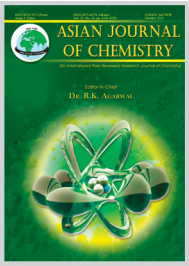
Asian Journal of Chemistry; Vol. 24, No. 8 (2012), 3383-3385

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in



Synthesis of Fluorine-Containing α-Acyloxycarboxamide Derivatives from Indane-1,2,3-trione, Isocyanides and 4-Fluorobenzoic Acid

ALI REZA KAZEMIZADEH* and ALI RAMAZANI

Research Laboratory of MCRs, Department of Chemistry, Zanjan Branch, Islamic Azad University, P.O. Box 49195-467, Zanjan, Iran

*Corresponding author: Fax: +98 241 4261221; Tel: +98 241 4261221; E-mail: alirezakazemizadeh@yahoo.com

(*Received*: 30 June 2011; *Accepted*: 6 March 2012) AJC-11148

Passerini reaction of indane-1,2,3-trione, isocyanides and 4-fluorobenzoic acid proceed at room temperature and the related fluorine-containing α-acyloxycarboxamide derivatives are synthesized in quantitative yields. The reactions are one-pot, single spot and the products were obtained without any purification.

Key Words: Fluorine-containing α-acyloxycarboxamide, Multicomponent reaction, Passerini reaction, Indane-1,2,3-trione, Isocyanide, 4-Fluorobenzoic acid.

INTRODUCTION

In recent years, combinatorial chemistry has emerged as a powerful tool for rapid identification and optimization of new lead compounds in drug discovery. In this field, the multi-component reaction (MCR) has been used very efficiently to generate chemical diversity in a few reaction steps[1]. A multi-component reaction is a process in which three or more easily accessible components are combined together in a single reaction vessel to produce a final product displaying features of all inputs and thus offers greater possibilities for molecular diversity per step with a minimum of synthetic time and effort. A multicomponent reaction is a domino process, a sequence of elementary steps according to a program in which subsequent transformations are determined by the functionalities produced in the previous step. A large and important class of multicomponent reactions are the isocyanide-based multicomponent reactions, that was introduced in 1921 by Passerini[2]. 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[3]. Today most isocyanide-based multicomponent reaction 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[4-8]. Passerini reactions involve an oxo-component, an isocyanide and a nucleophile and produce an α-acyloxycarboxamide in a single step. The Passerini reactions are beginning to find utility in synthetic and medicinal chemistry[9]. In continuation of our recent interest to isocyanide chemistry[10-17], we report the Passerini multi-component reaction between indane-1,2,3-trione (**1**), isocyanides (**2**) and 4-fluorobenzoic acid (**3**).

EXPERIMENTAL

Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Jasco FT-IR 6300 spectrometer. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution and TMS as internal standard) with a BRUKER DRX-250 AVANCE spectrometer at 250.0 and 62.5 MHz, respectively. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O-rapid analyzer. The results agreed favourably with the calculated values.

To a magnetically stirred solution of indane-1,2,3-trione (**1**) (0.2 mmol) and 4-fluorobenzoic acid (**3**) (0.2 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise a solution of isocyanides (**2**) (0.2 mmol) in CH_2Cl_2 (2 mL) at room temperature over 10 min. The mixture was stirred for 1 h for **4a-c** and 72 h for **4d** at room temperature. The solvent was removed under reduced pressure and pure products **(4a-d)** were obtained. The characterization data of the compounds are given below.

2-[(Cyclohexylamino)carbonyl]-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl 4-fluorobenzoate (4a): Light yellow powder: yield 95 %; m.p. 212.4-214.3 ºC (dec); IR (KBr, ν_{max}, cm^{-1}): 3320, 2935, 1725, 1647, 1528, 1275; ^1H NMR (250 MHz, $CDCl_3$): δ 1.18-1.97 (10H, m, 5 CH_2 of cyclohexyl), 3.76 (1H, m, N-CH), 6.51(1H, d, *J* = 7.8 Hz, NH), 7.14-8.08 (8H, m, arom CH); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 24.6, 25.3, 32.7 (CH_2 of cyclohexyl), 49.1 (NCH), 84.2 (C-O), 116.2 (d, $^2J_{CF}$ = 22.5 Hz), 123.3 (d, $^4J_{CF}$ = 3.1 Hz), 124.1, 132.9 (d, $^3J_{CF}$ = 10.0 Hz), 136.1, 141.5, 166.3 (d, $^1J_{CF}$ = 218.0 Hz) (aromatic carbons), 161.4 (CO of ester), 162.9 (CO of amide), 191.5 (CO of ketone); ^{19}F NMR (470 MHz, $CDCl_3$): δ -102.6; MS (EI, 70 eV): m/z (%) = 409 $[M]^+$ (4 %), 311 $[M\text{-}NHR]^+$ (1), 123 $[4\text{-}FC_6H_4CO]^+$ (100), 104 $[C_6H_4CO]^+$ (4), 95 $[C_6H_4F]^+$ (13), 83 $[C_6H_{11}]^+$ (3), 55 (6), 41 (4); Anal. calcd. for $C_{23}H_{20}NO_5F$ (409.42): C, 67.48; H, 4.92; N, 3.42. Found: C, 67.56; H, 4.97; N, 3.38.

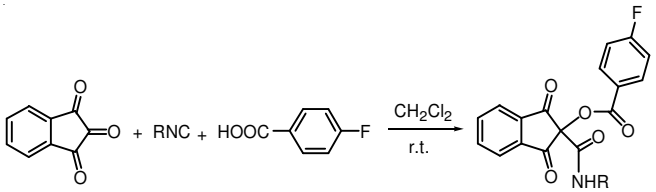
2-[(*Tert*-butylamino)carbonyl]-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl 4-fluorobenzoate (4b): Light yellow powder: yield 98 %; m.p. 210.5-211.3 ºC (dec); IR (KBr, ν_{max}, cm^{-1}): 3374, 3098, 2982, 1730, 1677, 1536, 1287; ^1H NMR (250 MHz, $CDCl_3$): δ 1.39 (9H, s, *t*-Bu), 6.46 (1H, s, NH), 7.13-8.07 (8H, m, arom CH); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 28.5 (CMe_3); 52.7 (N-C); 84.2 (C-O); 116.2 (d, $^2J_{CF}$ = 21.9 Hz), 123.3 (d, $^4J_{CF}$ = 3.8 Hz), 124.0, 132.8 (d, $^3J_{CF}$ = 9.4 Hz), 136.1, 141.6, 166.5 (d, $^1J_{CF}$ = 258.6 Hz)(aromatic carbons), 161.5 (CO of ester), 162.8 (CO of amide), 191.7 (CO of ketone); ^{19}F NMR (470 MHz, $CDCl_3$): δ -102.6; MS (EI, 70 eV): m/z (%) = 383 $[M]^+$ (3 %), 311 $[M\text{-}NHR]^+$ (4), 123 $[4\text{-}FC_6H_4CO]^+$ (100), 104 $[C_6H_4CO]^+$ (4), 95 $[C_6H_4F]^+$ (13), 76 (4), 57 $[t\text{-}Bu]^+$ (10), 41 (5); Anal. calcd. for $C_{21}H_{18}NO_5F$ (383.38): C, 65.79; H, 4.73; N, 3.65. Found: C, 65.69; H, 4.78; N, 3.69.

1,3-Dioxo-2-{[(1,1,3,3-tetramethylbutyl)amino]carbonyl}-2,3-dihydro-1*H*-inden-2-yl 4-fluorobenzoate (4c): Light yellow powder: yield 94 %; m.p. 207.5-209.5 ºC (dec); IR (KBr, ν_{max}, cm^{-1}): 3382, 2964, 1730, 1678, 1525, 1289 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.06 (9H, s, CMe_3), 1.46 (6H, s, CMe_2), 1.75 (2H, s, CH_2), 6.52 (1H, s, NH), 7.14-8.08 (8H, m, arom CH); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 28.9 (2Me), 31.5 (CMe_3), 31.7 (CMe_3), 51.9 (CH_2), 56.7 (N-C), 84.4 (C-O), 116.2 (d, $^2J_{CF}$ = 22.2 Hz), 123.4 (d, $^4J_{CF}$ = 3.8 Hz), 124.0, 132.8 (d, $^3J_{CF}$ = 9.4 Hz), 136.1, 141.6, 166.6 (d, $^1J_{CF}$ = 256.2 Hz) (aromatic carbons), 161.1 (CO of ester), 162.9 (CO of amide), 191.6 (CO of ketone); ^{19}F NMR (470 MHz, $CDCl_3$): δ -102.7 ; MS (EI, 70 eV): m/z (%) = 440 $[M+1]^+$ (2 %), 368 (16), 311 $[M\text{-}NHR]^+$ (53), 123 $[4\text{-}FC_6H_4CO]^+$ (100), 104 $[C_6H_4CO]^+$ (7), 95 $[C_6H_4F]^+$ (16), 76 (4), 57 (21), 41 (8); Anal. calcd. for $C_{25}H_{26}NO_5F$ (439.49): C, 68.32; H, 5.96; N, 3.19. Found: C, 68.24; H, 5.98; N, 3.26.

2-[({[(4-Methylphenyl)sulfonyl]methyl}amino)carbonyl]-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl 4-fluorobenzoate (4d): White powder: yield 92 %; m.p. 213.8-215.3 ºC (dec) ; IR (KBr, ν_{max}, cm^{-1}): 3346, 1729, 1686, 1508, 1272; ^1H NMR (250 MHz, $CDCl_3$): δ 2.37 (3H, s, CH_3), 4.72 (2H, d, *J* = 6.50 Hz, NCH_2), 6.76 (1H, br, NH), 7.10-8.09 (12H, m, arom CH); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 21.7 (CH_3), 59.9 (NCH_2), 83.9 (C-O), 116.2 (d, $^2J_{CF}$ = 22.2 Hz), 122.8 (d, $^4J_{CF}$ = 3.8 Hz), 124.2, 128.9, 130.2, 133.0 (d, $^3J_{CF}$ = 9.1 Hz), 133.2, 136.3, 141.0, 145.6, 166.7 (d, $^1J_{CF}$ = 255.8 Hz) (aromatic carbons), 162.2 (CO of ester), 162.8 (CO of amide), 190.0 (CO of ketone); ^{19}F NMR (470 MHz, $CDCl_3$): δ -102.1; MS (EI, 70 eV): m/z (%) = 312 (37), 311$[M\text{-}NHR]^+$ (49), 123 $[4\text{-}FC_6H_4CO]^+$ (100), 95 $[C_6H_4F]^+$ (19); Anal. calcd. for $C_{25}H_{18}NO_7FS$ (495.49): C, 60.60; H, 3.66, N, 2.83. Found: C, 60.53; H, 3.70; N, 2.78.

RESULTS AND DISCUSSION

The indane-1,2,3-trione (**1**), isocyanides (**2**) and 4-fluorobenzoic acid (**3**) in dichloromethane react together in a 1:1:1 ratio at room temperature to produce fluorine-containing α-acyloxycarboxamide derivatives (**4a-d**) (**Scheme-I**). The reaction proceeds smoothly and cleanly under mild conditions and no side reactions were observed. The structures of the products were deduced from their IR, ^1H NMR, ^{13}C NMR, ^{19}F NMR, mass spectrometry and elemental analyses. For example the ^1H NMR spectrum of **4a** exhibited distinct signals arising from cyclohexyl (δ_H = 1.18-1.97 ppm), NCH (3.76 ppm), NH (6.51 ppm) and aromatic CH (7.14-8.08). The ^{13}C NMR spectrum of **4a** showed 15 distinct resonances arising from CH_2 of cyclohexyl (24.6, 25.3, 32.7 ppm), NCH (49.1 ppm), C-O (84.2 ppm), aromatic carbons (116.2, 123.3, 124.1, 132.9, 136.1, 141.5 and 166.3 ppm), CO of ester (161.4 ppm), CO of amide (162. 9 ppm) and CO of ketone (191.5 ppm). The IR spectrum of **4a** showed an NH absorption at 3320 cm^{-1}. The mass spectra of the products displayed molecular ion peaks and the fragmentation patterns of them at the appropriate m/z values.



(1) (2) (3) (4a-d)

Scheme-I: Passerini multicomponent reaction of indane-1,2,3-trione (Table-1)

TABLE-1
SYNTHESIS OF FLUORINE-CONTAINING α-ACYLOXYCARBOXAMIDE DERIVATIVES (**4a-d**) (**SCHEME-I**)

Products	R	Yield (%)
4a	Cyclohexyl	95
4b	*t*-Bu	98
4c	1,1,3,3-Tetramethylbutyl	94
4d	Tosylmethyl	92

Conclusion

It is believed that the reported method offers a mild, simple, efficient and one-pot synthetic method for the preparation of fluorine-containing α-acyloxycarboxamide derivatives from Passerini multicomponent reaction of indane-1,2,3-trione. The reactions are single spot and 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.

REFERENCES

1. R.W. Armstrong, A.P. Combs, P.A. Tempest, S.D. Brown and S.D. Keating, *Acc. Chem. Res.*, **29**, 123 (1996).
2. (a) M. Passerini, *Gazz. Chim. Ital.*, **51**, 126 (1921); (b) M. Passerini, *Gazz. Chim. Ital.*, **51**, 181 (1921).
3. (a) I. Ugi, B. Werner and A. Dömling, *Molecules*, **8**, 53 (2003); (b) I. Ugi, *Pure Appl. Chem.*, **73**, 187 (2001).
4. L. Banfi, G. Guanti, R. Riva, A. Basso and E. Calcagno, *Tetrahedron Lett.*, **43**, 4067 (2002).
5. A.R. Karimi, A.R. Khorrami, Z. Alimohammadi, A.A. Mohammadi and M.R. Mohammadizadeh, *Monatsh. Chem.*, **137**, 1079 (2006).
6. A.G. Neo, J. Delgado, C. Polo, S. Marcaccini and C.F. Marcos, *Tetrahedron Lett.*, **46**, 23 (2005).
7. I. Ugi, R. Meyr, U. Fetzer and C. Steinbrückner, *Angew. Chem.*, **71**, 386 (1959).
8. P. Cristau, J.P. Vors and J. Zhu, *Tetrahedron Lett.*, **44**, 5575 (2003).
9. C. Hulme and V. Gore, *Curr. Med. Chem.*, **10**, 51 (2003).
10. A.R. Kazemizadeh and A. Ramazani, *Arkivoc,* 159 (2008).
11. A.R. Kazemizadeh and A. Ramazani, *J. Braz. Chem. Soc.*, **20**, 309 (2009).
12. A. Souldozi, A. Ramazani, N. Bouslimani and R. Welter, *Tetrahedron Lett.*, **48**, 2617 (2007).
13. E. Ahmadi, A. Ramazani and M.N. Haghighi, *Tetrahedron Lett.*, **48**, 6954 (2007).
14. S.M. Shoaei, A.R. Kazemizadeh and A. Ramazani, *Chinese J. Struct. Chem.*, **30**, 568 (2011).
15. (a) A. Ramazani, N. Shajari, A. Mahyari and Y. Ahmadi, *Mol. Diversity*, **15**, 521 (2011); (b) A. Ramazani, M. Rouhani, A. Rezaei, N. Shajari and A. Souldozi, *Helv. Chim. Acta*, **94**, 282 (2011).
16. A. Ramazani and A. Mahyari, *Helv. Chim. Acta*, **93**, 2203 (2010); (b) A. Ramazani, A. Rezaei, A.T. Mahyari, M. Rouhani and M. Khoobi, *Helv. Chim. Acta*, **93**, 2033 (2010); (c) A. Ramazani and A. Rezaei, *Org. Lett.*, **12**, 2852 (2010).
17. A.R. Kazemizadeh and A. Ramazani, *Curr. Org. Chem.*, **16**, 418 (2012).