Tetrahedron Letters 52 (2011) 5297–5300

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Lewis acid mediated diastereoselective synthesis of fused fluorinated spiroketal as potential biologically active compounds

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ARTICLE INFO

Article history:
Received 5 April 2011
Revised 27 July 2011
Accepted 1 August 2011
Available online 17 August 2011

ABSTRACT

A series of substituted dibenzalacetones prepared using standard procedures were condensed with 5-methyl, 5-phenyl, and 5-trifluoromethyl-1,3-cyclohexanediones respectively, in toluene containing BF_3·OEt as the Lewis acid catalyst. The reaction was found to be highly diastereoselective (*dr*, 9:1). The resulting spiroketals **1a–r** were formed in moderate to good yields. In addition, a synthetically and biologically useful by-product identified as chromenone **7** was observed.

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1. Introduction

The increased interest in fluorinated pharmaceutical and medicinal agents has led to the development of novel agents and new strategies in drug discovery and development. The synthesis of fluorinated compounds and their derivatives provide unlimited potential for creating novel biologically active lead compounds for use as therapeutics. The selective introduction of one or more fluorine atoms into specific positions in an organic molecule changes the molecules' physicochemical properties, including its stability, lipophilicity and bioavailability. The above behavior could be explained by the unique physical, chemical, and biological properties of fluorine.

The carbon–fluorine bond is generally stronger than the carbon–hydrogen bond. Thus many fluorine-containing compounds are stable and often avoid undesirable metabolic transformations. In addition, the increased lipophilicity often leads to ease of absorption and transportation of molecules within biological membranes, thereby improving their overall pharmacokinetic and pharmacodynamic properties. However, prediction of sites in a molecule at which fluorine substitution will result in optimal desired effects is still challenging. Therefore, the synthesis of fluorinated derivatives provides a diverse array of building blocks and chemical substructures for novel processes. An illustrative example of the effect of fluorine is the 1,2,5-thiadiazole-based structure with muscarinic activity shown below in Figure 1. The replacement of hydrogen atoms on an oxidizable site by fluorine atoms protects the molecule from hydroxylation processes mediated by P450 cytochrome enzymes.[1]

Spiroketals are secondary metabolites found in numerous natural products. Many simple spiroketals exhibit a range of biological activities.[2]

Research on their synthesis and chemical reactivity has attracted considerable attention in recent years, due to their increasing pharmacological importance.[3] In continuation of our interest in the synthesis of fluorinated compounds as potential biologically active molecules,[4,5] herein, we report a diastereoselective synthesis of fused fluorinated and non-fluorinated spiroketals **1a–r** (Table 3).

2. Results and discussion

The synthesis of spiroketal **1** was inspired from previous work by Giasuddin and co-workers, where dimedone and diarylideneacetones were refluxed in a mixture of toluene and *n*-heptane in the presence of $ZnCl_2$ to give spiroketal **4** in 70–76% yield as a single diastereomer after separation (Scheme 1).[3] Fluorinated cyclic β-diketone **8** was obtained utilizing a known procedure reported by our group,[6] while the formation of diarylideneacetones **3a–k** was achieved (Table 1) using standard procedures.[7] The *trans–trans* configuration of the dienes **3a–k** was confirmed by ^{1}H NMR (coupling constant, J = 12.8 Hz) as previously reported.[7,8] Higher yield of dibenzalacetones **3a–k** and faster reactions were observed, when the starting aldehyde contained less powerful electron-withdrawing groups (Table 1, entries 1–6).

In an attempt to reproduce the previous work reported by Giasuddin and co-workers,[3] dimedone **2** (2.2 equiv), diarylideneacetone **3a** (1.0 equiv) in toluene/*n*-heptane in the presence of 20 mol % of $ZnCl_2$ were refluxed for 16 h. The desired spiroketal **4** was obtained as a mixture of diastereomers in <30% yield, along with chromenone **7** as a by-product (Scheme 2). The formation of the by-product **7** was not reported by Giasuddin and co-workers.[3]

These unexpected results prompted us to further investigate other Lewis acids and reaction conditions (Table 2). After surveying a variety of reaction conditions, we found that increasing the equivalent of diketone **2** (2.2–2.5 equiv) eliminated the formation of the by-product chromenone **7**.

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0040-4039/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2011.08.004

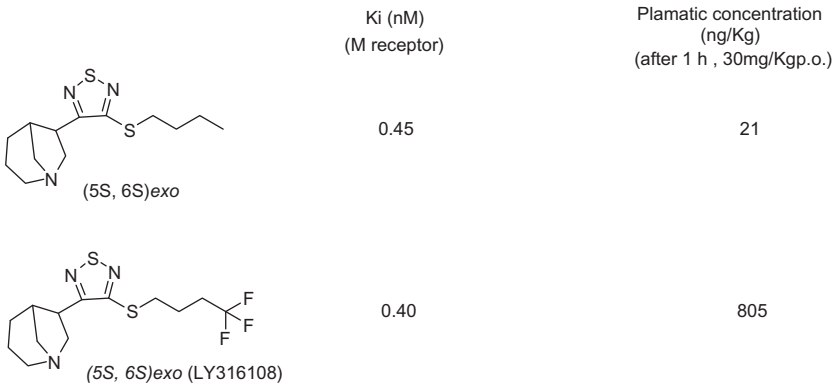
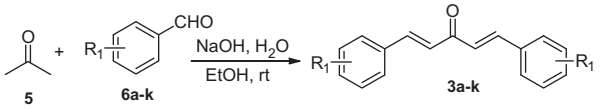


Figure 1. Protective effects of fluorine substitution on oxidative metabolisms. Effect of fluorination on plasmatic concentration of the muscarinic analgesic LY316108.[1]

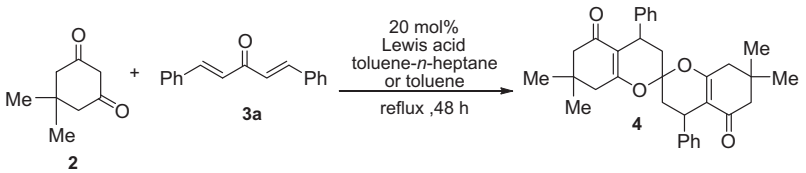
Table 1
Synthesis of dibenzalacetone derivatives **3a–k**



Entry[a]	R_1	5	6	Yield[b] (%)
1	H	**a**	**a**	94
2	4-F	**b**	**b**	90
3	4-CN	**c**	**c**	80
4	4-OMe	**d**	**d**	89
5	6-Br	**e**	**e**	85
6	4-Cl	**f**	**f**	83
7	4-CF_3	**g**	**g**	75
8	3-CF_3	**h**	**h**	70
9	3,5-CF_3	**i**	**i**	65
10	4-OCF_3	**j**	**j**	60
11	3,4-(OCH_{20})	**k**	**k**	85

[a] All reactions were carried out in 95% EtOH and (2.5 M) NaOH at room temperature.
[b] Yields refer to isolated pure products. All products were characterized by ^{1}H NMR spectra.

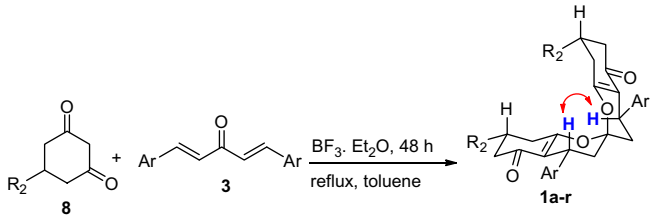
Table 2
Effect of lewis acid



Entry	Lewis acid	Conv[b] (%)	*dr*[a]
1	$ZnCl_2$	49	1:1
2	$SnCl_4$	48	3:2
3	TFA	45	1:1
4	$AlCl_3$	45	3:2
5	$TiCl_4$	55	3:1
6	$BF_3{\cdot}OEt_2$	87	7:1
7	TsOH/AcOH	43	1:1
8	$EtAlCl_2$	44	1:1
9[c]	$BF_3{\cdot}OEt_2$	94	9:1

[a] Diastereomeric ratios were measured using ^{1}H NMR.
[b] Conversion determined by LC/MS and ^{1}H NMR.
[c] Reaction was also carried out in toluene.

Table 3
Synthesis of spiroketal derivatives **1a–r**



Enrty[a]	R_2	Ar	Product	*dr*[a]	Yield[b] (%)
1	CH_3	C_6H_5–	**1a**	9:1	90
2	CF_3	C_6H_5–	**1b**	9:1	89
3	Ph	C_6H_5–	**1c**	9:1	92
4	CH_3	3,4-(OCH_{20})–C_6H_3–	**1d**	9:2	86
5	CH_3	3,4-(OCH_{20})–C_6H_3–	**1e**	9:1	87
6	Ph	3,4-(OCH_{20})–C_6H_3–	**1f**	9:1	89
7	CH3	4-F–C_6H_4–	**1g**	9:1	74
8	CF3	4-F–C_6H_4–	**1h**	9:2	71
9	Ph	4-F–C_6H_4–	**1i**	9:2	76
10	CH3	4-Cl–C_6H_4–	**1j**	9:2	73
11	CF3	4-Cl–C_6H_4–	**1k**	9:1	70
12	Ph	4-Cl–C_6H_4–	**11**	9:1	72
13	CH3	4-OCF_3–C_6H_4–	**1m**	9:2	85
14	CF3	4-OCF_3–C_6H_4–	**1n**	9:1	88
15	Ph	4-OCF_3–C_6H_4–	**1o**	9:2	87
16	CH3	4-OMe–C_6H_4–	**1p**	9:1	85
17	CF3	4-OMe–C_6H_4–	**1q**	9:2	80
18	Ph	4-OMe–C_6H_4–	**1r**	9:1	90

[a] Diastereomeric ratios were measured using ^{1}H NMR.
[b] Isolated yield.

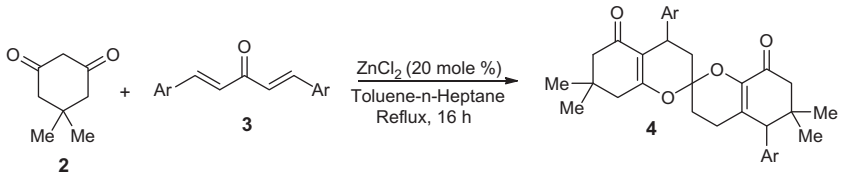
Table 2 summarizes the result obtained utilizing various Lewis acids, where $BF_3{\cdot}OEt_2$ gave good a diastereoselectivity ratio of 7:1 and 87% conversion (Table 2, entry 6). Using toluene as the solvent (entries1–9), $BF_3{\cdot}OEt_2$, gave better selectivity and conversion (9:1 *dr* and 94% conversion, Table 2, entry 9). $TiCl_4$ was also found to give moderate conversion in 3:1 *dr*. The origin of high diastereoselectivity observed using $BF_3{\cdot}OEt_2$ (Table 2, entry 6) is unclear but it is likely due to its ability to coordinate tightly with the carbonyl oxygen of the substituted Michael acceptor (dibenzylacetone **3a**).

It is noteworthy to mention that extending the reaction time to 48 h plays a significant role, which could be due to equilibration of the minor diastereomer to the more stable major diastereomer.[9] Also, the solvent effect on the conversion and selectivity of the reaction was evaluated using different solvents. For this study, $BF_3{\cdot}OEt_2$ was maintained as the Lewis acid under 48 h reflux and using various solvents (THF, DMF, methanol, DMSO, pyridine, toluene, 2-(methoxy)ethyl-ether, 1,2-dimethoxyethane, *n*-heptane, dichloromethane). Clearly, toluene is the optimal solvent to facilitate spiroketalization with 9:1 diastereoselectivity (Table 2, entry 9) and greater than 94% conversion. No product was formed when the following solvents: DMSO, DMF, MeOH and DCE were used. Since the reaction is facilitated by loss of water, the azeotropic effect of toluene appears to explain the result obtained.

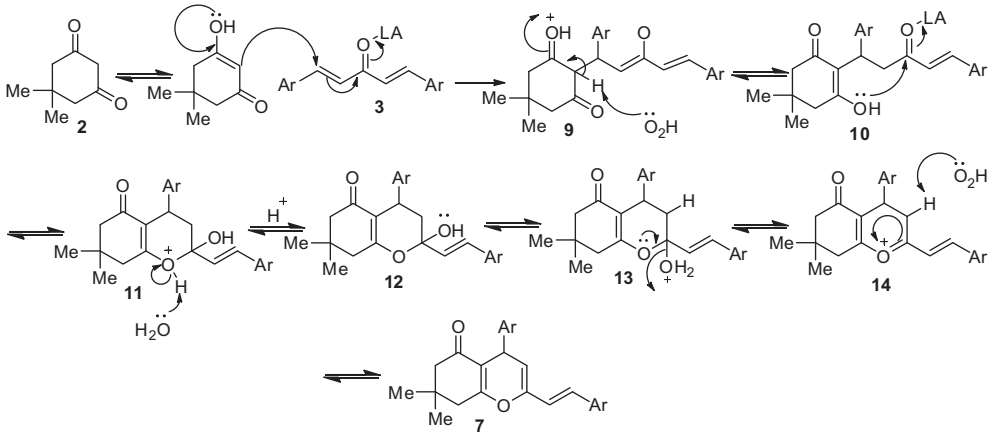
Next, we employed the observed optimal catalytic condition using differently substituted dibenzalacetone **3** and various 5-substituted diketones **8**, as shown in Table 3.

The nature of the groups in the 5 position of the cyclic β-diketones **8**, did not affect the reactivity or selectivity. As shown in Table 3, various derivatives of the spiroketal were obtained in 70–92% yield. It was observed that the electron withdrawing substitution on the dibenzalacetone (entries 7–12) tends to give lower but moderate yields (70–76%), while electron donating substitution on the dibenzalacetone (entries 4–6, and 13–18) gave excellent yields (80–92%). In all cases, high diastereomeric ratios in which both pendant aryl groups are in pseudoequatorial positions were obtained (Table 3). Though conformational studies showed that three possible diastereomers may be possible for spiroketal **1**, two diastereomers were observed by ^{1}H NMR in the course of our studies and we only isolated the major diastereomer, which is the diequatorial.

The plausible mechanism for the formation of the observed chromenone **7** is shown in Scheme 2. Further studies on the scope



Scheme 1. Synthesis of fused spiroketal **4**.



Scheme 2. Proposed mechanism for the formation of chromenone **7**.

and synthetic applications of chromenone **7** are in progress and will be described in due course.

In conclusion, a simple and efficient method for the diastereoselective synthesis of fused fluorinated and non-fluorinated spiroketals has been developed. Furthermore, the biological evaluation of the fluorinated spiroketals and chromenones derivatives is underway, and results will be reported in due course.

Acknowledgment

We are thankful to the U.S. Department of Education Title III Grant, Tennessee State University, for the financial support.

References and notes

1. Edwards, P. N. Principles and Commercial Applications. In *Organofluorine Chemistry*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: N-Y, 1994; pp 505–509.
2. Raju, B. R.; Saikia, A. K. *Molecules* **2008**, *13*, 1942–2038.
3. Giasuddin, A. M.; Syeda, A. A.; Khabir Uddin, Md.; Taifur Rahman, Md. *Tetrahedron Lett.* **2005**, *46*, 8217–8220.
4. Agbaje, C. O.; Fadeyi, O. O.; Adamson, F. S.; Myles, E. L.; Okoro, C. O. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 989–992.
5. Fadeyi, O. O.; Adamson, S. T.; Myles, E. L.; Okoro, C. O. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4172–4176.
6. Fadeyi, O. O.; Okoro, C. O. *Tetrahedron Lett.* **2008**, *49*, 4725–4727.
7. Organic Chemistry laboratory textbooks and online editions, Dibenzalacetone by aldo condensation.
8. Satya, P.; Monika Gupta *Synth. Commun.* **2005**, *35*, 213–222.
9. *General procedure for the synthesis of fused spiroketal* (***8a–r***)
A mixture of diketone **7** (2.5 mmol), trans–trans-dibenzalacetone **3a–k** (1 mmol) and 20 mol % $BF_3{\cdot}Et_2O$ (0.028 g, 0.2 mmol) in toluene (30 mL) was refluxed for 48 h under Dean–Stark trap. The progress of the reaction was monitored by TLC and GC/MS. After cooling the reaction mixture was reduced in volume and neutralized with saturated aqueous $NaHCO_3$ solution and then extracted with ether (5 × 20 mL). The combined ether extracts was dried over anhydrous sodium sulfate and evaporated in vacuo. The crude product was recrystallized from methanol to give **1a–r**.
7,7′-Dimethyl-4,4′-diphenyl-3,3′,4,4′,7,7′,8,8′-octahydro-2,2′-spirobi[chromene]-5,5′(6H,6′H)-dione ***1a***: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.81–3.90 (dd, 2H, J = 12.5, 7.3 Hz), 3.78–3.80 (d, 2H), 7.21–7.41 (m, 10H), 1.21–1.40 (s, 12H), 2.55–2.65 (m, 2H), 2.67–2.80 (m, 2H), 3.41–3.55 (m, 2H), 1.10–1.51 (dd, 2H, J = 8.0 Hz), 1.22–1.25 (dd, 2H, J = 8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 21.2, 103.4, 45.6, 31.8, 196.8, 47.4, 29.8, 40.1, 164.2, 111.3, 126.8, 128.8, 127.9, 141.7. LC/MS m/z; 597 $(M+H)^+$.
4,4′-Diphenyl-7,7′-bis(trifluoromethyl)-3,3′,4,4′,7,7′,8,8′-octahydro-2,2′-spirobi[chromene]-5,5′(6H,6′H)-dione ***1b***: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.01–4.04 (dd, 2H, J = 12.4, 7.3 Hz), 3.47–3.50 (m, 2H), 7.05–7.42 (m, 10H), 2.85–2.93 (m, 2H), 2.67–2.76 (m, 4H), 2.53–2.65 (m, 2H), 2.35–2.40 (ddd, 2H, J = 2H, J = 4.0, 8.0, 16.0 Hz), 1.81–1.89 (ddd, 2H, J = 2H, J = 4.0, 8.0, 16.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 140.7, 103.4, 45.6, 31.8, 196.8, 28.2, 30.1, 17.1, 164.2, 111.3, 126.8, 128.8, 127.9, 141.7. LC/MS m/z; 593 $(M+Na)^+$.
4,4′,7,7′-Tetraphenyl-3,3′,4,4′,7,7′,8,8′-octahydro-2,2′-spirobi[chromene]-5,5′(6H,6′H)-dione ***1c***: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.93–2.98 (dd, 2H, J = 12.5, 7.3 Hz), 3.12–3.35 (m, 4H), 7.22–7.35 (m, 20H), 3.42–3.56 (m, 2H), 2.73–2.82 (m, 2H), 2.47–2.61 (m, 2H), 1.78-1.85 (ddd, 2H, J = 4.0, 8.0, 16.0 Hz), 2.32–2.40 (ddd, 2H, J = 4.0, 8.0, 16.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 103.4, 45.6, 31.8, 196.8, 28.2, 30.1, 20.7, 164.2, 111.3, 126.8, 128.8, 127.9, 141.7, 126.2, 140.9. LC/MS m/z; 594 $(M+H)^+$.