Adducts of Diketene, Alcohols, and Aldehydes: Useful Building Blocks for 3,4-Dihydropyrimidinones and 1,4-Dihydropyridines

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Received 20 August 2010; revised 26 August 2010

Abstract: A novel, one-pot, solvent-free synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one and 1,4-dihydropyridines derivatives via a four-component cyclocondensation reaction of diketene, alcohol, and aldehyde with urea or ammonium acetate is presented.

Key words: dihydropyridines, dihydropyrimidines, diketene, multicomponent reaction, neat condition

Functionalized dihydropyrimidinones have recently emerged as an integral part of several calcium channel blockers, antihypertensives, and a1-adrenergic antagonists.[1a,b] Particularly, aryl-3,4-dihydropyrimidinones exhibit a wide spectrum of biological activity such as antiviral, antitumor, antibacterial, and anti-inflammatory behavior[1c,d] and they are used as a starting point for the preparation of complex heterocyclic scaffolds with pharmacological properties.[1e] These reasons have motivated researchers to extend the scope of the Biginelli-type reaction to other 1,3-dicarbonyl compounds such as β-ketolactones,[1f] β-diamides,[1g] and cyclic diketones.[1h]

1,4-Dihydropyridines are among the most widely used drugs. The heterocyclic ring in 1,4-dihydropyridines is a common feature of various bioactive compounds such as anticonvulsant, antidiabatic, antianxiety, antidepressive, antitumor, analgesic, seditative, vasodilator, bronchodilator, hypnotic, and anti-inflammatory agents.[2a,b] Some derivatives of 1,4-dihydropyridines, such as Nifedipine and Lacidipine (Figure 1), are used commercially as calcium channel blockers for the treatment of cardiovascular diseases[2c] including hypertension. They are also known as neuroprotectants, used for anti-platelet treatment of aggregators, and are important in the treatment of Alzheimer's disease as anti-ischemic agents.[2d]

However, a number of the reported protocols for the synthesis of dihydropyrimidinones[3] and 1,4-dihydropyridines[4] in high yields require solvents and catalysts, such as heavy metals, that are not acceptable in the context of cost or green chemistry. However, developments in this area require solvent-free methods and diversity in reagents that are potentially superior to existing methods with regard to generality, simplicity, high yields, and handling. In this respect, we are interested in introducing potential solvent-free or 'neat' diketene/alcohol/aldehyde adducts with new and interesting chemistry to overcome limitations due to the presence of general acids such as sulfuric acid or trifluoroacetic acid. This new solvent-free or 'neat' method is based on the use of diketene as an in situ source of various β-keto esters in the four-component synthesis of dihydropyrimidinones and 1,4-dihydropyridines. The solvent-free approach, simplicity, and variety of derivatives available (using various aldehydes and alcohols) of the four-component procedure presented here makes it an interesting alternative to three-component approaches.

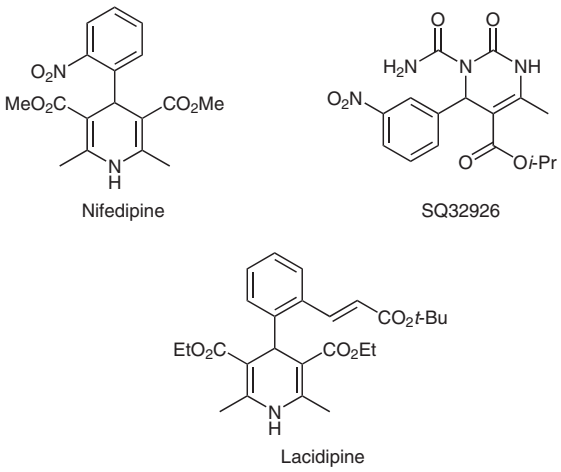

Figure 1 Examples of biologically active dihydropyrimidinone and 1,4-dihydropyridine derivatives

The three-component synthesis of dihydropyrimidinones and 1,4-dihydropyridines via Biginelli and Hantzsch conditions has been studied.[3,4] Chiba, Sato, and Kato,[5] reported the halogenation of diketene in a multistep synthesis to generate the halomethyl-dicarbonyl group through Biginelli heterocyclization. To our surprise, the one-pot reaction between diketene, urea, and an aldehyde in the presence of trifluoroacetic acid as a catalyst and methanol as a solvent, produced the Biginelli product, e.g. 3,4-dihydropyrimidin-2(1*H*)-ones. Also, this study showed that methanol is a main component of this reaction. Based on this finding, we have explored the potential of solvent-free diketene/alcohol/aldehyde adducts for four-component condensation of this adduct with ammonium acetate and urea under reflux conditions.

Earlier we reported the application of the in situ 1,3-dicarbonyl generated from diketene and alcohols or amines

SYNTHESIS 2010, No. 23, pp 4057–4060
Advanced online publication: 08.10.2010
DOI: 10.1055/s-0030-1258291; Art ID: Z21010SS
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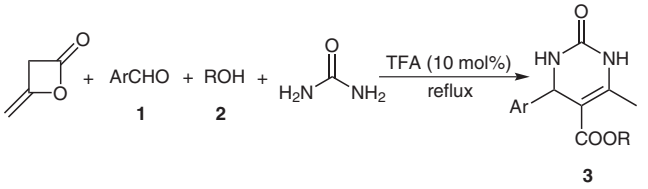
leading to the synthesis of novel furans or hydrazine enaminones, pyrans, and others.[6] Recently, we have shown that solvolytic and non-solvolytic ring-opening reactions of diketene are facilitated.[6] Here we wish to report the use of diketene, alcohols **2**, and aldehydes **1** under solvent-free conditions, with general catalysts such as sulfuric or trifluoroacetic acid for the one-pot synthesis of 3,4-dihydropyrimidinones **3** and 1,4-dihydropyridines **4** via four-component Biginelli-type and Hantzsch-type condensation protocols, respectively.

The solvent-free reaction of diketene, arylaldehydes **1**, and alcohols **2**, with urea in the presence of a catalytic amount of trifluoroacetic acid undergoes a Biginelli cyclocondensation reaction at reflux to produce 3,4-dihydropyrimidin-2(1*H*)-one derivatives **3** in 76–91% yields (Table 1).

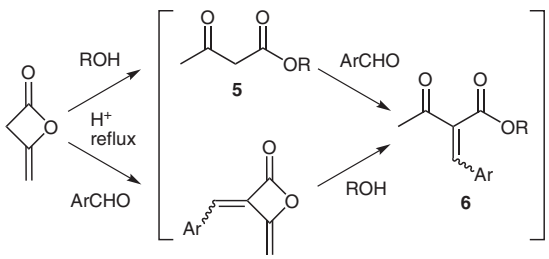
Table 1 Solvent-Free Four-Component Biginelli-Type Condensation



1 2 3

Product	Ar	R	Mp (°C)		Yield[a] (%)
			Found	Reported	
3a	Ph	Me	205–208	207–210[3b]	85
3b	Ph	Et	199–204	201–203[3b]	76
3c	2-ClC_6H_4	Me	253–255	252–253[3i]	83
3d	2-ClC_6H_4	Et	213–216	215–218[3b]	84
3e	3-ClC_6H_4	Me	208–211	208–210[3k]	83
3f	3-ClC_6H_4	Et	195–196	192–193[3g]	82
3g	4-ClC_6H_4	Me	205–207	204–207[3g]	89
3h	4-ClC_6H_4	Et	212–214	210–212[3g]	84
3i	4-$O_2NC_6H_4$	Me	236–238	235–237[3b]	91
3j	4-$O_2NC_6H_4$	Et	210–212	207–210[3b]	88

[a] Isolated and unoptimized yields.



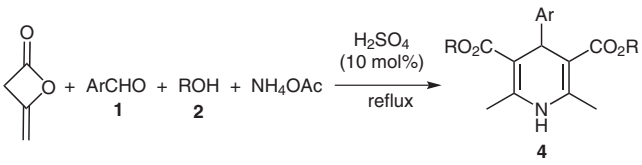
Scheme 1 Plausible mechanisms for the formation of dicarbonyl **5** and unsaturated adduct **6**

The reaction was found to be general, with ammonium acetate affording the 1,4-dihydropyridine products **4** in good yields. The results are summarized in Table 2.

Although we have not established the mechanism of these reactions, a possible explanation is proposed in Scheme 1. On the basis of the established chemistry of diketene,[6,7] it is reasonable to assume that the dihydropyrimidinones **3** and 1,4-dihydropyridines **4** apparently result from the initial addition of the alcohol or aldehyde to diketene to generation in situ 1,3-dicarbonyl **5** and unsaturated adduct **6** under acidic and reflux conditions, followed by Biginelli and Hantzsch conditions. These in situ generated intermediates under the reaction conditions give the corresponding 3,4-dihydropyrimidinones and 1,4-dihydropyridines derivatives (Tables 1 and 2).

In summary, we have described a novel, one-pot, solvent-free synthesis of 3,4-dihydropyrimidin-2(1*H*)-one and 1,4-dihydropyridine derivatives via a four-component cyclocondensation reaction of diketene, alcohol, and aldehyde with urea or ammonium acetate. In addition, the present method has the advantage that, not only is the reaction performed under one-pot, solvent-free conditions, but also, in addition to the aldehyde component, the alcohol component can be modified to achieve the synthesis of a variety of derivatives. The simplicity, variety of derivatives available, use of general acids of this four-component procedure makes it an interesting alternative to three-component approaches.

Table 2 Solvent-Free Four-Component Hantzsch-Type Condensation



1 2 4

Product	R	Ar	Mp (°C)		Yield[a] (%)
			Found	Reported	
4a	Me	Ph	162–164	–	80
4b	Me	2-$MeOC_6H_4$	159–161	170–171[4b]	70
4c	Me	3-$MeOC_6H_4$	165–167	168–170[4b]	71
4d	Me	4-ClC_6H_4	155–157	–	82
4e	Me	4-$O_2NC_6H_4$	160–162	165–168[4c]	78
4f	Et	Ph	155–157	154–159[4d,e]	83
4g	Et	2-ClC_6H_4	126–128	125–126[4f,g]	75
4h	Et	3-ClC_6H_4	125–127	120–121[4d]	75
4i	Et	4-ClC_6H_4	146–148	144–148[4d,g]	77
4j	Et	4-$O_2NC_6H_4$	128–130	129–132[4d,g]	81

[a] Isolated and unoptimized yields.

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Diketene, aldehydes, alcohols, NH_4OAc, and urea were obtained from Merck (Germany) and Fluka (Switzerland). Melting points were measured on an Electrothermal 9100 apparatus. ^1H and ^{13}C NMR spectra were measured ($CDCl_3$ or DMSO-d_6 soln) with a Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrophotometer.

In Table 1, identification of the products **3a** and **3h** was ascertained by high field ^1H and ^{13}C NMR, IR and comparison with available mp and spectroscopic literature data and **3i** by ^1H NMR, IR, and mp data. Compounds **3b–g,j** were characterized by comparison of their IR, and mp with literature data.

In Table 2, identification of the products **4a**,**d**,**f**, and **4h–j** was ascertained by high field ^1H and ^{13}C NMR and IR and comparison with available mp and spectroscopic literature data. Compounds **4b**,**c** and **4e–j** were characterized by comparison of their mp with literature data.

Methyl 6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3a); Typical Procedure

Equivalent amounts of neat adduct diketene (0.084 g, 1 mmol), MeOH (0.032 g, 1 mmol), and benzaldehyde (0.106 g, 1 mmol) in TFA (10 mol%) were magnetically stirred at reflux for 10 min, urea (0.06 g, 1 mmol) was added, and then the mixture was refluxed with stirring for the appropriate time (TLC monitoring). The reaction was cooled to 25 °C and the solid was washed with cooled H_2O and petroleum ether–Et_2O; yield: 0.21 g (85%).

IR (KBr): 3320, 3315, 1700, 1661, 1585, 1420 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 2.36 (s, CH_3), 3.63 (s, OCH_3), 5.41 (d, $^3J_{HH}$ = 2.1 Hz, CHNH), 5.53 (br, NH), 7.25–7.34 (m, C_6H_5), 7.56 (br, NH).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.08, 55.78, 60.36, 101.43, 126.49, 128.03, 128.81, 143.55, 146.21, 152.79, 166.04.

Ethyl 4-(4-Chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3h)

Yield: 0.25 g (84%).

IR (KBr): 3290, 3185, 1692, 1641, 1533, 1433 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.17 (d, $^3J_{HH}$ = 7.1 Hz, OCH_2CH_3), 2.33 (s, CH_3), 4.08 (d, $^3J_{HH}$ = 7.1 Hz, OCH_2CH_3), 5.37 (d, $^3J_{HH}$ = 2.0 Hz, CHNH), 6.08 (br, NH), 7.24 (d, $^3J_{HH}$ = 8.1 Hz, 2 CH of C_6H_4), 7.28 (d, $^3J_{HH}$ = 8.1 Hz, 2 CH of C_6H_4), 8.26 (br, NHCH).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.17, 18.64, 55.12, 60.14, 101.17, 128.03, 128.88, 132.16, 142.24, 146.47, 153.39, 165.44.

Methyl 6-Methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3i)

Yield: 0.26 g (91%).

IR (KBr): 3345, 3090, 1706, 1631, 1507, 1425 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 2.45 (s, CH_3), 3.73 (s, OCH_3), 5.60 (s, CHNH), 5.75 (br, NH), 7.58 (d, $^3J_{HH}$ = 7.6 Hz, 2 CH of C_6H_4), 7.26 (d, $^3J_{HH}$ = 7.6 Hz, 2 CH of C_6H_4), 8.37 (br, NHCH).

Dimethyl 2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4a); Typical Procedure

Neat adduct diketene (0.17 g, 2 mmol), MeOH (0.032 g, 1 mmol), and benzaldehyde (0.106 g, 1 mmol) in H_2SO_4 (10 mol%) were stirred magnetically at reflux for 10 min, NH_4OAc (0.077 g, 1 mmol) was added, and then the mixture was refluxed with stirring the appropriate time (TLC monitoring). The reaction was cooled to 25 °C and the solid was washed with cooled H_2O and petroleum ether–Et_2O; yield: 0.24 g (80%).

IR (KBr): 3287, 1700, 1656, 1463, 1213, 1105 cm^{-1}.

^1H NMR (500.13 MHz, DMSO-d_6): δ = 2.28 (s, 6 H), 3.54 (s, 6 H), 4.89 (s, 1 H), 7.09–7.45 (m, 5 H), 8.87 (s, 1 H).

^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 18.47, 37.27, 51.10, 101.23, 127.27, 127.31, 128.37, 129.69, 146.13, 148.29, 168.64.

Dimethyl 4-(4-Chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4d)

Yield: 0.27 g (82%).

IR (KBr): 3329, 1697, 1650, 1470, 1219, 1127 cm^{-1}.

^1H NMR (500.13 MHz, $CDCl_3$): δ = 2.35 (s, 6 H), 3.67 (s, 6 H), 4.99 (s, 1 H), 5.73 (s, 1 H), 7.19–7.28 (m, 4 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 19.56, 39.01, 50.99, 103.73, 128.14, 129.07, 131.84, 144.22, 145.98, 167.81.

Diethyl 2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4f)

Yield: 0.27 g (83%).

IR (KBr): 3342, 1700, 1657, 1473, 1198, 1129 cm^{-1}.

^1H NMR (500.13 MHz, $CDCl_3$): δ = 1.23 (t, $^3J_{HH}$ = 7.0 Hz, 6 H), 2.34 (s, 6 H), 4.12 (q, $^3J_{HH}$ = 7.0 Hz, 4 H), 4.91 (s, 1 H), 5.68 (s, 1 H), 7.07–7.43 (m, 5 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.91, 19.56, 39.43, 59.82, 103.14, 127.25, 127.32, 128.34, 129.61, 146.19, 148.25, 167.34.

Diethyl 4-(3-Chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4h)

Yield: 0.27 g (75%).

IR (KBr): 3320, 1690, 1642, 1475, 1200, 1136 cm^{-1}.

^1H NMR (500.13 MHz, $CDCl_3$): δ = 1.25 (t, $^3J_{HH}$ = 7.1 Hz, 6 H), 2.37 (s, 6 H), 4.13 (q, $^3J_{HH}$ = 7.1 Hz, 4 H), 4.99 (s, 1 H), 5.62 (s, 1 H), 7.11–7.29 (m, 4 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.18, 19.61, 39.74, 59.81, 103.82, 126.25, 126.31, 128.29, 129.04, 1433.60, 144.02, 149.73, 167.30.

Diethyl 4-(4-Chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4i)

Yield: 0.28 g (77%).

IR (KBr): 3345, 1695, 1649, 1480, 1210, 1137 cm^{-1}.

^1H NMR (500.13 MHz, $CDCl_3$): δ = 1.22 (t, $^3J_{HH}$ = 7.2 Hz, 6 H), 2.33 (s, 6 H), 4.09 (q, $^3J_{HH}$ = 7.2 Hz, 4 H), 4.96 (s, 1 H), 5.65 (s, 1 H), 7.17 (d, $^3J_{HH}$ = 8.4 Hz, 2 H), 7.21 (d, $^3J_{HH}$ = 8.4 Hz, 2 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.26, 19.58, 39.31, 59.80, 103.10, 128.31, 129.42, 131.73, 143.88, 146.32, 167.39.

Diethyl 2,6-Dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4j)

Yield: 0.30 g (81%).

IR (KBr): 3324, 1695, 1647, 1473, 1205, 1131 cm^{-1}.

^1H NMR (500.13 MHz, $CDCl_3$): δ = 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 6 H), 2.31 (s, 6 H), 4.19 (q, $^3J_{HH}$ = 7.1 Hz, 4 H), 4.76 (s, 1 H), 5.67 (s, 1 H), 7.53 (d, $^3J_{HH}$ = 7.9 Hz, 2 H), 8.12 (d, $^3J_{HH}$ = 8.4 Hz, 2 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.81, 19.56, 39.37, 59.84, 103.41, 124.1, 128.73, 145.5, 146.92, 156.3, 167.32.

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References

(1) (a) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806. (b) Kappe, C. O.; Fabian, W. M. F. *Tetrahedron* **1997**, *53*, 2803. (c) Singh, K.; Singh, J.; Deb, P. K.; Singh, H. *Tetrahedron* **1999**, *55*, 12873. (d) Fu, N. Y.; Yuan, Y. F.; Cao, Z.; Wang, S. W.; Wang, J. T.; Peppe, C. *Tetrahedron* **2002**, *58*, 4801. (e) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043. (f) Byk, G.; Gettlieb, H. E.; Herscovici, J.; Mirkin, F. *J. Comb. Chem.* **2000**, *2*, 732. (g) Mokrosz, J. L.; Paluchowska, M. H.; Szneler, E.; Drozdz, B. *Arch. Pharm. (Weinheim, Ger.)* **1989**, *322*, 231. (h) Abelman, M. M.; Smith, S. C.; James, D. R. *Tetrahedron Lett.* **2003**, *44*, 4559.

(2) (a) Janis, R. A.; Triggle, D. J. *J. Med. Chem.* **1983**, *26*, 775. (b) Godfraid, T.; Miller, R.; Wibo, M. *Pharmocol. Rev.* **1986**, *38*, 321. (c) Gaudio, A. C.; Korolkovas, A.; Takahata, Y. *J. Pharm. Sci.* **1994**, *83*, 1110. (d) Klusa, V. *Drugs Future* **1995**, *20*, 135.

(3) (a) Chen, X. H.; Xu, X. Y.; Liu, H.; Cun, L. F.; Gong, L. Z. *J. Org. Chem.* **2000**, *65*, 3864. (b) Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem.* **2003**, *68*, 587. (c) Hassani, Z.; Islami, M. R.; Kalantari, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4479. (d) Zumpe, F. L.; Flüb, M.; Schmitz, K.; Lender, A. *Tetrahedron Lett.* **2007**, *48*, 1421. (e) Kalita, H. R.; Phukan, P. *Catal. Commun.* **2007**, *8*, 179. (f) Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454. (g) Sabitha, G.; Kumar Reddy, G. S. K.; Reddy, C. S.; Yadav, J. S. *Synlett* **2003**, 858. (h) Shaabani, A.; Bazgir, A.; Teimouri, F. *Tetrahedron Lett.* **2003**, *44*, 857. (i) Lu, J.; Ma, H. *Synlett* **2000**, 63. (j) Reddy, Y. T.; Rajitha, B.; Reddy, P. N.; Kumar, B. S.; Rao, V. P. *Synth. Commun.* **2004**, *34*, 3821. (k) Suzuki, I.; Suzumura, Y.; Takeda, K. *Tetrahedron Lett.* **2006**, *47*, 7861.

(4) (a) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1. (b) Filipan-Litvić, M.; Litvić, M.; Cepanec, I.; Vinković, V. *Molecules* **2007**, *12*, 2546. (c) Alarcon, C.-L.; Vergara, L. J. N.; Squella, J. A. *Electrochim. Acta* **2003**, *48*, 2505. (d) Debache, A.; Boulcina, R.; Belfaitah, A.; Rhouati, S.; Carbonib, B. *Synlett* **2008**, 509. (e) Osnaya, R.; Arroyo, G. A.; Parada, L.; Delgado, F.; Trujillo, J.; Salmón, R.; Miranda, M. *ARKIVOC* **2003**, *(xi)*, 112. (f) Minga, L.; Si, G. W.; Rong, W. L.; Feng, L. Y.; Zheng, Y. H. *J. Mol. Catal. A: Chem.* **2006**, *258*, 133. (g) Loev, B.; Goodman, M. M.; Snader, K. M.; Tedeschi, R.; Macko, E. *J. Med. Chem.* **1974**, *17*, 956. (h) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957. (i) Eisner, D.; Kuthan, U. J. *Chem. Rev.* **1972**, *72*, 1. (j) Sharma, G. V. M.; Reddy, K. L.; Lakshmi, P. S.; Krishna, P. R. *Synthesis* **2006**, 55. (k) Zolfigol, M. A.; Salehi, P.; Safaiee, M. *Lett. Org. Chem.* **2006**, *3*, 153. (l) Zolfigol, M. A.; Safaiee, M. *Synlett* **2004**, 827. (m) Moghadam, M.; Nasr, M.; Tangestaninejad, S.; Mirkhani, V. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2026. (n) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141.

(5) Chiba, T.; Sato, H.; Kato, T. *Heterocycles* **1984**, *22*, 493.

(6) (a) Alizadeh, A.; Zohreh, N.; Rostamnia, S. *Tetrahedron* **2007**, *63*, 8083. (b) Alizadeh, A.; Zohreh, N.; Zhu, L. G. *Tetrahedron* **2009**, *65*, 2684. (c) Alizadeh, A.; Zohreh, N.; Zhu, L.-G. *Synthesis* **2009**, 464. (d) Alizadeh, A.; Babaki, M.; Zohreh, N. *Synthesis* **2008**, 3295. (e) Alizadeh, A.; Zohreh, N.; Zhu, L. G. *Synthesis* **2008**, 2073. (f) Alizadeh, A.; Hosseinpour, R.; Rostamnia, S. *Synthesis* **2008**, 3742.

(7) (a) Hyatt, J. A. *J. Org. Chem.* **1984**, *49*, 5102. (b) Sato, M.; Kanuma, N.; Kato, T. *Chem. Pharm. Bull.* **1982**, *30*, 4359. (c) Sato, M.; Kanuma, N.; Kato, T. *Chem. Pharm. Bull.* **1982**, *30*, 1315. (d) Baldwin, S. W.; Wilkinson, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 3634. (e) Boeckman, R. K.; Thomas, A. J. *J. Org. Chem.* **1982**, *47*, 2823. (f) Jager, G. *Chem. Ber.* **1972**, *105*, 137. (g) Kato, T.; Kubota, Y. *Yakugaku Zasshi* **1967**, *87*, 1212. (h) Kato, T.; Kubota, Y. *Yakugaku Zasshi* **1969**, *89*, 1477.

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