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# Novel and efficient aqueous phase synthesis of N-substituted azepines via tandem Michael addition and cyclization in the presence of β-cyclodextrin

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ABSTRACT

N-substituted azepines were synthesized for the first time in water under neutral conditions by the reaction of aromatic amines, dimethyl/diethyl acetylene dicarboxylate, 2,5-dimethoxytetrahydrofuran mediated by β-cyclodextrin in high yields. β-Cyclodextrin can be recovered and reused with just a small loss of catalytic activity.



Azepine and its analogues exhibit varied biological activities, such as antihistaminic, spasmolytic, serotonin antagonistic, anticonvulsive, antiemetic, anti-inflammatory, and fungicidal activities.[1] These derivatives are also used in antimalarial drug therapy,[2a–c] anti-HIV,[2d] stomach disorders,[3] antiarrhythmic,[4] hypertension (glaucoma),[5] and other pharmaceutical applications.[6] There are numerous drugs, such as Imipramine (**1**), Carbamazepine (**2**), Oxcarbazepine (**3**), containing the azepine skeleton as shown in Figure 1.

A number of synthetic routes have been developed for azepines, because of their interesting biological activities. In general these can be synthesized by the insertion of nitrenes derived by the thermolysis of azides, cyclization of diene conjugated nitrile ylides prepared by the base catalyzed dehalogenation of the corresponding imidoyl chlorides, and [4+2] cycloaddition reactions.[7] Intramolecular aza-Wittig reaction has been one of the convenient methods for the synthesis of azepines. Tietze and Schimpf reported an interesting synthetic protocol for azepines by the intramolecular Heck reaction.[8] Toste and co-worker, developed Au(III)-catalyzed synthesis of *N*-arylazepines via inter molecular annulation between propargyl ester and *N*-phenylimine.[9] Wender et al. reported the preparation of N-substituted azepines by transition metal-catalyzed aza [5+2] cycloaddition strategy, involving various imines.[10] However, the existing methods have a number of drawbacks, such as the use of transition metal catalysts, anhydrous organic solvents, low yields, and moisture sensitive reagents. Thus, in view of these shortcomings, there is a need to develop a mild and eco-friendly synthetic protocol for the synthesis of substituted azepines by replacing flammable toxic or carcinogenic organic solvents with water using a recyclable activator/catalyst in the context of green chemical methodologies.

Presently organic reactions in aqueous phase have attracted the attention of researchers because of the added advantages of water as an environmentally benign and economically affordable solvent. However, the fundamental problem in performing the reactions in water is that many organic substrates are hydrophobic and insoluble in water. Cyclodextrins, possessing hydrophobic cavities, are well known supramolecular catalysts, which by reversible formation of host–guest complexes, activate the organic molecules and catalyze the reactions. As part of our ongoing program toward the development of greener chemical approaches for the synthesis of novel reaction intermediates and heterocyclic moieties,[11] herein

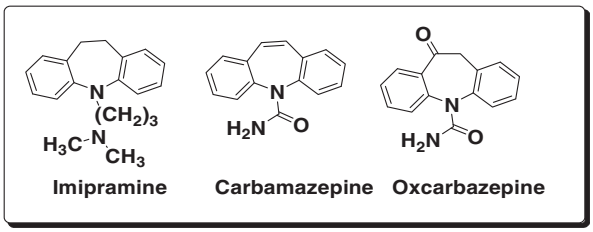


**Figure 1.** Some marketed drugs with azepine skeleton.

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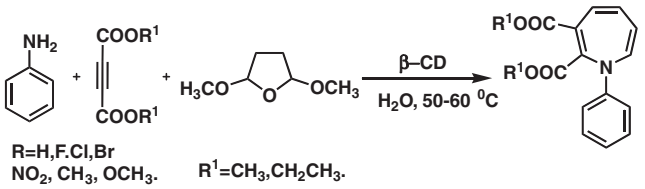


**Scheme 1.** Synthesis of N-substituted azepines.

**Table 1**
Optimization of reaction conditions using different catalysts[a]

| Entry | Catalyst | Yield[b] (%) |
|---|---|---|
| 1 | γ-Cyclodextrin | 78 |
| 2 | α-Cyclodextrin | 38 |
| 3 | β-Cyclodextrin | 92 |
| 4 | (2-Hydroxy propyl)-β-cyclodextrin | 42 |
| 5 | Methyl-β-cyclodextrin | 40 |
| 6 | Water | 36 |

[a] All reactions were carried out using aniline (1.0 mmol), DMAD (1.0 mmol), and 2,5-dimethoxytetrahydrofuran (1.0 mmol), β-CD (1.0 mmol).
[b] Yield obtained after column chromatography.

we report the synthesis of N-substituted azepines by the reaction of aromatic amines, DMAD/DEAD with 2,5-dimethoxytetrahydrofuran, using β-cyclodextrin[12] as a reusable catalyst under supramolecular catalysis, for the first time in water.

In this study, a model reaction was conducted by reacting aniline, DMAD/DEAD with 2,5-dimethoxytetrahydrofuran in water at room temperature to obtain the corresponding N-substituted azepine in low yields (36%). The poor solubility of aniline in water at elevated temperature resulted in the formation of undesired products. When the same reaction was conducted using β-CD at room temperature the product was obtained in moderate yield (65%). However by a controlled experiment using β-CD, as a supramolecular catalyst, at 50–60 °C the product was obtained in excellent yield (92%)[13] (Scheme 1). In due course of methodology development, for the first time various cyclodextrins, such as α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, 2-hydroxy propyl-β-cyclodextrin, and methyl-β-cyclodextrin were examined for their efficiency as promoters in carrying out the reaction under supramolecular catalysis.

Of these cyclodextrins (Table 1), β-CD and γ-CD were found to be superior mediators and both gave moderate to excellent yields of the desired substituted azepine. As β-cyclodextrin was inexpensive and readily available when compared to γ-cyclodextrin, β-cyclodextrin was selected as a better choice to carry out the

**Table 2**
Synthesis of N-substituted azepines[a]

| Entry | Aniline | DMAD/DEAD | 2,5-Dimethoxy tetrahydro furan | Product | Yield[b] (%) |
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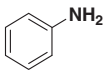
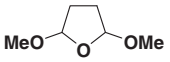
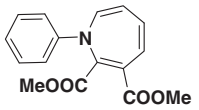
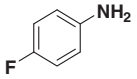
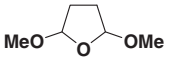
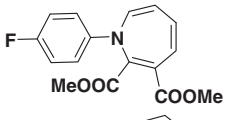
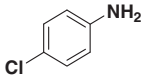
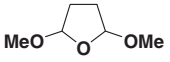
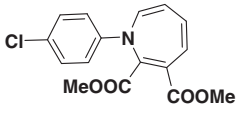
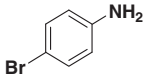
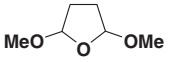
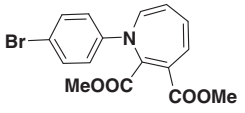
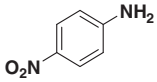
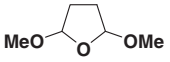
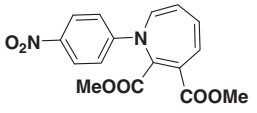
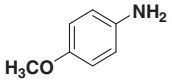
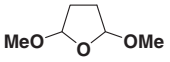
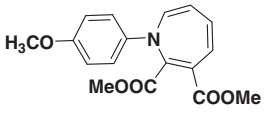
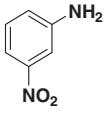
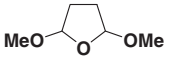
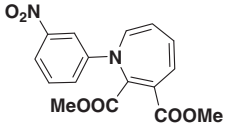
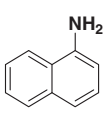
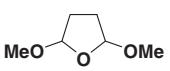
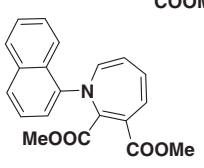
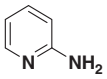
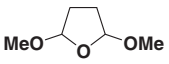
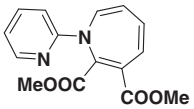
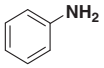
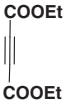
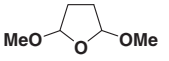
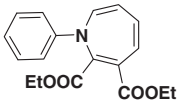
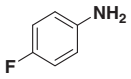
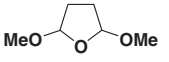
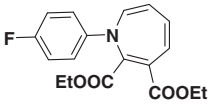
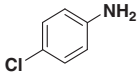
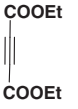
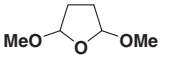
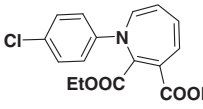
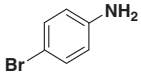
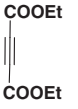
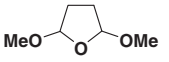
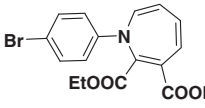
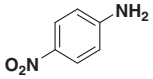
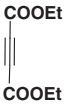
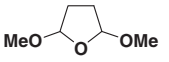
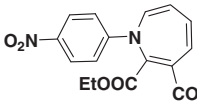
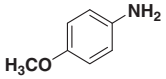
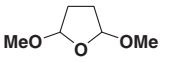
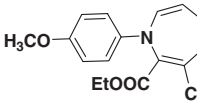
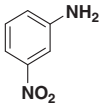
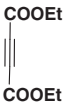
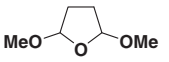
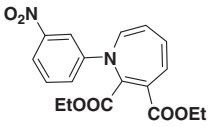
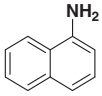
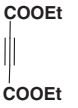
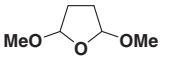
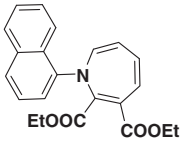
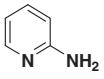
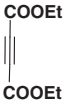
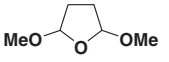
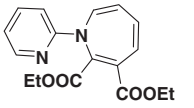
| 1 |  |  |  |  | 92 |
| 2 |  |  |  |  | 91 |
| 3 |  |  |  |  | 92 |
| 4 |  |  |  |  | 90 |
| 5 |  |  |  |  | 86 |
| 6 |  |  |  |  | 94 |
| 7 |  |  |  |  | 80 |
| 8 |  |  |  |  | 91 |

(*continued on next page*)

**Table 2** (*continued*)

| Entry | Aniline | DMAD/DEAD | 2,5-Dimethoxy tetrahydro furan | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 9 |  |  |  |  | 89 |
| 10 |  |  |  |  | 95 |
| 11 |  |  |  |  | 92 |
| 12 |  |  |  |  | 90 |
| 13 |  |  |  |  | 91 |
| 14 |  |  |  |  | 86 |
| 15 |  |  |  |  | 96 |
| 16 |  |  |  |  | 82 |
| 17 |  |  |  |  | 82 |
| 18 |  |  |  |  | 88 |
| 19 |  |  |  | No reaction | |
| 20 |  |  |  | No reaction | |
| 21 |  |  |  | No reaction | |

[a] Reaction conditions: Aniline (1.0 mmol), DMAD/DEAD (1.0 mmol), 2,5-dimethoxytetrahydrofuran (1.0 mmol), β-cyclodextrin (1.0 mmol), 50–60 °C, 4–7 h.
[b] Isolated yield.

reaction. Next, the scope of this reaction has been extended to cover different substitutions on azepine nitrogen, by reacting various aromatic amines, DMAD/DEAD with 2,5-dimethoxytetrahydrofuran to obtain the corresponding N-substituted azepine in quantitative yields. In general, all the reactions were clean, and the *N*-aryl-1*H*-azepine-2,3-dicarboxylates were obtained in excellent yields (80–96%) (Table 2). Substitution on the aromatic ring played a crucial role in governing the product yield as it can be seen from Table 2. Electron-donating groups on aniline gave good yields (Table 2, entry 15) while electron-withdrawing groups on aniline gave lower yields, (Table 2, entries 5, 7, 14 and 16) in comparison with aniline (Table 2, entry 1).

With optimized the reaction conditions on hand, we attempted to synthesize N-substituted azepines by reacting aliphatic amines,

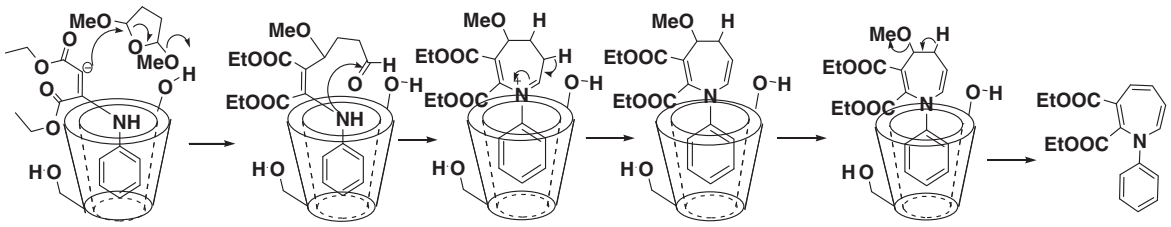


**Figure 2.** Possible mechanistic pathway for the formation of N-substituted azepines using β-cyclodextrin.

**Table 3**
Recyclability of β-CD

| Cycles | Yield (%) | Catalyst recovered (%) |
|---|---|---|
| Native | 92 | 91 |
| 1 | 88 | 89 |
| 2 | 85 | 85 |
| 3 | 81 | 83 |

and *ortho*-substituted anilines with 2,5-dimethoxytetrahydrofuran in the presence of DMAD/DEAD, but no reaction was observed even after prolonged reaction times (Table 2). Compared to *p*-substituted anilines *meta*-substituted anilines gave lower yields of the products. All the products were characterized by $^{1}H$, $^{13}C$ NMR, IR, and mass spectrometry.[14] The catalytic activity of the β-CD was established by the fact that azepine formation was not observed in satisfactory yield in the absence of β-cyclodextrin. The evidence for the formation of *N*-aryl substituted azepine in the presence of β-CD was supported by $^{1}H$ NMR studies of inclusion complex between aniline and β-CD. The hydrophobic environment of the cyclodextrin facilitates the formation of *N*-arylazepines via inclusion complex of aniline/DMAD or DEAD carbanion stabilized by the primary and secondary-OH groups of cyclodextrin, which further reacts with 2,5-dimethoxytetrahydrofuran and subsequent cyclization followed by elimination leads to the desired product as indicated in Figure 2.

All the reactions were carried out with a catalytic amount (10 mol %) of β-CD in water. But for NMR studies inclusion complex was prepared by taking β-CD and aniline in a 1:1 ratio. A comparative study of $^{1}H$ NMR spectra of aniline, β-CD, and β-CD/aniline complex has indicated the upfield shift of aromatic protons as well as amine protons of aniline in the $^{1}H$ NMR spectrum (in DMSO-$d_6$) of aniline/β-CD. In the $^{1}H$ NMR spectrum (DMSO-$d_6$) of aniline, the aromatic protons from *ortho* position appear as a doublet at 6.61 ppm ($J$ = 8.2 Hz), while *meta* and *para* protons appear as a triplet at 7.06 ($J$ = 7.4 Hz) and 6.55 ($J$ = 6.7 Hz), respectively. Singlet at 5.05 ppm represents amine protons of aniline. The upfield shift of aniline protons in the NMR spectrum of β-CD/aniline complex confirms the incorporation of aniline inside the hydrophobic cavity of β-CD on complexation. Apart from the upfield shift of aniline protons due to the incorporation of the aromatic ring inside the β-CD cavity, the protons located in the β-CD cavity ($C_3$–H and $C_5$–H) are also shifted upfield due to magnetic anisotropy caused by the aniline molecule.[12b] In all these reactions β-CD can be recovered and reused. After the reaction, the reaction mass was cooled to room temperature and β-CD was filtered and washed with ice-cold water and dried. The recovered β-CD was further used in the reaction with the same substrates and checked for the yields and catalytic activity of the recovered catalyst (β-CD), as shown in Table 3. It was observed that the yields of N-substituted azepines diminished slightly after two to three recycles.

In summary, we have developed an eco-friendly method to synthesize N-substituted azepines in excellent yields under neutral conditions in one-pot involving catalysis by β-cyclodextrin in water.

## Acknowledgments

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.082.

## References and notes

1. Fouche, J.; Leger, A. German Patent 2031,236, 1971; *Chem. Abstr.* **1971**, *74*, 76346r.
2. (a) Banerjee, R.; Liu, J.; Beatty, W.; Pelosof, L.; Klemba, M.; Goldberg, D. E. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 990; (b) Ersmark, K.; Feierberg, I.; Bjelic, S.; Hamelink, E.; Hackett, F.; Blackman, M. J.; Hulten, J.; Samuelsson, B.; Aqvist, J.; Hallberg, A. *J. Med. Chem.* **2004**, *47*, 110; (c) Liu, J.; Gluzman, I. Y.; Drew, M. E.; Goldberg, D. E. *J. Biol. Chem.* **2005**, *280*, 1432; (d) Kukla, M. J.; Breslin, H. J.; Diamond, C. J.; Grous, P. P.; Ho, C. Y.; Miranda, M.; Rodgers, J. D.; Sherill, R. G.; De Clercq, E.; Pauwels, R.; Andries, K.; Moens, L. J.; Janssen, M. A. C.; Janssen, P. A. J. *J. Med. Chem.* **1991**, *34*, 3187–3197.
3. Heys, J. R.; Senderoff, S. G. *J. Org. Chem.* **1989**, *54*, 4702.
4. Cross, P. E.; Arrowsmith, J. E. Eur. Patent 285,323, 1988; *Chem. Abstr* .**1989**, *110*, 173115.
5. (a) Das, J. U.S. Patent 4774,239, 1988; *Chem. Abstr.* **1989**, *110*, 23752.; (b) Kimball, S. D.; Floyd, D. M.; Das, J.; Hunt, J. T.; Krapcho, J.; Rovnyak, G.; Duff, K. J.; Lee, V. G.; Moquin, R. V.; Hedberg, S. A.; Moreland, S.; Brittain, R. J.; MCMullen, D. M.; Normandin, D. E.; Cucinotta, G. G. *J. Med. Chem.* **1992**, *35*, 780; (c) Neumeyer, J. L.; Kula, N. S.; Baldessarini, R. J.; Baindur, N. *J. Med. Chem.* **1992**, *35*, 1466.
6. (a) Grunewald, G. L.; Dahanukar, V. H.; Criscione, K. R. *Bioorg. Med. Chem.* **2001**, *9*, 1957; (b) Grunewald, G. L.; Caldwell, T. M.; Q, Li.; Criscione, K. R. *J. Med. Chem.* **2001**, *44*, 2849.
7. Katritzky, A. R., II ed. In *Comprehensive Heterocyclic Chemistry*; Pergamon, 1996; Vol. 9, p 21.
8. Tietze, L. F.; Schimpf, R. *Synthesis* **1993**, 876.
9. Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 9244.
10. Wender, P. A.; Pedersen, T. M.; Scanio, M. J. C. *J. Am. Chem. Soc.* **2002**, *124*, 15154.
11. (a) Narender, M.; Reddy, M. S.; Kumar, V. P.; Reddy, V. P.; Rao, K. R.; Nageswar, Y. V. D. *J. Org. Chem.* **2007**, *72*, 1849; (b) Madhav, B.; Murthy, S. N.; Reddy, V. P.; Rao, K. R.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2009**, *50*, 6025; (c) Murthy, S. N.; Madhav, B.; Kumar, A. V.; Rao, K. R.; Nageswar, Y. V. D. *Helv. Chim. Acta* **2009**, *92*, 2118; (d) Murthy, S. N.; Madhav, B.; Reddy, V. P.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2010**, *51*, 3649; (e) Shankar, J.; Karnakar, K.; Srinivas, B.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2010**, *51*, 3938.
12. (a) Rao, K. R.; Nageswar, Y. V. D.; Srilakshmi, K.; Surendra, K. *Adv. Org. Synth.* **2005**, *1*. Bentham science Publishers Ltd; (b) Murthy, S. N.; Madhav, B.; Kumar, A. V.; Rao, K. R.; Nageswar, Y. V. D. *Tetrahedron* **2009**, *65*, 5251; Cyclodextines as Promoters in Aqueous Organic synthesis. (c) Rao, K. R.; Nageswar, Y. V. D.; Sridhar, R.; Reddy, V. P. *Curr. Org. Chem.* **2010**, *14*, 1308.
13. *General experimental procedure for the synthesis of azepines using β-cyclodextrin*: β-Cyclodextrin (10 mol %) was dissolved in water (20 ml), and to this clear solution, aniline (1.0 mmol) was added, stirred for 15 min, and followed by the addition of dimethyl/diethyl acetylenedicarboxylate (DMAD/DEAD 1.0 mmol) and 2,5-dimethoxytetrahydrofuran (1.0 mmol). The reaction mixture was heated at 60 °C until completion of the reaction as indicated by TLC. The reaction mixture was cooled to 5 °C and β-cyclodextrin was filtered. The aqueous layer was extracted with ethyl acetate (4 × 10 ml). The combined organic layers were washed with water, saturated brine solution, and dried over anhydrous $Na_2SO_4$. The combined organic layers were evaporated under reduced pressure and the resulting crude product was purified by column chromatography by using ethyl acetate and hexane (0.7:9.3) as eluent. The product was confirmed by IR, $^{1}H$ & $^{13}C$ NMR, mass spectra.

14. *Data for the representative examples of synthesized compounds*:
*(2E,4Z,6Z)-Dimethyl 1-phenyl-1H-azepine-2,3-dicarboxylate*: (Table 2, entry 1) yellow oil; $R_f$ (6.5% EtOAc/*n*-hexane); IR (KBr): $\nu_{max}$ 3833, 3419, 2925, 2855, 1729, 1649, 1219, 771 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, TMS) $\delta$ 13.3 (d, 1H, arom, $J$ = 12.8 Hz), 8.06 (d, 1H, arom, $J$ = 13.5 Hz), 7.42 (t, 2H, arom, $J$ = 15.8 Hz), 7.3–7.23 (m, 2H, arom), 6.96 (s, 1H, arom), 6.76 (d, 1H, arom, $J$ = 4.5 Hz), 6.46 (d, 1H, arom, $J$ = 4.5 Hz), 3.86–3.70 (m, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$,TMS) $\delta$ 165.9, 150.2, 149.5, 148.3, 139.9, 137.1, 95.7, 71.7, 52.3, 32.8, 28.9; Mass (ESI-MS): $m/z$ 308 $(M+Na)^+$; HRMS $m/z$ calcd for $C_{16}H_{15}NO_4$ 308.0980; found 308.0898 $(M+Na)^+$.

*(2E,4Z,6Z)-Dimethyl 1-(4-fluorophenyl)-1H-azepine-2, 3-dicarboxylate*: (Table 2, entry 2) light yellow oil; $R_f$ (7% EtOAc/*n*-hexane); IR (KBr): $\nu_{max}$ 3450, 2952, 1721, 1640, 1514, 1483, 1443, 1325, 1290, 1237, 1192, 1140, 1098, 1058, 799 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, TMS) $\delta$ 13.21 (d, 1H, arom, $J$ = 13.0 Hz), 7.93 (d, 1H, arom, $J$ = 13.5 Hz), 7.26–7.06 (m, 4H), 6.72 (d, 1H, arom, $J$ = 4.3 Hz), 6.43 (d, 1H, arom, $J$ = 4.3 Hz), 3.85 (d, 6H, $J$ = 10.7 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$, TMS) $\delta$ 168.8, 167.7, 162.3, 158.7, 148.4, 143.5, 136.4, 120.3, 119.4, 118.4, 116.8, 112.8, 52.0, 51.8, 29.5; Mass (ESI-MS); $m/z$ 326 $(M+Na)^+$; HRMS $m/z$ calcd for $C_{16}H_{14}NO_4F$ 326.0804; found 326.0810 $(M+Na)^+$.