

Three component reaction of indane-1,2,3-trione, tosylmethyl isocyanide and benzoic acid derivatives

Ali Reza Kazemizadeh and Ali Ramazani*

Chemistry Department, Zanzan University, P O Box 45195-313, Zanzan, Iran

E-mail: aliramazani@gmail.com

Abstract

The Passerini reactions of indane-1,2,3-trione, tosylmethyl isocyanide, and benzoic acid derivatives proceed at room temperature giving sterically congested 2,2-disubstituted indane-1,3-dione derivatives in quantitative yield. The reactions are one-pot, and the products obtained did not require any purification.

Keywords: Passerini reaction, isocyanide, indane-1,2,3-trione

Introduction

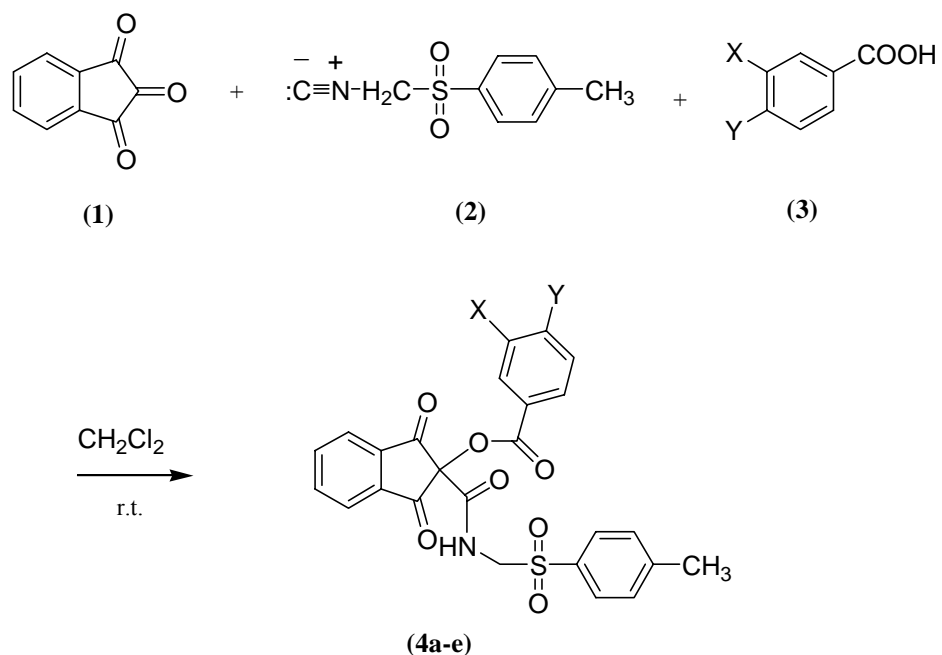
Multicomponent reactions (MCRs), reactions involving at least three starting materials in a one-pot reaction, remain the most efficient method of rapidly introducing molecular diversity.¹⁻⁵ As such, they have found widespread use in organic and diversity-oriented synthesis as they provide access highly functionalized molecules in simple and straightforward one-step transformations.⁶ Among the known multicomponent reactions to date, the most valuable reactions are those based on isocyanides. Isocyanide-based multicomponent reactions (abbreviated to IMCRs by Ugi and Dömling) by virtue of their synthetic potential, their inherent atom efficiency, convergent nature, ease of implementation, and the generation of molecular diversity, have attracted much attention because of the advantages that they offer to the field of combinatorial chemistry.⁷ IMCRs are particularly interesting because they are more versatile and diverse than the remaining MCRs. The great potential of isocyanides for the development of multicomponent reactions lies in the diversity of bond forming processes available, their functional group tolerance, and the high levels of chemo-, regio-, and stereoselectivity often observed. The outstanding position of IMCRs can be traced back to the exceptional reactivity of the functional group of the isocyanide. No other functional group reacts with nucleophiles and electrophiles at the same atom, leading to the so-called α -adduct. Other functional groups typically react at different atoms with nucleophiles and electrophiles. Moreover, there is virtually no restriction on the nature of the nucleophiles and electrophiles in IMCRs. Other major primary reaction pathways of isocyanides

are radical reactions, α -acidity, and an intrinsic high affinity toward metallorganic reagents and their subsequent reactions. Also, IMCRs among MCRs are at the minority overall, at the moment; nevertheless, they provide the largest chemical space.⁸

Isocyanide based multi-component reactions have been known about 80 years, with the first described in 1921 and named after its founder, Passerini.^{9,10} The chemistry of the isocyanides began in 1859 when Lieke had prepared allyl isocyanide as the first isocyanide.¹¹ Lieke, like many chemists today, was immediately struck by their strange repulsive odor, one of the only negatives of this branch of chemistry. The classical syntheses of isocyanides were developed in 1867 by Gautier.¹² For the following century only 12 isocyanides were known and rather few types of reactions had been described. Thus for a whole century, from 1859 to 1958, isocyanides were not readily available, and the chemistry of the isocyanides remained under investigated part of organic chemistry.¹³ In 1921, Passerini pioneered the use of isocyanides and successfully developed a three-component synthesis of α -acyloxycarboxamide by reaction of a carboxylic acid, an aldehyde, and an isocyanide.⁹ Today most IMCR chemistry relates to the classical reactions of Passerini and Ugi. Indeed, the large number of different scaffolds now available mostly builds on these two IMCRs and their combination with other types of reactions.¹⁴⁻²² Passerini reactions involve an oxo-component, an isocyanide, and a nucleophile. Ugi reactions are defined as the reaction of a Schiff base or an enamine with a nucleophile and an isocyanide, followed by a (Mumm) rearrangement reaction. The Passerini reactions are beginning to find utility in the drug discovery process, and total syntheses of biologically relevant natural products.²³ In connection with our recent interest to isocyanide chemistry,²⁴⁻²⁷ we report the Passerini multicomponent reaction between, indane-1,2,3-trione (**1**), tosylmethyl isocyanide (**2**) and benzoic acid derivatives (**3**).

Results and Discussion

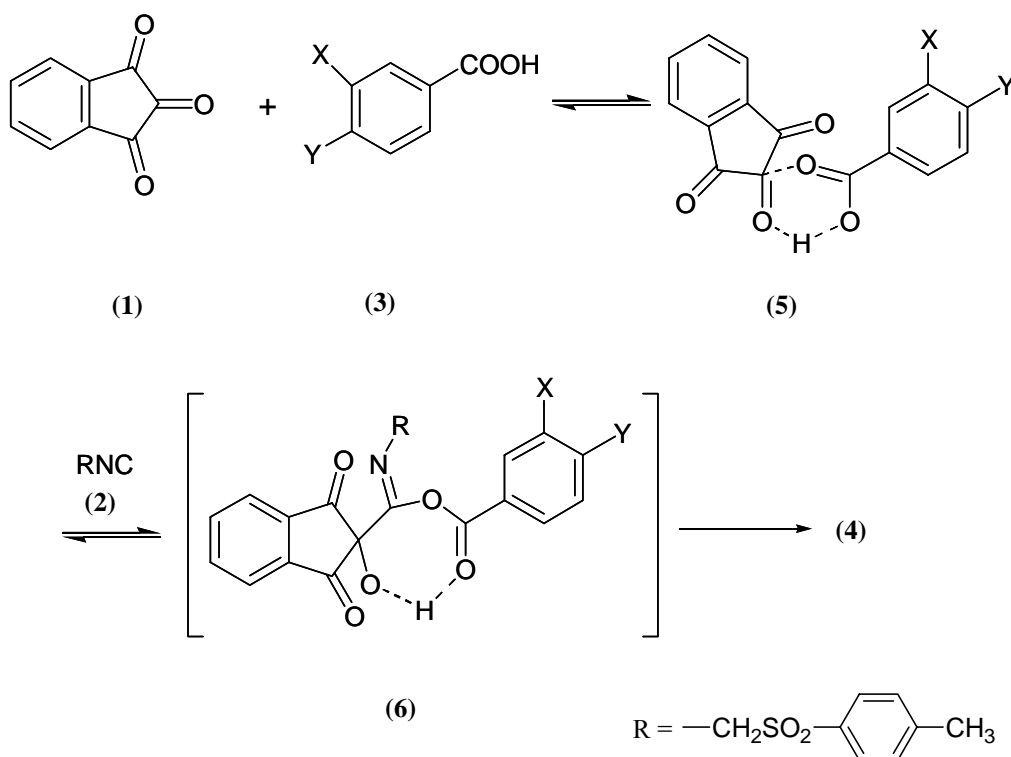
The indane-1,2,3-trione (**1**), tosylmethyl isocyanide (**2**) and benzoic acid derivatives (**3**) in dichloromethane were allowed to react in a 1:1:1 ratio at room temperature to produce α -acyloxycarboxamides (**4a-e**) (Scheme 1). The reaction proceeds smoothly and cleanly under mild conditions and the products obtained did not require any purification. The structures of the products were deduced from their IR, ¹H NMR, ¹³C NMR and elemental analyses. For example the ¹H NMR spectrum of **4a** exhibited distinct signals arising from CH₃ ($\delta_{\text{H}}= 2.44$), NCH₂ ($\delta_{\text{H}}= 4.70$), NH ($\delta_{\text{H}}= 6.51$) and aromatic CH ($\delta_{\text{H}}= 7.26- 8.40$). The ¹³C NMR spectrum of **4a** showed 17 distinct resonances arising CH₃ ($\delta_{\text{C}}= 21.7$), NCH₂ ($\delta_{\text{C}}= 59.8$), C-O ($\delta_{\text{C}}= 83.7$), aromatic carbons ($\delta_{\text{C}}= 124.2, 126.5, 128.5, 128.9, 130.2, 130.3, 132.9, 134.8, 136.2, 141.1$ and 145.6), CO of ester ($\delta_{\text{C}}= 162.2$), CO of amide ($\delta_{\text{C}}= 163.7$), CO of ketone ($\delta_{\text{C}}= 190.0$). The IR spectrum showed an NH absorption at 3423 cm^{-1} .



Products	X	Y	Yield(%)
4a	H	H	96
4b	H	Me	97
4c	Me	H	96
4d	H	Br	95
4e	Br	H	97

Scheme 1

A plausible mechanism for the formation of compounds (**4a-e**) is shown in Scheme 2. First, the acid (**3**) was supposed to attack indane-1,2,3-trione (**1**) to form (**5**) and then this reacted with isocyanide (**2**) to form (**4**)²⁸ (Scheme 2).



Scheme 2

Conclusions

We believe that the reported method offers a mild, simple, efficient and one-pot synthetic method for the preparation of sterically congested 2,2-disubstituted indane-1,3-dione derivatives from the Passerini multicomponent reaction of indane-1,2,3-trione. The products were obtained in quantitative yield and without any purification. Its ease of work-up, high yields and mild reaction conditions make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.

Experimental Section

Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Indan-1,2,3-trione is obtained from heating ninhydrin in oven (*ca.* 100-120 °C).²⁹ The methods were used to follow the reactions are TLC and NMR. TLC and NMR indicated that there is no side product. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-460 spectrometer. ¹H and ¹³C NMR spectra were measured (CDCl₃ solution) with a

BRUKER DRX-250 AVANCE spectrometer at 250.0 and 62.5 MHz, respectively. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer.

General procedure

To a magnetically stirred solution of indane-1,2,3-trione (**1**) (0.032 g, 0.2 mmol) and benzoic acid derivatives (**3**) (0.2 mmol) in dry CH₂Cl₂ (5 ml) was added isocyanide (**2**) (0.039 g, 0.2 mmol) at rt over 10 min. The mixture was stirred for 24 h at rt. The solvent was removed under reduced pressure and single spot products (**4a-e**) were obtained. The characterization data of the compounds are given below.

2-[[[(4-Methylphenyl)sulfonyl]methyl]amino]carbonyl]-1,3-dioxo-2,3-dihydro-1H-indene-2-yl benzoate (4a). White powder, m.p. 174-175 °C, yield 96%. IR (KBr) (ν_{\max} cm⁻¹): 3423 (NH), 1731, 1692, 1600, 1515, 1277, 1146. ¹H NMR (250 MHz, CDCl₃): δ_{H} 2.44 (3H, s, CH₃), 4.70 (2H, d, J = 6.50 Hz, NCH₂), 6.51 (1H, br, NH), 7.26-8.40 (13H, m, arom CH); ¹³C NMR (62.5 MHz, CDCl₃): δ_{C} 21.7 (CH₃), 59.8 (NCH₂), 83.7 (C-O), 124.2, 126.5, 128.5, 128.9, 130.2, 130.3, 132.9, 134.8, 136.2, 141.1 and 145.6 (aromatic carbons), 162.2 (CO of ester), 163.7 (CO of amide), 190.0 (CO of ketone). *Anal.* Calcd. for C₂₅H₁₉NO₇S (477.48): C, 62.89; H, 4.01; N, 2.93; S, 6.71. Found: C, 62.82; H, 3.98; N, 2.96; S, 6.80.

2-[[[(4-Methylphenyl)sulfonyl]methyl]amino]carbonyl]-1,3-dioxo-2,3-dihydro-1H-indene-2-yl 4-methylbenzoate (4b). White powder, m.p. 239-240 °C, yield 97%. IR (KBr) (ν_{\max} cm⁻¹): 3477 (NH), 1723, 1685, 1608, 1523, 1285, 1146. ¹H NMR (250 MHz, CDCl₃): δ_{H} 2.40 and 2.47 (6H, 2 s, 2 CH₃), 4.69 (2H, d, J = 6.75 Hz, NCH₂), 6.38 (1H, br, NH), 7.26-8.24 (12H, m, arom CH); ¹³C NMR (62.5 MHz, CDCl₃): δ_{C} 21.4 and 21.7 (2 CH₃), 60.5 (NCH₂), 83.8 (C-O), 123.6, 128.7, 129.2, 129.6, 130.8, 133.6, 135.8, 135.9, 140.7, 144.7 and 145.6 (aromatic carbons), 162.8 (CO of ester), 162.9 (CO of amide), 190.4 (CO of ketone). *Anal.* Calcd. for C₂₆H₂₁NO₇S (491.51): C, 63.53; H, 4.31; N, 2.85; S, 6.52. Found: C, 63.50; H, 4.34; N, 2.90; S, 6.55.

2-[[[(4-Methylphenyl)sulfonyl]methyl]amino]carbonyl]-1,3-dioxo-2,3-dihydro-1H-indene-2-yl 3-methylbenzoate (4c). White powder, m.p. 213-214 °C (dec), yield 96%. IR (KBr) (ν_{\max} cm⁻¹): 3400 (NH), 1723, 1685, 1600, 1523, 1285, 1146. ¹H NMR (250 MHz, CDCl₃): δ_{H} 2.38 and 2.42 (6H, 2 s, 2 CH₃), 4.71 (2H, d, J = 7.25 Hz, NCH₂), 6.65 (1H, br, NH), 7.26-8.08 (12H, m, arom CH); ¹³C NMR (62.5 MHz, CDCl₃): δ_{C} 21.3 and 21.7 (2 CH₃), 59.8 (NCH₂), 83.7 (C-O), 124.2, 126.4, 127.5, 128.9, 130.0, 130.2, 130.8, 132.9, 135.6, 136.2, 138.9, 141.0 and 145.6 (aromatic carbons), 162.3 (CO of ester), 163.9 (CO of amide), 190.0 (CO of ketone). *Anal.* Calcd. for C₂₆H₂₁NO₇S (491.51): C, 63.53; H, 4.31; N, 2.85; S, 6.52. Found: C, 63.58; H, 4.35; N, 2.81; S, 6.49.

2-[[[(4-Methylphenyl)sulfonyl]methyl]amino]carbonyl]-1,3-dioxo-2,3-dihydro-1H-indene-2-yl 4-bromobenzoate (4d). White powder, m.p. 213-214 °C (dec), yield 95%. IR (KBr) (ν_{\max} cm⁻¹): 3369 (NH), 1731, 1685, 1592, 1508, 1277, 1146. ¹H NMR (250 MHz, CDCl₃): δ_{H} 2.41 (3H, s, CH₃), 4.73 (2H, d, J = 6.75 Hz, NCH₂), 6.70 (1H, br, NH), 7.27-8.08 (12H, m, arom CH); ¹³C NMR (62.5 MHz, CDCl₃): δ_{C} 21.7 (CH₃), 59.9 (NCH₂), 83.9 (C-O), 124.2, 125.4, 128.9, 130.0, 130.2, 131.7, 132.3, 132.9, 136.3, 141.0 and 145.6 (aromatic carbons), 162.1 (CO of

ester), 163.2 (CO of amide), 189.9 (CO of ketone). *Anal.* Calcd. for C₂₅H₁₈BrNO₇S (556.38): C, 53.97; H, 3.26; Br 14.36; N, 2.52, S, 5.76. Found: C, 53.92; H, 3.23; Br, 14.40; N, 2.48; S, 5.78.

2-[[[(4-Methylphenyl)sulfonyl]methyl]amino]carbonyl]-1,3-dioxo-2,3-dihydro-1H-indene-2-yl 3-bromobenzoate (4e). White powder, m.p. 231-232 ° C (dec), yield 97%. IR (KBr) (ν_{\max} cm⁻¹): 3408 (NH), 1723, 1685, 1592, 1523, 1269, 1146. ¹H NMR (250 MHz, CDCl₃): δ_{H} 2.44 (3H, s, CH₃), 4.71 (2H, d, J = 7.00 Hz, NCH₂), 6.84 (1H, br, NH), 7.26-8.30 (12H, m, arom CH); ¹³C NMR (62.5 MHz, CDCl₃): δ_{C} 21.5 (CH₃), 60.6 (NCH₂), 84.2 (C-O), 122.5, 123.8, 128.5, 128.8, 129.5, 129.7, 130.1, 133.5, 133.6, 136.1, 137.4, 140.8 and 144.8 (aromatic carbons), 162.3 (CO of ester), 163.0 (CO of amide), 190.1 (CO of ketone). *Anal.* Calcd. for C₂₅H₁₈BrNO₇S (556.38): C, 53.97; H, 3.26; Br 14.36; N, 2.52, S, 5.76. Found: C, 53.94; H, 3.28; Br, 14.38, N, 2.49; S, 5.81.

Acknowledgements

The authors are thankful to the Zanjan University for partial support of this work.

References

1. Sapi, J.; Laronze, J.-Y. *Arkivoc* **2004**, (vii), 208.
2. Zhu, J.; Bienayme', H. *Multicomponent reactions*; Wiley-VCH: Weinheim, 2005.
3. Ugi, I. *Angew. Chem. Int. Ed.* **1962**, *1*, 8.
4. Hazeri, N.; Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Ziyaadini, M.; Marandi, G.; Khandan-Barani, K.; Bijanzadeh, H. R. *Arkivoc* **2007**, (viii), 34.
5. Dömling, A.; Beck, B.; Herdtweck, E.; Antuch, W.; Oefner, C.; Yehia, N.; Gracia-Marques, A. *Arkivoc* **2007**, (vxii), 99.
6. Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.
7. (a) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53. (b) Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187.
8. Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
9. (a) Passerini, M.; Simone, L. *Gazz. Chim. Ital.* **1921**, *51*, 126. (b) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181.
10. Passerini, M.; Ragni, G. *ibid.* **1931**, *61*, 964.
11. Lieke, W. *Justus Liebigs Ann. Chem.* **1859**, *112*, 316.
12. Gautier, A. *Justus Liebigs Ann. Chem.* **1867**, *142*, 289.
13. Ugi, I. *Isonitrile Chemistry*; Academic Press: New York, 1971.
14. Banfi, L.; Guanti, G.; Riva, R.; Basso, A.; Calcagno, E. *Tetrahedron Lett.* **2002**, *43*, 4067.
15. Neo, A. G.; Delgado, J.; Polo, C.; Marcaccini, S.; Marcos, C. F. *Tetrahedron Lett.* **2005**, *46*, 23.

16. Karimi, A. R.; Rajabi Khorrami, A.; Alimohammadi, Z.; Mohammadi, A. A.; Mohammadizadeh, M. R. *Monats. Chem.* **2006**, *137*, 1079.
17. Banfi, L.; Guanti, G.; Riva, R. *Chem. Commun.* **2000**, 985.
18. Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386.
19. Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267.
20. Hoffmann, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 3337.
21. Achatz, S.; Dömling, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6360.
22. Cristau, P.; Vors, J. P.; Zhu, J. *Tetrahedron Lett.* **2003**, *44*, 5575.
23. Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51.
24. Souldozi, A.; Šlepokura, K.; Lis, T.; Ramazani, A. *Z. Naturforsch.* **2007**, *62b*, 835.
25. Souldozi, A.; Ramazani, A. *Tetrahedron Lett.* **2007**, *48*, 1549.
26. Souldozi, A.; Ramazani, A.; Bouslimani N.; Welter, R. *Tetrahedron Lett.* **2007**, *48*, 2617.
27. Ahmadi, E.; Ramazani, A.; Nekomanesh Haghighi, M. *Tetrahedron Lett.* **2007**, *48*, 6954.
28. Baker, R. H.; Stanonis, D. *J. Am. Chem. Soc.* **1951**, *73*, 699.
29. Ramazani, A.; Kazemizadeh, A. R.; Ahmadi, E.; Noshiranzadeh N.; Souldozi A. *Curr. Org. Chem.* **2008**, *12*, 59.