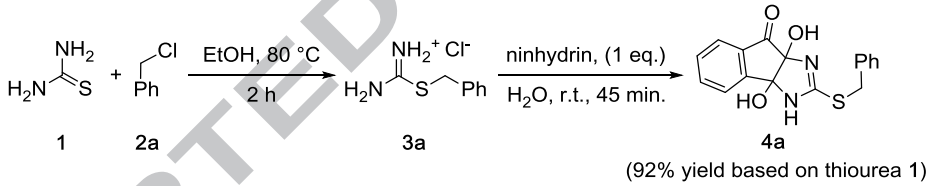
Keywords: 3a,8a-dihydroxyindeno[1,2-*d*]imidazoles, 9b-hydroxy-1*H*-imidazo[5,1-*a*]isoindole-1,5(9b*H*)-diones, oxidation, periodic acid, lead(IV) acetate

The imidazolyl moiety[1] has a wide-range of applications as building blocks in the development of new drugs,[2] organometallic catalysis,[3] coordination chemistry,[4] and asymmetric catalysis.[5] Isoindole is an important heterocyclic ring system which occurs as the core structure in a variety of naturally occurring alkaloids and synthetic compounds,[6] possessing a diverse pharmacological profile including antimicrobial,[7] anthelmintic,[8a-b] insecticidal,[8c] cyclooxygenase isoenzyme (COX-2),[9a] thrombin inhibition[9b] and anticancer activities.[9c] They also have broad applications as organic light-emitting devices (OLED)[10] and as key structural moieties for the preparation of oligoacenes[11a-b] and porphyrins.[11c-d] Among the imidazole fused isoindoles, the synthesis and biological activity of imidazo[5,1-*a*]isoindole derivatives are more widely investigated. There are several reported procedures for the preparation of these compounds, however, the majority of these methods suffer from one or more drawbacks such as the use of structurally complex and expensive catalysts and starting materials, harsh reaction conditions, multi-step procedures leading to low overall yields, and low chemoselectivity.[12-19]

Recently we reported the oxidative cleavage of a series of vicinal cyclic diols, prepared from the addition reactions of ninhydrin with several 1,3-binucleophiles; e.g. urea,[20]

aminouracil,[21] enol,[22a] and enamine[22b-c] derivatives, using lead(IV) acetate or periodic acid under various conditions. In all cases the reactions progressed *via* eight-membered heterocyclic intermediates containing 1-donor-5-acceptor groups, similar to that shown in Scheme 3 (intermediate **E**). Depending on the employed oxidant, reaction conditions, and the nature of substituents, these intermediates were converted to spiro[20-22b] or fused[22c] N/O-containing heterocycles.

As a part of our ongoing program on the synthesis of novel heterocycles,[23] we have investigated the synthesis and oxidation of 3a,8a-dihydroxy-2-(alkyl/benzylthio)indeno[1,2-*d*]imidazol-8(3*H*)-ones **4**. To begin, 2-(benzylthio)-3a,8a-dihydroxy-3a,8a-dihydroindeno[1,2-*d*]imidazol-8(3*H*)-one **4a** was prepared in high yield from the one-pot, two-step reaction of thiourea and benzylchloride in EtOH, followed by the addition of ninhydrin (Scheme 1). Addition of benzyl chloride to thiourea gave 2-benzylisothiouronium chloride **3a** which was directly subjected to the addition reaction with ninhydrin at room temperature to give 3a,8a-dihydroxyindeno[1,2-*d*]imidazole **4a** whose structure was determined by ^{1}H and ^{13}C-NMR spectroscopy as well as mass spectrometry.



Scheme 1. One-pot synthesis of 3a,8a-dihydroxyindeno[1,2-*d*]imidazole **4a**

Next, with the expectation of the formation of either compound **5** or **6** (Fig. 1),[20-22] we investigated the oxidative cleavage of 3a,8a-dihydroxyindeno[1,2-*d*]imidazole **4a** using two oxidants; lead(IV) acetate and periodic acid under different conditions.

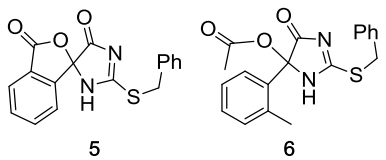
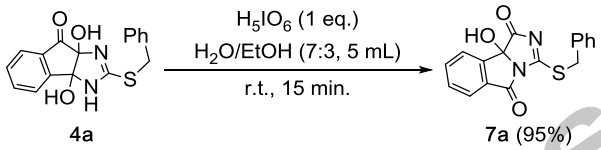


Figure 1. Expected products[20-22] from the oxidative cleavage of 3a,8a-dihydroxyindeno[1,2-*d*]imidazole **4a**

After extensive screening, we found that the reaction proceeded best with periodic acid in aqueous EtOH at room temperature (Scheme 2). Although, the ^{1}H and ^{13}C-NMR and mass spectrometry data of the obtained compound was initially indicative of spiro[imidazole-4,1'-isobenzofuran] **5** (Fig. 1), to our surprise, single crystal X-ray crystallography showed that the reaction proceeded with the formation of 3-(benzylthio)-9b-hydroxy-1*H*-imidazo[5,1-*a*]isoindole-1,5(9b*H*)-dione **7a** (Fig. 2).



Scheme 2. Preparation of 3-(benzylthio)-9b-hydroxy-1*H*-imidazo[5,1-*a*]isoindole-1,5(9b*H*)-dione **7a**

The ^{1}H NMR spectrum of **7a** exhibited an AB-quartet pattern at δ 4.60 arising from two diastereotopic CH_2 protons as well as a broad singlet at δ 8.15 for the OH proton. Nine aromatic H-atoms were observed as multiplets in the range of δ 7.20–8.05. The ^{1}H-decoupled ^{13}C NMR spectrum of **7a** showed 15 distinct resonances which were in agreement with the proposed structure. The signals at δ 36.1, δ 166.1, δ 180.9 and δ 185.1 correlated with the benzylic CH_2 functional group, the S-Bz substituted carbon of the imidazole moiety and the carbonyl groups, respectively. The quaternary carbon connected to the hydroxyl group resonated at δ 90.6. The structure of product **7a** was further confirmed by mass spectrometry, which showed a molecular ion peak at 324.

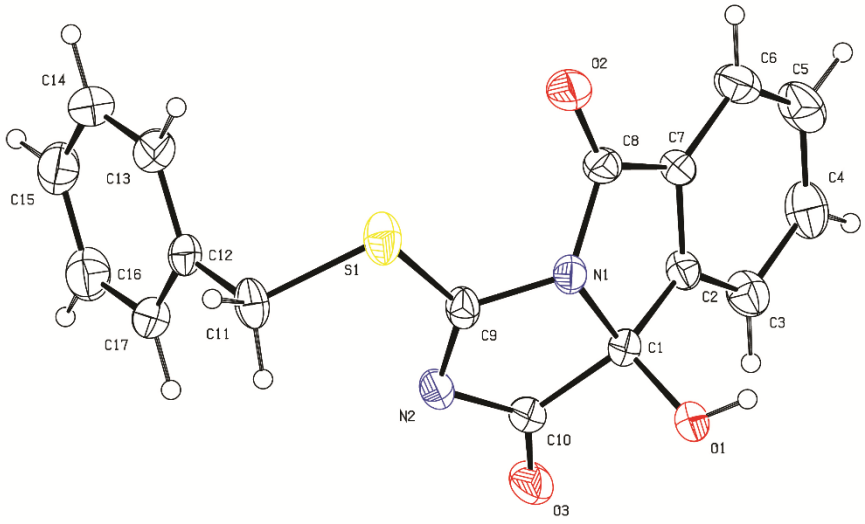
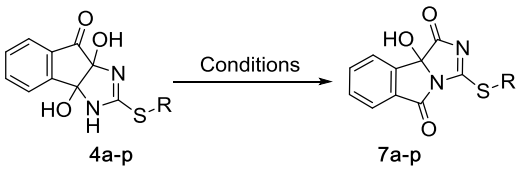


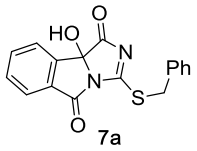
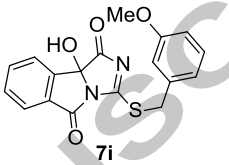
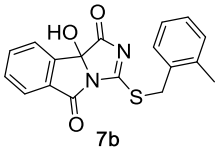
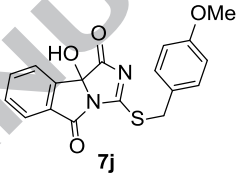
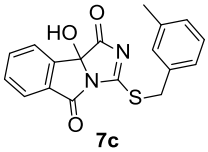
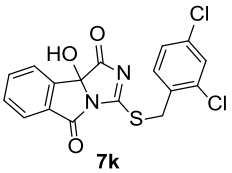
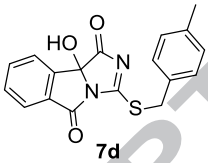
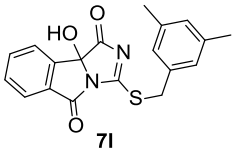
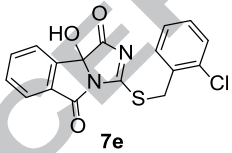
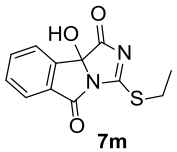
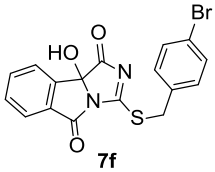
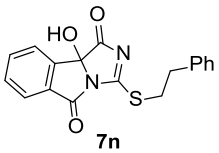
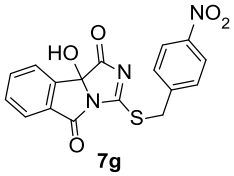
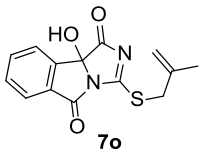
Figure 2. Single crystal X-ray structure of **7a** (CCDC 1506317).

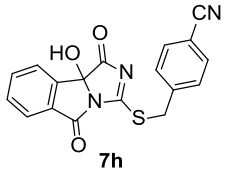
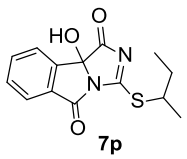
In order to evaluate the feasibility of this new strategy for the synthesis of 3-(alkyl/benzylthio)-9b-hydroxy-1*H*-imidazo[5,1-*a*]isoindole-1,5(9b*H*)-dione derivatives **7**, various thioalkyl and thioaryl substituted 3a,8a-dihydroxyindeno[1,2-*d*]imidazoles **4** were subjected to the oxidation reaction with periodic acid in aqueous EtOH at room temperature. All reactions were complete in less than 20 minutes and the precipitated products **7** were purified by recrystallization from EtOH or column chromatography (Table 1).

Table 1. Synthesis of 3-(alkyl/benzylthio)-9b-hydroxy-1*H*-imidazo[5,1-*a*]isoindole-1,5(9b*H*)-diones **7a-p** from the oxidation of 3a,8a-dihydroxyindeno[1,2-*d*]imidazole derivatives **4a-p**



Conditions: a: H_5IO_6 (1 eq.), H_2O/EtOH (7:3, 5 mL), r.t., 15 min.
b: $Pb(OAc)_4$ (1 eq.), AcOH (3 mL), r.t., 15 min.

Entry	Product (7)	Yield[a]	Yield[b]	Entry	Product (7)	Yield[a]	Yield[b]
1	 **7a**	92	93	**9**	 **7i**	85	85
2	 **7b**	95	90	**10**	 **7j**	95	90
3	 **7c**	90	84	**11**	 **7k**	88	90
4	 **7d**	90	83	**12**	 **7l**	98	86
5	 **7e**	85	91	**13**	 **7m**	77	80
6	 **7f**	96	85	**14**	 **7n**	90	83
7	 **7g**	90	93	**15**	 **7o**	80	77

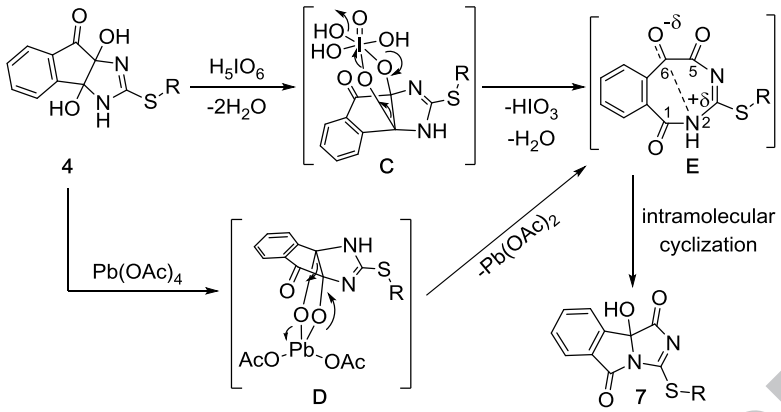
8	 **7h**	93	81	**16**	 **7p**	80	89

[a]Isolated yield using the H_5IO_6/H_2O/EtOH system; [b]Isolated yield using the $Pb(OAc)_4$/AcOH system

As shown in Table 1, the procedure worked well for both alkyl and benzyl substituted diols **4**. The oxidation reaction of diols **4a-p** proceeded rapidly, however, the benzyl substituted products **7a-l** were more conveniently precipitated from the reaction mixture. Therefore, benzyl substituted products **7a-l** were obtained in relatively higher yields than the corresponding alkyl substituted products **7m-p**.

Notably, the oxidation of 3a,8a-dihydroxyindeno[1,2-*d*]imidazole derivatives **4a-p** with lead(IV) acetate in acetic acid at room temperature also progressed efficiently to give the corresponding 9b-hydroxy-1*H*-imidazo[5,1-*a*]isoindole-1,5(9b*H*)-diones **7a-p** in good to excellent yields. Although, from an eco-friendly point of view, the aqueous periodic acid system is preferred.

A proposed mechanism is shown in Scheme 3. Benzo[*e*][1,3]diazocine-1,5,6(2*H*)-trione **E** resulting from the oxidation of diols **4** with periodic acid or lead(IV) acetate proceeds *via* intermediates **C** and **D**, respectively. Due to the suitable positioning of electron-donating (N-2) and electron-withdrawing (C-6) atoms, strong transannular interactions between N-2 and C-6 are predominant in benzodiazocine cycle **E**. Unlike our previous studies[20-23,25] where this type of transannular interaction caused ring cleavage at the C(1)-N(2) bond, in the case of benzodiazocine **E**, this interaction led to cyclization.



Scheme 3. Proposed mechanism for the preparation of imidazo[5,1-*a*]isoindoles **7** *via* oxidation of dihydroxyindenoimidazolones **4**

In summary we have studied the oxidation of dihydroxyindeno[1,2-*d*]imidazolones using periodic acid in aqueous ethanol and lead(IV) acetate in acetic acid. Using these oxidation systems we have introduced two highly efficient procedures for the synthesis of 9b-hydroxy-1*H*-imidazo[5,1-*a*]isoindole-1,5(9b*H*)-dione derivatives.

Acknowledgements

The authors thank the Research Council of the Persian Gulf University of Bushehr for financial support of this work.

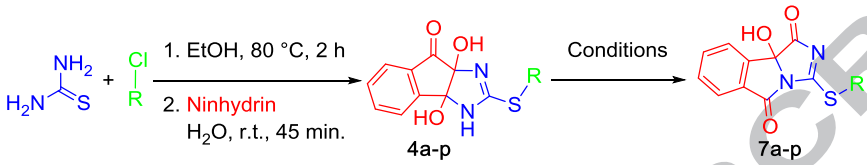
References and notes

1. (a) Xi, N.; Huang, Q.; Liu, L. in: Comprehensive heterocyclic chemistry III, Vol. 4, (Eds.: Katrirzky, A. R.; Rees, C. W.), Elsevier, Amsterdam 2008, pp 143–364. (b) Revuelta, J.; Machetti, F.; Cicchi, S. in: Modern heterocyclic chemistry, Vol. 2, (Eds.: ßlvarez-Builla, J.; Vaquero, J. J.; Barluenga, J.), Wiley-VCH, Weinheim, 2011, pp 809–923.
2. (a) Boiani, M.; Gonzalez, M. *Mini-Rev. Med. Chem.* **2005**, *5*, 409. (b) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.
3. Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.
4. Nieto, I.; Cervantes-Lee, F.; Smith, J. M. *Chem. Commun.* **2005**, 3811.
5. Cesar, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619.
6. (a) Speck, K.; Magauer, T. *Beilstein J. Org. Chem.* **2013,** *9*, 2048. (b) Sović, I.; Karminski-Zamola, G. *Chem. Ind.: J. Chemists Chem. Engin.* **2014**, *63*, 173. (c) Heugebaert, T. S. A.; Romana, B. I.; Stevens, C. V. *Chem. Soc. Rev.* **2012**, *41*, 5626. (d) Meng, X.-B.; Han, D.; Zhang, S.-N.; Guo, W.; Cui, J.-R.; Li, Z.-J. *Carbohydr. Res.* **2007**, *342*, 1169.

7. (a) El-Gohary, N.; Shaaban, M. I. *Arch. Pharm. Chem. Life Sci*. **2015**, *348*, 666. (b) El-Tamany, El-S. H.; Sowellim, S. Z.; Hamed, A. A.; Radwan, A. S. *Res. Chem. Intermed.* **2015**, *41*, 2675.
8. (a) Sena, V. L. M.; Srivastava, R. M.; Silva, R. O.; Lima, V. L. M. *Farmaco* **2003**, *58*, 1283. (b) Bamnela, R.; Shrivastava, S. P. *Indian J. Chem*. **2014**, *53*B, 1128. (c) Hall, I. H.; Voorstad, P. J.; Chapman, J. M.; Cocolas, G. H. *J. Pharm. Sci.* **1983**, *72*, 845.
9. (a) Portevin, B.; Tordjman, C.; Pastoureau, P.; Bonnet, J.; Nanteuil G. D. *J. Med. Chem.* **2000**, *43*, 4582. (b) Masic, L. P.; Mlinsek, G.; Solmajer, T.; Bakija, A. T.; Stegnard, M.; Kikelj, D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 789. (c) Kashinath, K.; Jadhava, P. D.; Reddy, D. S. *Org. Biomol. Chem*. **2014**, *12*, 4098. (d) Pongprom, N.; Bachitsch, H.; Bauchinger, A.; Ettefagh, H.; Haider, T.; Hofer, M.; Knafl, H.; Slanz , R.; Waismeyer, M.; Wieser, F.; Spreitzer, H. *Monatshefte Chemie Chem. Month*. **2010**, *14*, 53.
10. (a) Gauvina, S.; Santerrea, F.; Dodeleta, J. P.; Dingb, Y.; Hlilb, A. R.; Hayb, A. S.; Andersonc, J.; Armstrongc, N. R.; Gorjancd, T. C.; D'Ioriod, M. Thin Solid Films **1999**, *353*, 218. (b) Mi, B.-X.; Wang, P.-F.; Liu, M.-W.; Kwong, H.-L.; Wong, N.-B.; Lee, C.-S.; Lee, S.-T. *Chem. Mater*. **2003**, *15*, 3148.
11. (a) Chen, Y.-L.; Lee, M. H.; Wong, W.-Y.; Lee, A. W. M. *Synlett* **2006**, 2510. (b) Chen, Z.; Müller, P.; Swager, T. M. *Org. Lett.* **2006**, *8*, 273. (c) Ito, S.; Murashima, T.; Uno, H.; Ono, N. *Chem. Commun*. **1998**, 1661. (d) Ito, S.; Ochi, N.; Uno, H.; Murashima, T.; Ono, N. *Chem. Commun.* 2000, 893.
12. Xu, X.; Zhao, L.; Li, Y.; Soul, J.-F.; Doucet, H. *Adv. Synth. Catal*. **2015**, *357*, 2869.
13. Hosseinkhani, B.; Islami, M. R.; Hosseinkhani, S. *Synlett* **2015,** *26*, 2277.
14. (a) Yasmin, N.; Ray, J. K. *Synlett* **2010**, 924. (b)Csende, F.; Miklós, F.; Stájer, G. *Current Org. Chem.* **2012**, *16*, 1005.
15. Laha, J K.; Dayal, N.; Singh, S.; Bhimpuria, R. *Eur. J. Org. Chem.* **2014**, 5469.
16. Byun, Y.-S.; Jung, C.-H.; Park, Y.-T. *J. Heterocyclic Chem.* **1995**, *32*, 1835.
17. Das, S.; Fro1hlich, R.; Pramanik, A. *Org. Lett.* **2006**, *8*, 4263.
18. Aldabbagh, F.; Clyne, M. A. *Lett. Org. Chem.* **2006**, *3*, 510.
19. Arai, N.; Takahashi, M.; Mitani, M.; Mori, A. *Synlett* **2006**, 3170.
20. Mohammadizadeh, M. R.; Firoozi, N.; *Tetrahedron Lett.* **2010**, 51, 2467.
21. Mohammadizadeh, M. R.; Bahramzadeh, M.; Taghavi, S. Z.; *Tetrahedron Lett*. **2010**, *51*, 5807.
22. (a) Mohammadizadeh, M. R.; Saberi, D.; Taghavi, S. Z. *Tetrahedron Lett*. **2016**, *57*, 264. (b) Mahdavinia, G. H.; Mohammadizadeh, M. R.; Ariapour, N.; Alborz, M. *Tetrahedron Lett*. **2014**, *55*, 1967. (c) Mohammadizadeh, M. R.; Firoozi, N.; Aradeh, R. *Helv. Chim. Acta* **2011**, *94*, 410.
23. Saberi, D.; Mohammadizadeh, M. R.; Esmaeili, R. *Helv. Chim. Acta* **2015**, *98*, 1411.
24. Qiu, K.; Wang, R. *Synthesis* **2015**, *47*, 3186.
25. Mohammadizadeh, M. R.; Basti, F. *J. Iran. Chem. Soc*. **2015**, *12*, 1171.

Novel and Highly Efficient Synthesis of 3-(Alkyl/benzylthio)-9b-hydroxy-1*H*-imidazo[5,1-*a*]isoindole-1,5(9b*H*)-dione Derivatives

Azar Jamaleddini, Mohammad Reza Mohammadizadeh*
Department of Chemistry, Faculty of sciences, Persian Gulf University, Bushehr 75169, Iran
*Corresponding author. Tel./fax: +98 77334541494; mrmohamadizadeh@pgu.ac.ir.



Conditions: a: H_5IO_6, H_2O/EtOH (7:3, 5 mL), r.t., 15 min., 80-98%; b: $Pb(OAc)_4$, AcOH (3 mL), r.t., 15 min., 77-93%

*Simple method for the synthesis of structurally complex compounds

*Procedures are fast and highly efficient

*The starting materials are simple and commercially available