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A high speed parallel synthesis of 1,2-diaryl-1-ethanones via a clean-chemistry C–C bond formation reaction☆

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Abstract—In this report, we describe the parallel as well as conventional synthesis of 1,2-diaryl-1-ethanones via environmentally benign acylation of arenes with in situ generated arylacetyl trifluoroacetates. A wide variety of arylacetic acids **I** participated in trifluoroacetic anhydride/ phosphoric acid mediated C–C bond formation reaction when reacted with arenes of type **II** to give 1,2-diaryl-1-ethanones **III** in good to excellent yield. Under the solvent-free conditions these chemical transformations that normally require longer reaction time can be performed within minutes in good yield.

1. Introduction

1,2-Diaryl-1-ethanones are versatile intermediates[1] for the synthesis of pavine, isopavine and protoberberine groups of alkaloids,[1a] as well as valuable synthons of various bioactive molecules[1c,d] in the field of new drug discovery. This is exemplified by the development of several pyridinyloxazoles as CSBP (p38) kinase inhibitors,[2] 2,4,5-triarylimidazole as IL-1 biosynthesis inhibitors[3a] or acetylene analogues[3b] and estrogen receptor-β potency-selective ligands. They are also useful as potent and selective inhibitors of catechol-*O*-methyltransferase.[4] A member of this class BIA 3-202, is currently under clinical development for the treatment of Parkinson's disease. 1,2-Diaryl-1-ethanones have recently attracted attention due to their usefulness as synthetic templates in the development of selective COX-2 inhibitors[5,6] such as Valdecoxib,[5b] DuP 697[6a] (Fig. 1) etc.

The COX-2 inhibitors are known to be useful for the treatment of inflammation and other related diseases with reduced gastrointestinal side effects, when compared to traditional NSAIDs (non-steroidal anti-inflammatory drugs). In connection with our work on the development of cyclooxygenase (COX-2) inhibitors,[7] we planned to synthesize various heterocycles with a central ring of the 1,2-diaryl-heterocycle class.[7,8] Therefore, we needed a wide variety of appropriately functionalized 1,2-diaryl-1-ethanones **III** (Fig. 2, Ar_1 and Ar_2 represents diverse aryl groups). Due to their enormous importance, especially in pharmaceutical research, several methodologies have been developed by researchers from academia and industry for the synthesis of 1,2-diaryl-1-ethanones.[9] Among the methods available in the literature for the synthesis of **III**, the simplest involves Friedel–Crafts acylation[6b] of arenes using arylacetyl chloride or acid. This method involves the use of stoichiometric amounts of $AlCl_3$ or $ZnCl_2$–$POCl_3$

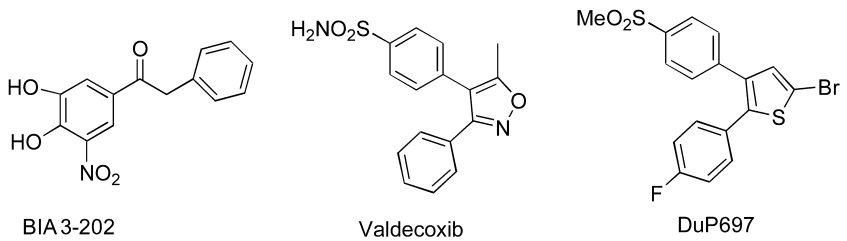

Figure 1. Structure of BIA 3-202 and some COX-2 selective inhibitors.

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Keywords: 1,2-diaryl-1-ethanone; trifluoroacetic anhydride; phosphoric acid; acylation.

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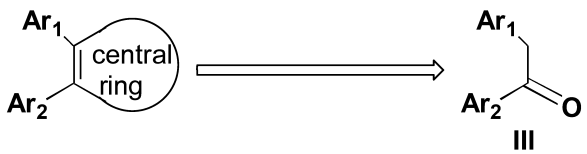


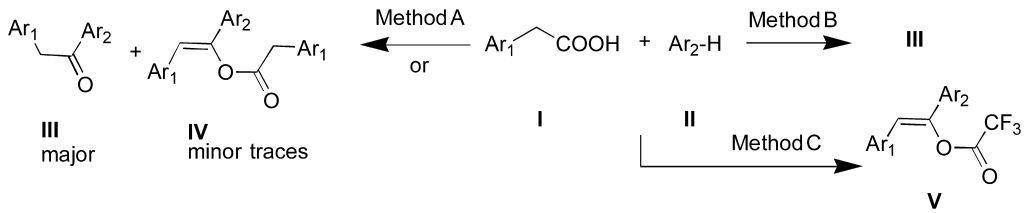
Figure 2. Synthetic strategy for the development of new COX-2 inhibitor.

mixture, which leads to the formation of environmentally harmful gaseous HCl, especially when applied to large-scale synthesis. Non-availability of starting material is another major drawback of this protocol, as in most cases, preparation of the arylacetyl chloride is cumbersome due to their moisture-sensitive nature and tendency to decompose. Use of other reagents such as $BF_3{\cdot}Et_2O$ or CF_3SO_3H in a modified Friedel–Crafts acylation processes has been examined and reported to be inefficient for the synthesis of **III**.[9b,d] To overcome all these difficulties we focused our attention on the development of an alternative method that could be utilized for the straightforward preparation of **III**.

2. Results and discussion

The use of acyl trifluoroacetate,[10] generated in situ from a carboxylic acid and trifluoroacetic anhydride (TFAA), for aromatic acylation has been reported very recently.[11] This method has been viewed as a useful alternative, especially for large scale preparation, to the Friedel–Crafts acylation process. Surprisingly, despite its application for the synthesis of a variety of aromatic ketones,[11] use of this methodology for the synthesis of **III** remained undisclosed. We therefore, assayed the applicability and scope of this protocol for the synthesis of 1,2-diaryl-1-ethanones of our interest. Accordingly, when arylacetic acids (**I**) were treated with 3 equiv. of arene (**II**) in a solvent such as acetonitrile in the presence of 85% phosphoric acid and excess trifluoroacetic anhydride at 50°C for 30–180 min, 1,2-diaryl-1-ethanones (**III**) were obtained as the major product in good to excellent yields (Method A, Scheme 1). However, we have observed that either **III** or the corresponding enolester of trifluoroacetate (**V**) was formed as the exclusive product when the reaction was performed at 25°C for 1 min in the absence of solvent (Methods B and C, Scheme 1). Here, in this report, we disclose our preliminary findings on a simple and rapid entry to 1,2-diaryl-1-ethanones from readily available starting materials using parallel synthesis techniques. Results of our acylation reaction are summarized in Table 1.

As can be seen from Table 1 the solvent free acylation reaction (Scheme 1, Method B) tolerated a variety of substituents on Ar_2. A substituent like the methoxy or methylsulfanyl group was found to be highly effective (entries 1, 2, 5 and 7), compared to weak electron donating groups such as ethyl or methyl (entries 4 and 6). Interestingly, only mono acylation was observed in the case of biphenyl (entry 3). The molar ratio of reactants, trifluoroacetic anhydride (TFAA) and phosphoric acid was optimized to achieve maximum yield and was found to be a 1:1.2:1.2:4 ratio of **I**, **II**, H_3PO_4 and TFAA. The use of excess TFAA (6 equiv.) led to the formation of the enol trifluoroacetate ester **V** (**9** and **10**) as the exclusive product (Scheme 2). This could be converted to the corresponding ketone **III** (**2** and **7**, Scheme 2) in methanol in the presence of K_2CO_3 in high yield. The acylation reaction was carried out at 25°C for 1 min and was found to be vigorous and exothermic. Any increase in the reaction temperature led to the generation of dark colored unidentified material. The acylation reaction, as well as yield of products was not



Scheme 1. *Reagents and conditions*: Method A: H_3PO_4, $(CF_3CO)_2O$, acetonitrile, 50°C, 30–180 min; Method B: H_3PO_4, $(CF_3CO)_2O$, 25°C, 1 min; Method C: H_3PO_4, $(CF_3CO)_2O$ (excess), 25°C, 0.5 min.

Table 1. Synthesis of 1,2-diaryl-1-ethanones (**III**) via acylation of arenes (**II**) with arylacetic acids (**I**)

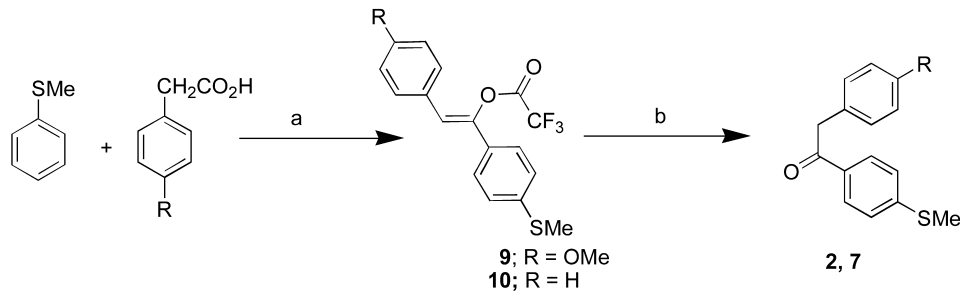
Entry no.	I Ar_1	II Ar_2–H	Compound no.[a]	Yield (%)[b] **III**		
				Method B	Method A	Parallel synthesis (Method B)
1	Phenyl	2-Methylanisole	**1**	91	–	90
2	4-Methoxyphenyl	Thioanisole	**2**	97	92[c]	93
3	Phenyl	Biphenyl	**3**	52	–	55
4	Phenyl	Ethylbenzene	**4**	38	–	42
5	Phenyl	Anisole	**5**	80	–	77
6	Phenyl	Toluene	**6**	40	–	44
7	Phenyl	Thioanisole	**7**	71	74	75
8	Phenyl	1,3-Dimethoxybenzene	**8**	46	41	45

Method A: **I** (1 equiv.), **II** (3 equiv.), 85% H_3PO_4 (1 equiv.) and TFAA (4 equiv.) in acetonitrile at 50°C for 30 min. Method B: Reactions were carried out by using **I** (1 equiv.), **II** (1.2 equiv.), 88–93% H_3PO_4 (1.2 equiv.) and TFAA (4 equiv.) at 25°C for 1.0 min.

[a] Identified by ^1H NMR, IR, Mass.

[b] Isolated yields of pure product.

[c] Reaction was carried out at 80°C for 180 min.



Scheme 2. *Reagents and conditions*: (a) Method C, yield 50–60%; (b) K_2CO_3, MeOH, 25°C, 1 min, yield 93–95%.

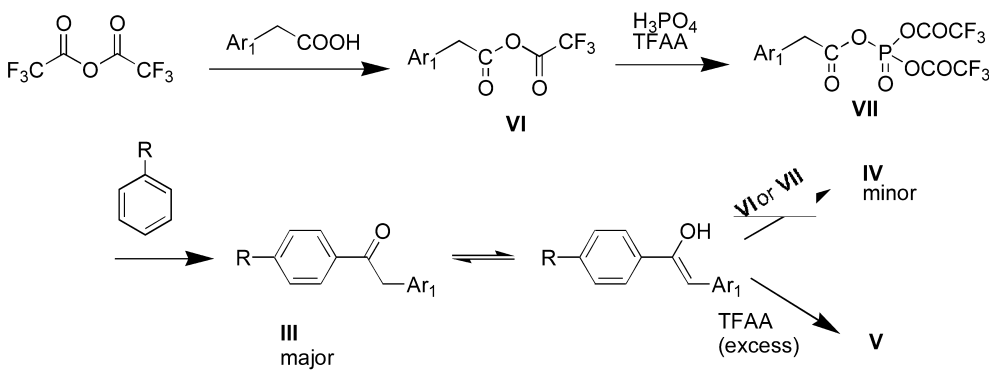
affected by the presence of atmospheric oxygen or moisture. Therefore, this method allows reactions in open flasks thereby avoiding the risk of high-pressure development.

A brief study was carried out on Method A also (entries 2, 7 and 8, Table 1) where the reactions were usually performed at 50–80°C. External heating was necessary to initiate the reaction in such cases. Duration of the reaction time varied from 30 to 180 min and any reduction of reaction time was also found to be less effective. Acetonitrile was used as solvent due to its water miscible nature. However, use of other solvent like THF, dioxane was also investigated and found to be less effective.

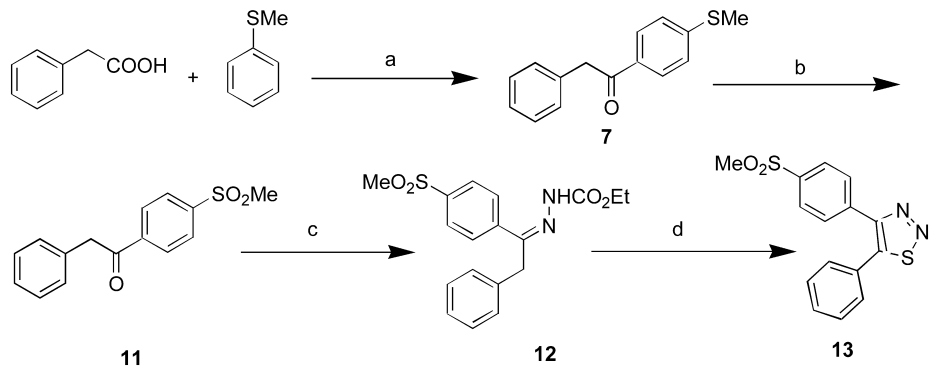
Comparisons of reaction times for both procedures (Method A and B) clearly indicate that the rate of acylation is accelerated from hours to minutes in the absence of solvent (entries 2, 7 and 8, Table 1). For example, acylation of thioanisole using 4-methoxyphenylacetic acid in the presence of acetonitrile requires 180 min at 80°C for 98% completion (entry 2, Table 1). However, the same conversion can be achieved in a shorter time (1 min) at a lower temperature (25°C) in the absence of acetonitrile. Thus, Method B enjoys distinct advantages over Method A as it requires less reaction time, milder reaction conditions and does not require any solvent. Moreover, Method A yielded side products as detected in few cases. These were identified as enol-ester **IV** of the corresponding ketone and arylacetic acid.

All the ketones synthesized (**1**–**8**) were well characterized by the ^{1}H NMR, Mass and IR spectra (carbonyl stretching frequencies in the region of 1680–1660 cm^{-1}) and the pure materials were found to be a single regioisomer. NMR spectra of crude materials were also inspected in several cases for the detection of other possible regioisomers. This study however, remained inconclusive and therefore further investigation is in progress to confirm the possibility of formation of other isomer as a side product. The structures of the enolesters (**9** and **10**) were established from spectroscopic data[12] (carbonyl stretching frequencies in the region of 1800–1790 cm^{-1} in IR spectra). The crude enolesters isolated from the reaction mixture was found to exist as a mixture of both *Z* and *E*-isomer in a ratio of *Z*/*E*=3:1. In the ^{1}H NMR spectra the olefinic hydrogen of *Z*-isomer was at δ 6.77 or 6.71 as a singlet, which appeared in a more up field region i.e. δ 7.02 or 6.90 in the case of *E*-isomer.[12b] Stereochemistry (*E* or *Z*) of the double bond in the case of major isomer of **10** was assigned based on their NOESY1D spectral data. The NOESY1D spectrum of this isomer showed a cross peak between *o*-hydrogens of both the aryl groups (δ 7.46 and 7.42) and olefinic hydrogen (6.77 δ) indicating the *syn* orientation of the hydrogen and the aryl moiety across the double bond.

The reaction mechanism[11c] for Method A could be envisaged as shown in Scheme 3. The role of phosphoric acid has been viewed as a covalent catalyst which leads to the generation of arylacetyl bis(trifluoroacetyl)phosphate **VII** from the acylation precursor acyl trifluoroacetate **VI** generated in situ. Since **VII** participates in faster acylation reaction with arenes[11c] than **VI**, it acetylates the aromatic substrate to afford the desired ketone **III**. The formation of minor product **IV** in the case of Method A could be accounted for by the enolization of ketone **III** under the acidic reaction conditions followed by *O*-acylation[13a,b] in the presence of either mixed anhydride **VI** or the phosphate **VII**. However, the reason for dramatic rate enhancement in the absence of solvent (Method B) is not fully understood. In situ generation of activated dicationic intermediates[13c] could be a possible reason for such an observation. Interestingly, a highly exothermic and vigorous reaction



Scheme 3.



Scheme 4. *Reagents and conditions*: (a) Method B in Scheme 1; (b) Oxone™, acetone–H_2O (2:1), 1 h, 84%; (c) NH_2NHCO_2Et, *p*-toluenesulfonic acid (catalytic amount), toluene, reflux, 24 h, 72% (d) $SOCl_2$, reflux, 3 h, 51%.

was observed when hydrochloric acid was used in place of orthophosphoric acid. Further investigation is in progress to clarify whether the reaction follows a similar mechanistic sequence (Scheme 3) in the absence of solvent (Method B).

Parallel synthesis strategy has been shown to provide an attractive lead development tool for the refinement of biological activity.[14] The strategy has been utilized successfully to generate a library of heterocycles by several laboratories. For example preparation of a series of thiazoles using this strategy has been reported recently.[14b] We therefore, utilized this approach for the synthesis of a number of novel compounds having potential biological interest as well as synthetic analogues of existing bioactive molecules. To demonstrate the feasibility of this approach in the present case the substrates (**I** and **II**) in Table 1 were subjected to eight simultaneous reactions according to the conditions described in Method B. This parallel acylation of arenes was carried out using a Buchi Syncore® Reactor/Polyvap where reaction temperature and time could be monitored with accuracy. After workup the individual ethanones were isolated in good yields (Table 1). In many cases (entries 1, 2, 5 and 7, Table 1), products appeared as solid and were found to be analytically pure after usual work-up. However, pure products were isolated in other cases where crystallization of the crude products was required for further purification.

With 1,2-diaryl-1-ethanones (**III**) that were readily available, synthesis of various diaryl heterocycles was investigated. Thus diphenyl-1,2,3-thiadiazole **13**,[15a,b] a potent and selective COX-2 inhibitor developed by Merck as a novel anti-inflammatory agent, and its analogues were prepared by treating **III** e.g. **11** obtained from **7**, with ethyl carbazate (followed by several steps) according to the procedure described in the literature (Scheme 4).[15b,c] Similarly, ketone **2** has been utilized for the synthesis of compound having potential platelet aggregation inhibitory activity[16a] as well as selective COX-2 inhibitor[16b] whereas **5** was used for the synthesis of human neutrophile elastase inhibitor.[16c] However, we have a long term interest in the palladium mediated[17a] synthesis of benzofurans[17b,c] (**VIII**, Scheme 5) due to their immense biological significance and therefore, ketone **5** and **6** was converted to the 2,3-diarylbenzofuran (**IX**, Scheme 5) under palladium catalysis.[17d]

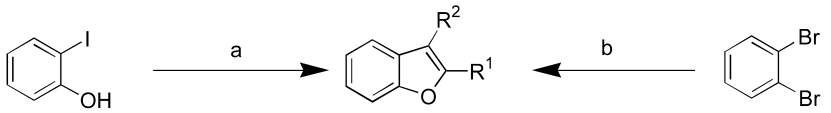
3. Conclusion

In summary, we have described an efficient synthesis of symmetrically/unsymmetrically substituted 1,2-diaryl-1-ethanones via acylation of arenes with in situ generated arylacetyl trifluoroacetates. Advantages of the present protocol are: (i) ready availability of the starting materials and mild reaction conditions, (ii) environmentally safe as the protocol is free from the use of inorganic Lewis acids as well as chlorinated hydrocarbons as solvent, (iii) simple operational procedure. The protocol is certainly superior to the classical Friedel–Crafts acylation technique and other multi step synthesis. Acylation rate can be accelerated by omitting the use of solvent thereby reducing the reaction time from hours to minutes. This high-speed transformation was utilized for the parallel synthesis of 1,2-diaryl-1-ethanones leading to the compounds of potential biological importance. Further studies on substrate tolerability, reaction mechanism and application of this methodology in organic synthesis as well as in the lead discovery arena are under investigation.

4. Experimental

4.1. General methods

All the solvents used were commercially available and



VIII R^1 = Aryl; R^2 = H
IX R^1 = $C_6H_4CH_3$-*p*; R^2 = C_6H_5
= $C_6H_4OCH_3$-*p*; = C_6H_5

Scheme 5. *Reagents and conditions*: (a) HC≡CR^1 (R^1=aryl), $(PPh_3)_2PdCl_2$; Ref. 17b,c; (b) **5** or **6**, $Pd(OAc)_2$, PPh_3, Cs_2CO_3; Ref. 17d.

distilled before use. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254; Merck), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (SRL 230–400 mesh) using distilled petroleum ether, ethyl acetate, dichloromethane, chloroform and methanol. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$, DMSO-d_6 or MeOH-d_4 solution on Varian Gemini 200 or 500 MHz spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ=0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in Hertz. Infrared spectra were recorded on a Perkin–Elmer 1650 FT-IR spectrometer. UV spectra were recorded on Shimadzu UV 2100S UV–Vis recording spectrophotometer. Melting points were determined using Buchi melting point B-540 apparatus and are uncorrected. Thermal analysis data was generated with the help of Shimadzu DSC-50 detector. MS spectra were obtained on a HP-5989A mass spectrometer. Purity was determined by HPLC (AGIL-AUTO) using the condition specified in each case: column, mobile phase (range used), flow rate (ranges used), detection wavelength, retention times. Microanalyses were performed using Perkin–Elmer 2400 C H N S/O analyzer. Arenes and arylacetic acids are commercially available and used without further purification.

4.2. Synthesis of 1,2-diaryl-1-ethanones

Method A (*typical procedure*). Preparation of **2**. A solution of 4-methoxyphenylacetic acid (3.65 g, 21.97 mmol), thioanisole (8.18 g, 65.86 mmol) and 85% phosphoric acid (2.10 g, 21.97 mmol) in anhydrous acetonitrile (80 mL) was stirred at 50°C. To this mixture was added a solution of trifluoroacetic anhydride (12.30 mL, 87.88 mmol) in anhydrous acetonitrile (40 mL) rapidly with vigorous stirring at 50°C. The mixture was stirred for 1 h at the same temperature and poured into ice-cold water (200 mL) with stirring. The solid separated was filtered off, washed with water (3×30 mL) followed by petroleum ether (2×15 mL). Compound **2** was isolated in 92% yield as light yellow solid.

Method B (*parallel synthesis*). Parallel synthesis was carried out using eight reaction flasks simultaneously each containing the appropriate arene and arylacetic acid. To a mixture of phenylacetic acid (7.35 mmol), arene (8.82 mmol) and 88–93% orthophosphoric acid (8.82 mmol) was added trifluoroacetic anhydride (29.52 mmol) rapidly with vigorous stirring at 25°C. The mixture turned into a dark colored solution and a vigorous exothermic reaction was observed. The mixture was stirred for 1 min at the same temperature and poured into ice-cold water (50 mL) with stirring. In many cases products appeared as solid, and the filtered solid, after washing with cold hexane (2×10 mL), was often analytically pure. However, oily mass separated in other cases was extracted with ethylacetate (3×20 mL). Organic layers collected, combined, washed with water (3×30 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to give the crude product. Crystallization of the crude product from appropriate solvent afforded desired product.

Method C. Preparation of **9** and **10** was carried out using appropriate arylacetic acid (7.35 mmol), thioanisole (8.82 mmol), 88–93% orthophosphoric acid (8.82 mmol) and trifluoroacetic anhydride (44.10 mmol) according to the procedure described in Method B. The crude product isolated from the reaction mixture was found to be a mixture of both *Z* and *E*-isomer in a ratio of *Z*/*E*=3:1. They were separated by column chromatography. However, we were unable to prepare analytically pure *E*-isomer which was found to be contaminated with *Z*-isomer.

4.2.1. 1-(4-Methoxy-2-methyl-phenyl)-2-phenyl-ethanone (1). Light yellow powder, mp 135–136°C (ethanol, lit.[18a] 136°C); IR: ν_{max} (KBr, cm^{-1}): 1669, 1605; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.88 (d, J=8.6 Hz, 1H), 7.83 (s, 1H), 7.36–7.26 (m, 5H), 6.83 (d, J=8.3 Hz, 1H), 4.23 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3); Mass (CI method, I-butane): 241 (M+1, 100). Elemental analysis found C, 79.68; H, 6.73; $C_{16}H_{16}O_2$ requires C, 79.97; H, 6.71%.

4.2.2. 2-(4-Methoxy-phenyl)-1-(4-methylsulfanyl-phenyl)-ethanone (2). Light yellow solid, mp 119.5°C (ethanol, lit.[18b] 121–123°C); IR: ν_{max} (KBr, cm^{-1}): 1681, 1586; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.92 (d, J=8.3 Hz, 2H), 7.24–7.03 (m, 4H), 6.87 (d, J=8.4 Hz, 2H), 4.19 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 2.52 (s, 3H, SCH_3); Mass (CI method, I-butane): 273 (M+1, 100). Elemental analysis found C, 70.46; H, 5.90; $C_{16}H_{16}O_2S$ requires C, 70.56; H, 5.92%.

4.2.3. 1-Biphenyl-4-yl-2-phenyl-ethanone (3). White solid, mp 152–153°C (ethanol, lit.[18c] 151°C); IR: ν_{max} (KBr, cm^{-1}): 1678; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10 (d, J=8.3 Hz, 2H), 7.69 (d, J=8.3 Hz, 2H), 7.66–7.13 (m, 10H), 4.34 (s, 2H); Mass (CI method, I-butane): 273 (M+1, 100). Elemental analysis found C, 88.41; H, 5.82; $C_{20}H_{16}O$ requires C, 88.20; H, 5.92%.

4.2.4. 1-(4-Ethyl-phenyl)-2-phenyl-ethanone (4). Light yellow solid, mp 62–63°C (ethanol, lit.[18d] 62°C); IR: ν_{max} (KBr, cm^{-1}): 1680, 1608; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.97 (d, J=8.4 Hz, 2H), 7.33–7.07 (m, 7H), 4.25 (s, 2H, CH_2), 2.72 (q, J=7.0 Hz, 2H, CH_2), 1.26 (t, J=7.1 Hz, 3H, CH_3); Mass (CI method, I-butane): 225 (M+1, 100). Elemental analysis found C, 85.60; H, 7.22; $C_{16}H_{16}O$ requires C, 85.68; H, 7.19%.

4.2.5. 1-(4-Methoxy-phenyl)-2-phenyl-ethanone (5). Light brown solid, mp 135°C (petroleum ether, lit.[18e] 135°C); IR: ν_{max} (KBr, cm^{-1}): 1680, 1600; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.01 (d, J=8.9 Hz, 2H), 7.33–7.27 (m, 5H), 6.94 (d, J=8.9 Hz, 2H), 4.25 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3); Mass (CI method, I-butane): 227 (M+1, 100). Elemental analysis found C, 79.67; H, 6.22; $C_{15}H_{14}O_2$ requires C, 79.62; H, 6.24%.

4.2.6. 2-Phenyl-1-*p*-tolyl-ethanone (6). White solid, mp 110–111°C (ethanol, lit.[18f] 109.6–111.1°C); IR: ν_{max} (KBr, cm^{-1}): 1681, 1603; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.93 (d, J=8.1 Hz, 2H), 7.41–7.25 (m, 7H), 4.28 (s, 2H, CH_2), 2.42 (s, 3H, CH_3); Mass (CI method, I-butane): 211 (M+1, 100). Elemental analysis found C, 85.61; H, 6.82; $C_{15}H_{14}O$ requires C, 85.68; H, 6.71%.

4.2.7. 1-(4-Methylsulfanyl-phenyl)-2-phenyl-ethanone (7). Light yellow solid, mp 101°C (ethanol, lit.[18g] 99.4–99.8°C); IR: ν_{max} (KBr, cm^{-1}): 1664, 1598; ^1H NMR (200 MHz, $CDCl_3$): δ 7.92 (d, J=8.6 Hz, 2H), 7.32–7.14 (m, 7H), 4.24 (s, 2H, CH_2), 2.49 (s, 3H, SCH_3); Mass (CI method, I-butane): 243 (M+1, 100). Elemental analysis found C, 74.41; H, 5.81; $C_{15}H_{14}OS$ requires C, 74.35; H, 5.82%.

4.2.8. 1-(2,4-Dimethoxy-phenyl)-2-phenyl-ethanone (8). White solid, mp 55–56°C (ethanol, lit.[18h] 56°C); IR: ν_{max} (KBr, cm^{-1}): 1664, 1598; ^1H NMR (200 MHz, $CDCl_3$): δ 7.83 (d, J=8.9 Hz, 1H), 7.30–7.23 (m, 5H), 6.55 (dd, J=8.9, 2.2 Hz, 1H), 6.46 (d, J=2.2 Hz, 1H), 4.30 (s, 2H, CH_2), 3.91 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3); Mass (CI method, I-butane): 257 (M+1, 100). Elemental analysis found C, 74.88; H, 6.28; $C_{16}H_{16}O_3$ requires C, 74.98; H, 6.29%.

4.2.9. (*Z*)-2-(4-Methoxyphenyl)-1-(4-methylsulfanyl-phenyl)-1-ethenyl 2,2,2-trifluoroacetate (9). Semi solid; 60% yield; IR: ν_{max} (KBr, cm^{-1}): 1789, 1607; ^1H NMR (200 MHz, $CDCl_3$): δ 7.43 (d, J=8.9 Hz, 2H), 7.40 (d, J=8.3 Hz, 2H), 7.26 (d, J=8.3 Hz, 2H), 6.90 (d, J=8.9 Hz, 2H), 6.71 (s, 1H, –CH═C), 3.83 (s, 3H, OCH_3), 2.50 (s, 3H, SCH_3); Mass (CI method, I-butane): 369 (M+1, 100). Elemental analysis found C, 58.57, H, 4.11; $C_{18}H_{15}F_3O_3S$ requires C, 58.69, H, 4.10.

(*E*)-2-(4-Methoxyphenyl)-1-(4-methylsulfanylphenyl)-1-ethenyl 2,2,2-trifluoroacetate. Gum; ^1H NMR (200 MHz, $CDCl_3$): δ 7.42 (d, J=8.9 Hz, 2H), 7.38 (d, J=8.3 Hz, 2H), 7.25 (d, J=8.3 Hz, 2H), 7.02 (s, 1H, –CH═C), 6.88 (d, J=8.9 Hz, 2H), 3.82 (s, 3H, OCH_3), 2.49 (s, 3H, SCH_3).

4.2.10. (*Z*)-1-(4-Methylsulfanylphenyl)-2-phenyl-1-ethenyl 2,2,2-trifluoroacetate (10). Semi solid; 50% yield; IR: ν_{max} (KBr, cm^{-1}): 1801, 1600; ^1H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, J=7.6 Hz, 2H), 7.42 (d, J=8.3 Hz, 2H), 7.39–7.04 (m, 5H), 6.77 (s, 1H, –CH═C), 2.51 (s, 3H, SCH_3); Mass (CI method, I-butane): 339 (M+1, 100). Elemental analysis found C, 60.15, H, 3.91; $C_{17}H_{13}F_3O_2S$ requires C, 60.35, H, 3.87.

(*E*)-1-(4-Methylsulfanylphenyl)-2-phenyl-1-ethenyl 2,2,2-trifluoroacetate. Gum; ^1H NMR (200 MHz, $CDCl_3$): δ 7.49–7.13 (m, 9H), 6.91 (s, 1H, –CH═C), 2.50 (s, 3H, SCH_3).

4.2.11. (*Z*)-1-(4-Methylsulfanylphenyl)-2-phenyl-1-ethenyl-2-phenylacetate (IVa). Semi solid; 9% yield; ^1H NMR (200 MHz, $CDCl_3$): δ 7.90 (d, J=8.5 Hz, 2H), 7.35–7.13 (m, 12H), 6.77 (s, 1H, –CH═C), 3.69 (s, 2H), 2.51 (s, 3H, SCH_3); Mass (CI method, I-butane): 361 (M^+, 100). Elemental analysis found C, 76.81, H, 5.57; $C_{23}H_{20}O_2S$ requires C, 76.64, H, 5.59.

4.2.12. (*Z*)-1-(2,4-Dimethoxyphenyl)-2-phenyl-1-ethenyl-2-phenylacetate (IVb). Semi solid; 10% yield; ^1H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, J=8.7 Hz, 1H), 7.34–7.10 (m, 10H), 6.76 (s, 1H, –CH═C), 6.57–6.47 (m, 2H), 3.90 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.68 (s, 2H); Mass (CI method, I-butane): 375 (M^+, 100). Elemental analysis found C, 77.11, H, 5.90; $C_{24}H_{22}O_4$ requires C, 76.99, H, 5.92.

4.3. Cleavage of enolesters (V)

General procedure. A mixture of enolester **9** or **10** (2 mmol) and K_2CO_3 (303 mg, 2.2 mmol) in methanol (2 mL) was stirred at 25°C for 1 min and the mixture was diluted with cold water (10 mL) with vigorous stirring. Solid separated was filtered, washed with water (2×2 mL) followed by petroleum ether (2×2 mL) and dried under vacuum to afford pure product (**2** or **7**).

4.3.1. Preparation of 1-(4-methylsulfonylphenyl)-2-phenyl-1-ethanone (11). To a suspension of 1-(4-methylsulfanyl-phenyl)-2-phenyl-ethanone (**7**) (0.59 g, 2.43 mmol) in acetone (20 mL), water (10 mL) was added Oxone (2.48 g, 4.03 mmol) and the mixture was stirred at 25°C for 1 h. After completion of the reaction, acetone was removed under low vacuum and the resulting mixture was diluted with cold water (20 mL). The mixture was then extracted with EtOAc (3×20 mL). Organic layers collected, combined, washed with cold water (2×30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give the title compound in 84% yield (0.56 g). Mp 165–166°C (lit.[18g] 164.5–166°C); ^1H NMR (200 MHz, $CDCl_3$): δ 8.16 (d, J=8.3 Hz, 2H), 8.03 (d, J=8.3 Hz, 2H), 7.31–7.26 (m, 5H), 4.32 (s, 2H, CH_2), 3.06 (s, 3H, SO_2CH_3); Mass (CI method, I-butane): 274 (M^+, 100).

4.3.2. Preparation of *N* ^{1}-[1-(4-methanesulfonyl-phenyl)-2-phenyl-ethylidene]-hydrazinocarboxylic acid ethyl ester (12). A mixture of **11** (0.68 g, 2.5 mmol), ethyl carbazate (0.28 g, 2.8 mmol) and *p*-toluenesulfonic acid (10 mg) in toluene (20 mL) was refluxed with the simultaneous removal of water for 24 h. The mixture was cooled and the solid appeared was filtered. The residue washed with toluene (3 mL) followed by hexane (2×3 mL) to afford the title compound in 72% yield (0.65 g). ^1H NMR (200 MHz, $CDCl_3$): δ 8.00 (d, J=8.3 Hz, 2H), 7.88 (d, J=8.3 Hz, 2H), 7.30–7.25 (m, 5H), 6.43 (bs, D_2O exch., 1H, NH), 4.25–4.15 (m, 2H, OCH_2), 4.04 (s, 2H, CH_2), 3.05 (s, 3H, SO_2CH_3) 1.30–1.23 (t, J=7.3 Hz, 3H, CH_3); Mass (CI method, I-butane): 361 (M^+, 100). Elemental analysis found C, 59.71; H, 5.49; N, 7.89; $C_{18}H_{20}N_2O_4S$ requires C, 59.98; H, 5.59; N, 7.77%.

4.3.3. Preparation of 4-(4-methylsulfonylphenyl)-5-phenyl-[1,2,3]-thiadiazole (13). A mixture of **12** (400 mg, 1.12 mmol) and $SOCl_2$ (4 mL) was refluxed for 3 h. The excess $SOCl_2$ was removed under vacuum and the residue was purified by column chromatography using 3:2 petroleum ether–EtOAc as eluant to give the desired product in 51% yield (180 mg). Mp 153–154°C (lit.[15a] 154–155°C); IR: ν_{max} (KBr, cm^{-1}): 1605, 1527; ^1H NMR (200 MHz, $CDCl_3$): 8.1 (d, J=8.4 Hz, 2H), 7.99 (d, J=8.4 Hz, 2H), 7.51–7.47 (m, 5H), 3.06 (s, 3H, SO_2CH_3); Mass (CI method, I-butane): 317 (M^+, 100).

4.4. General method for the synthesis[17d] of 3,4-diaryl benzofurans (IX)

A mixture of 1,2-dibromobenzen (2 mmol), $Pd(OAc)_2$

(0.10 mmol), PPh_3 (0.4 mmol) and Cs_2CO_3 (4 mmol) in *o*-xylene (5 mL) was heated to reflux under nitrogen atmosphere with stirring. After 2 h the mixture was cooled to room temperature and ketone **5** or **6** (2 mmol) was added it. The mixture was again heated to reflux with stirring for 6 h. After completion of the reaction, the mixture was cooled to room temperature and then directly transferred to a silica gel column. The product was isolated by eluting the column using 1–10% EtOAc–petroleum ether.

4.4.1. 2-(4-Methylphenyl)-3-phenylbenzo[*b*]furan (IXa). Pale yellow solid; 67% yield; mp 96–97°C (lit.[17d] 97–97.5°C).

4.4.2. 2-(4-Methoxyphenyl)-3-phenylbenzo[*b*]furan (IXb). White solid; 51% yield; mp 97°C (lit.[17d] 98.5–99°C).

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References

1. (a) Dyke, S. F.; Tiley, E. P.; White, A. W. C.; Gale, D. P. *Tetrahedron* **1975**, *31*, 1219–1222, and references cited therein. (b) Grant, S. P.; Hurst, D. R.; Cordray, T. L.; Beam, C. F. *Org. Prep. Proced. Int.* **2001**, *33*, 91–95. (c) Churruca, F.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2002**, *4*, 1591–1594. (d) Olivera, R.; SanMartin, R.; Dominguez, E.; Solans, X.; Urtiaga, M. K.; Arriortua, M. I. *J. Org. Chem.* **2000**, *65*, 6398–6411. (e) Aidhen, I. S.; Narasimhan, N. S. *Tetrahedron Lett.* **1991**, *32*, 2171–2172. (f) Chen, C.; Yun-Fei, Z.; Xin-Jun, L.; Zi-Xian, L.; Qiu, X.; Nicholas, L. *J. Med. Chem.* **2001**, *44*, 4001–4010.
2. Revesz, L.; Di Padova, F. E.; Buhl, T.; Feifel, R.; Gram, H.; Hiestand, P.; Manning, U.; Zimmerlin, A. G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1261–1264.
3. (a) Gallagher, T. F.; Fier-Thompson, S. M.; Garigipati, R. S.; Sorenson, M. E.; Smietana, J. M.; Lee, D.; Bender, P. E.; Lee, J. C.; Laydon, J. T.; Griswold, D. E.; Chabot-Fletcher, M. C.; Breton, J. J.; Adams, J. L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1171–1176. (b) Meyers, M. J.; Sun, J.; Carlson, K. E.; Marriner, G. A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2001**, *44*, 4230–4251.
4. (a) Learmonth, D. A.; Vieira-Coelho, M. A.; Benes, J.; Alves, P. C.; Borges, N.; Freitas, A. P.; Soares-de-Silva, P. *J. Med. Chem.* **2002**, *45*, 685–695. (b) Benes, J.; Soares-da-Silva, P.; Manuel Vieira, A.; Learmonth, D. A. Eur. Pat. Appl. EP 1010688 A1, June 21, 2000, 17 pp; *Chem. Abstr.* **2000**, *133*, 43310.
5. (a) Almansa, C.; de Arriba, A. F.; Cavalcanti, F. L.; Gomez, L. A.; Miralles, A.; Merlos, M.; Garcia-Rafanell, J.; Forn, J. *J. Med. Chem.* **2001**, *44*, 350–361. (b) Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775–777.
6. (a) Leblanc, Y.; Gauthier, J. Y.; Ethier, D.; Guay, J.; Mancini, J.; Riendeau, D.; Tagari, P.; Vickers, P.; Wong, E.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2123–2128. (b) Carter, J. S.; Rogier, D. J.; Graneto, M. J.; Seibert, K.; Koboldt, C. M.; Zhang, Y.; Talley, J. J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1167–1170. (c) Habeeb, A. G.; Rao, P. N. P.; Knaus, E. E. *Drug Dev. Res.* **2000**, *51*, 273–286.
7. (a) Pal, M.; Rao, Y. K.; Rajagopalan, R.; Misra, P.; Kumar, P. M.; Rao, C. S. World Patent Application WO 01/90097, November 29, 2001; *Chem. Abstr.* **2002**, *136*, 5893. (b) Pattabiraman, V. R.; Padakanti, P. S.; Veeramaneni, V. R.; Pal, M.; Yeleswarapu, K. R. *Synlett* **2002**, 947–951. (c) Padakanti, S.; Veeramaneni, V. R.; Pattabiraman, V. R.; Pal, M.; Yeleswarapu, K. R. *Tetrahedron Lett.* **2002**, *43*, 8715–8719. (d) Pal, M.; Veeramaneni, V. R.; Srinivas, P.; Murali, N.; Akhila, V.; Premkumar, M.; Rao, C. S.; Misra, P.; Ramesh, M.; Yeleswarapu, K. R. *Indian J. Chem.* **2003**, *42B*, 593–601. (e) Pal, M.; Veeramaneni, V. R.; Nagabelli, M.; Kalleda, S. R.; Misra, P.; Casturi, S. R.; Yeleswarapu, K. R. Presented at the International Symposium on Drug Discovery and Process Research (DDPR-2003), Shivaji University, Kolhapur, India, January 23–25, 2003; Paper number O-5.
8. (a) Pal, M.; Batchu, V. R.; Khanna, S.; Yeleswarapu, K. R. *Tetrahedron* **2002**, *58*, 9933–9940. (b) Pal, M.; Veeramaneni, V. R.; Yeleswarapu, K. R. Presented at the symposium on Current Perspective in Organic Chemistry (CPOC-2002), Indian Association for the Cultivation of Science, Kolkata, India, January 24–25, 2002; Paper number 6.
9. For synthesis from α-aminonitrile see Ref. 1a,d,e. For acylation in the presence of Lewis acids see; (a) Al-Maharik, N. I.; Seppo, A. A. K.; Mutikainen, I.; Waehaelae, K. *J. Org. Chem.* **2000**, *65*, 2305–2308. (b) Devi, N.; Jain, N.; Krishnamurty, H. G. *Indian J. Chem. Sect. B.* **1993**, 874–875, and references cited therein. (c) Wahala, K.; Hase, T. A. *J. Chem. Soc. Perkin Trans. 1* **1991**, *12*, 3005–3008. For acylation in the presence of CF_3SO_3H see; (d) Hwang, J. P.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron* **2000**, *56*, 7199–7203. For palladium mediated acylation see; (e) Sato, T.; Naruse, K.; Enokiya, M.; Fujisawa, T. *Chem. Lett.* **1981**, *8*, 1135–1138. For synthesis using Grignard reagent see; (f) Learmonth, D. A.; Alves, P. C. *Synth. Commun.* **2002**, *32*, 641–649. For synthesis via pinacol rearrangement catalyzed by $AlCl_3$ see; (g) Rashidi-Ranjbar, P.; Kianmehr, E. *Molecules* **2001**, *6*, 442–447. For benzotriazole-assisted synthetic methodology see: (h) Katritzky, A. R.; Oniciu, D. C. *Bull. Soc. Chim. Belg.* **1996**, *105*, 635–638. For synthesis via self coupling of phenylacetic acid in the presence of PPA see: Ref. 1f and (i) Palmquist, U.; Nilsson, A.; Pettersson, T.; Ronlan, A.; Parker, V. D. *J. Org. Chem.* **1979**, *44*, 196–203. For a multistep sequences consisting of Perkin condensation and Crutius rearrangement see Ref. 6b. Synthesis via clay catalyzed rearrangement of phenyloxiranes (j) Martinez, R.; Velasco, M.; Martinez, I.; Menconi, I.; Ramirez, A.; Angeles, E.; Regla, I.; Lopez, R. *J. Het. Chem.* **1997**, *34*, 1865–1866.
10. For the use of acyl trifluoroacetate as general acylating agent see: (a) Tedder, J. M. *Chem. Rev.* **1955**, 787–827. (b) Bourne, E. J.; Stacey, M.; Tatlow, J. C.; Worrall, R. *J. Chem. Soc.* **1954**, 2006, and references cited therein.
11. For the first successful TFA/H_3PO_4-mediated aromatic acylation see: (a) Galli, C. *Synthesis* **1979**, 303–304. See also: (b) Gray, A. D.; Smyth, T. P. *J. Org. Chem.* **2001**, *66*, 7113–7117. (c) Smyth, T. P.; Corby, B. W. *J. Org. Chem.*

1998, *63*, 8946–8951. (d) Goldfinger, M. B. World Patent application WO 2000052075 A1, September 8, 2000, 13 pp; *Chem. Abstr.* **2000**, *133*, 223216.

12. (a) Bach, R. D.; Woodard, R. A.; Anderson, T. J.; Glick, M. D. *J. Org. Chem.* **1982**, *19*, 3707–3712. (b) Larock, R. C.; Oertle, K.; Beatty, K. M. *J. Am. Chem. Soc.* **1980**, *6*, 1966–1974.
13. (a) Shcherbakova, I. V.; Potemkina, N. N.; Dorofeenko, G. N.; Kuznetsov, E. V. *Zh. Org. Khim.* **1977**, *13*, 1341. *Chem. Abstr.*, *87*, 134354. (b) McGarrity, J. F.; Cretton, A.; Pinkerton, A. A.; Schwarzenbach, D.; Flack, H. D. *Angew. Chem.* **1983**, *95*, 426–427. (c) Possible formations of activated dicationic intermediates have been explored earlier see: Olah, G. A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 767–788. See also Ref. 8d.
14. (a) Villalgordo, J. M.; Cbrecht, D.; Obrecht, D. *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*; Pergamon: Oxford, 1998. (b) Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J. *J. Org. Chem.* **2001**, *66*, 2588–2596.
15. (a) Lau, C. K. US Patent Application US 5677318, October 14, 1997, 13 pp; *Chem. Abstr.* **1997**, *127*, 341793. (b) Gautheir, J. Y.; Leblanc, Y.; Black, W. C.; Chan, C.-C.; Cromlish, W. A.; Gordon, R.; Kennedy, B. P.; Lau, C. K.; Leger, S.; Wang, Z.; Ethier, D.; Guay, J.; Mancini, J.; Riendeau, D.; Tagari, P.; Vickers, P.; Wong, E.; Xu, L.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 87–92. (c) Hurd, C. D.; Mori, R. I. *J. Am. Chem. Soc.* **1955**, *77*, 5359–5364.
16. (a) Thomas, E. W.; Nishizawa, E. E.; Zimmermann, D. C.; Williams, D. J. *J. Med. Chem.* **1985**, *28*, 442–446. (b) Lee, K.-W.; Choi, Y. H.; Joo, Y. H.; Kim, J. K.; Shin, S. S.; Byun, Y. J.; Yeonjoon, K.; Chung, S. *Bioorg. Med. Chem.* **2002**, *10*, 1137–1142. (c) Imaki, K.; Okada, T.; Nakayama, Y.; Nagao, Y.; Kobayashi, K.; Sakai, Y.; Mohri, T.; Amino, T.; Nakai, H.; Kawamura, M. *Bioorg. Med. Chem.* **1996**, *4*, 2115–2134.
17. (a) Pal, M.; Parasuraman, K.; Gupta, S.; Yeleswarapu, K. R. *Synlett* **2002**, 1976–1982. (b) Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc. Perkin Trans. 1* **1997**, 2815–2820. (c) Kundu, N. G.; Pal, M.; Mahanty, J. S.; Dasgupta, S. K. *J. Chem. Soc. Chem. Commun.* **1992**, 41–42. (d) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn* **1999**, *72*, 2345–2350.
18. (a) Thoi, L. V.; Hoang, N. V. *Isr. J. Chem.* **1963**, *1*, 418–425. (b) Fitzi, K.; Pfister, R. US 3901908, 1975; *Chem.Abstr.*, *83*, 206272. (c) Allen, B. *J. Am. Chem. Soc.* **1932**, *54*, 736–747. (d) Ghosh, K.; Bhattacharya, A. J. *Indian J. Chem. Sect. B* **1977**, *15B*, 678–680. (e) Verma, B. S.; Dhindsa, K. S.; Sangwan, N. K. *Indian J. Chem. Sect. B* **1993**, *32*, 239–243. (f) Feldstein;, V. W. *J. Am. Chem. Soc.* **1954**, *76*, 1626–1627. (g) Coan, S. B.; Trucker, D. E.; Becker, E. I. *J. Am. Chem. Soc.* **1955**, *77*, 60–63. (h) Baker, R. *J. Chem. Soc.* **1932**, 1798–1803.