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"D-Glucose" phase transfer catalyzed synthesis of benzimidazolyl oxadiazole derivatives

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ABSTRACT

*2-(Chloromethyl)benzimidazole (**1**) on condensation with 2-mercapto-1,3,4-oxadiazoles **(2)** gave 2-[5-phenyl-1,3,4-oxadiazol-2-thiomethyl]-1H-benzimidazole **(5)**. Alternatively, **5** could also be prepared by the treatment of o-phenylenediamine **(3)** with 1,3,4-oxadiazole-2-thioacetic acid **(4)** under Philips conditions. **5** on treatment with dialkyl sulfate in acetonitrile using D-glucose as PTC gave the corresponding N-alkylated derivative i.e. benzimidazolylalkylthiooxadiazole **(7)**. The latter i.e. **7(a-e)** could also be prepared, alternatively, by the reaction of 2-(chloromethyl)-N-methylbenzimidazole **(6)** with 2-mercapto-1,3,4-oxadiazoles **(2)**. Even though, there are several other PTC's reported in literature, for the first time we employed D-glucose as PTC because it has got characteristics similar to that of crown ethers and polyethylene glycol. Furthermore, it is readily available, reasonably cheap, non-toxic and eco-friendly in character.*

Keywords: Benzimidazole, 5-substituted-2-thio-1,3,4-oxadiazoles, D-glucose, phase transfer catalyst

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INTRODUCTION

Literature search reveals that the derivatives of 1,3,4-oxadiazoles possesses significant biological activity.[1-3] Particularly, the 2-aryl-5-substituted-1,3,4-oxadiazoles have been reported to show anti-bacterial, anti-fungal, anti-inflammatory, analgesic and hypoglycemic activities.[4-10] Additionally, the utility of benzimidazole derivatives for building the various organic heterocycles and for preparation of better chemotherapeutic agents has also been well documented in literature.[11,12] Combining these facts with our interest to build new benzimidazole derivatives, we now wish to report the synthesis of *N*-alkyl-2'-(5-phenyl-1,3,4-

oxadiazole-2-thiomethyl)benzimidazoles and their derivatives in two different routes employing D-glucose as phase transfer catalyst.

MATERIALS AND METHODS

Melting points were determined in open capillaries in sulfuric acid bath and are uncorrected. TLC analysis was carried out on glass plates coated with silica gel GF-245 and visualized using Iodine/UV lamp. IR spectra were recorded on a Perkin-Elmer model 446 instrument in KBr phase. ^{1}H NMR were recorded in $CDCl_3$/DMSO-d_6 using 400 MHz Varian Gemini spectrometer and mass spectra were recorded on a LCMS spectrometer, model HP-5989A. Elemental analyses were carried out on a Perkin–Elmer 240C CHN analyzer. The required starting materials, 2-(chloromethyl)benzimidazole **(1)**, 2-mercapto-1,3,4-oxadiazoles **(2)** 1,3,4-oxadoazole-2-thioacetic acid **(4)** & 2-(chloromethyl)-*N*-methylbenzimidazole **(6)** were synthesized according to the literature methods reported earlier.[14-24] **3** was obtained from commercial suppliers.

General procedure for the synthesis of 5 from 1 and 2:
A mixture of **2** (1.78 g, 0.01 mol), K_2CO_3 (1.65 g, 0.012 mol), D-glucose (0.004 g), **1** (1.66 g, 0.01 mol) and DMF (50 ml) was stirred at room temperature for 2h. At the end of this period, the reaction mixture was poured into ice-water. The separated product was filtered, washed with water, dried and recrystallised from ethyl acetate to obtain pure **5** (Table 1).

5a: IR (KBr): 3437-2924 cm^{-1} (vb, medium, –NH-); ^{1}H-NMR spectrum (DMSO d_6/TMS): (ppm) δ 4.80 (s, 2H, -C**H**$_2$-S-), 7.10-8.00 (complex m, 9H, **aryl protons**), 12.60 (s, 1H, D_2O exch., –N**H**); ^{13}C-NMR (DMSO d_6/TMS) δ (ppm) 20.3 (-**C**H$_2$-S-), 122.1, 122.9, 126.4, 129.3, 132.0, 138.1, 152.9, 161.5, 165.6 (**aromatic carbons**); MS: m/z, 309 (M^+ + 1). Anal. Calcd. for $C_{16}H_{12}N_4OS$: C, 62.32; H, 3.92; N, 18.17. Found C, 62.30; H, 3.92; N, 18.19.

5b: IR (KBr): 3430-2933 cm^{-1} (vs, medium, –NH-); ^{1}H-NMR spectrum (DMSO d_6/TMS): (ppm) δ 2.30 (s, 3H, Ar-C**H**$_3$), 4.80 (s, 2H, -C**H**$_2$-S-), 7.00-8.00 (complex m, 8H, **aryl protons**), 12.50 (s, 1H, D_2O exch., –N**H**); MS: m/z, 323 (M^+ + 1). Anal. Calcd. for $C_{16}H_{14}N_4OS$: C, 63.33; H, 4.38; N, 17.38. Found C, 63.30; H, 4.40; N, 17.37.

5c: IR (KBr): 3207-2859 cm^{-1} (vb, medium, –NH-); ^{1}H-NMR spectrum (DMSO d_6/TMS): (ppm) δ 4.90 (s, 2H, -C**H**$_2$-S-), 7.30-8.40 (complex m, 8H, **aryl protons**), 12.92 (s, 1H, D_2O exch., –N**H**); MS: m/z, 353 (M^+ + 1).. Anal. Calcd. for $C_{16}H_{11}N_5O_3S$: C, 54.38; H, 3.14; N, 19.82. Found C, 54.36; H, 3.15; N, 19.80.

5d: IR (KBr): 3437 cm^{-1} (vb, medium, –NH); ^{1}H-NMR spectrum (DMSO d_6/TMS): (ppm) δ 4.87 (s, 2H, -C**H**$_2$-S-), 7.25-8.30 (complex m, 8H, **aryl protons**), 12.87 (s, 1H, D_2O exch., –NH); ^{13}C-NMR (DMSO d_6/TMS) δ (ppm) 30.3 (-**C**H$_2$-S-), 121.3, 124.9, 126.8, 131.7, 132.8, 138.1, 164.6 (**aromatic carbons**); MS: m/z, 353 (M^+ + 1). Anal. Calcd. for $C_{16}H_{11}N_5O_3S$: C, 54.38; H, 3.14; N, 19.82. Found C, 54.36; H, 3.16; N, 19.81.

5e: IR (KBr): 3200-2935 cm^{-1} (vb, medium, –NH-); ^{1}H-NMR spectrum (DMSO d_6/TMS): (ppm) δ 4.82 (s, 2H, -C**H**$_2$-S-), 7.20-7.90 (complex m, 8H, **aryl protons**), 12.60 (s, 1H, D_2O exch., –

N**H**); MS: m/z, 343 (M^+ + 1). Anal. Calcd. for $C_{16}H_{11}ClN_4OS$: C, 56.06; H, 3.23; N, 16.34. Found C, 56.08; H, 3.24; N, 16.31.

General procedure for the Synthesis of 5 from 3 and 4 (Alternate synthesis):
A mixture of **3** (2.36 g, 0.01 mol), **4** (1.08 g, 0.01 mol) and aq. HCl (4N, 100 ml) was refluxed for 12-14h. At the end of this period, the reaction mass was diluted with water and P^H was adjusted to ≈7.0 with aq. NH_3. The separated product was filtered, washed with water and dried to obtain **5** (Table 1).
5a: *Yield 74%, m.p. 165-67^{0}C*
5b: *Yield 72%, m.p. >250^{0}C*
5c: *Yield 77%, m.p. 169-72^{0}C*
5d: *Yield 68%, m.p. 176-80^{0}C*
5e: *Yield 75%, m.p. 165-68^{0}C*

General procedure for the Synthesis of 7 from 5:
A mixture of **5** (3.08 g, 0.01 mol), K_2CO_3 (1.65 g, 0.012 mol), D-glucose (0.004 g) and acetonitrile (30 ml) was stirred at room temperature for 30mins. Later, alkylating agent i.e., dialkyl sulfate (1.0 ml, 0.011 mol) was added and the whole mixture stirred at room temperature for 3h. At the end of this period, the reaction mass was poured into ice-water (150 ml) and stirred for another 30 min. The separated solid was filtered, washed with water, dried and recrystallized from ethyl acetate to obtain pure **7** (Table 1).

7a: IR (KBr): Showed absence of any broad medium band in the region 3000-3500 cm^{-1} which is a diagnostic peak due to –NH– stretching; ^{1}H-NMR spectrum (DMSO d_6/TMS) showed signals at δ 3.89 (s, 3H, -N-C**H**$_3$), 4.93 (s, 2H, -C**H**$_2$-S-), 7.16-7.94 (complex m, 9H, **aryl protons**); ^{13}C-NMR spectrum (DMSO d_6/TMS) showed signals at δ 28.7 (-**C**H$_2$), 30.0 (-N-**C**H$_3$) and other signals due to aromatic carbons 118.8, 121.0, 122.4, 126.4, 129.3, 132.0, 135.9, 141.8, 149.3, 162.6, 165.4; MS: m/z, 323 (M^+ + 1). Anal. Calcd. for $C_{17}H_{14}N_4OS$: C, 63.33; H, 4.38; N, 17.38. Found C, 63.31; H, 4.39; N, 17.39.

7b: IR (KBr): Showed absence of –NH- stretching in the region 3000-3500 cm^{-1}; ^{1}H-NMR spectrum (DMSO d_6/TMS) showed signals at δ 2.30 (s, 3H, Ar-C**H**$_3$), 3.75 (s, 3H, -N-C**H**$_3$), 4.93 (s, 2H, -C**H**$_2$-S-), 7.11-7.55 (complex m, 8H, **aryl protons**); MS (CI): m/z 336 (M^++H).

7c: IR (KBr): Showed absence of –NH- stretching in the region 3000-3500 cm^{-1}; ^{1}H-NMR spectrum (DMSO d_6/TMS) showed signals at δ 3.89 (s, 3H, -N-C**H**$_3$), 4.93 (s, 2H, -C**H**$_2$-S-), 7.05-7.64 (complex m, 8H, **aryl protons**); MS: m/z 367 (M^++H).

7d: IR (KBr): Showed absence of –NH- stretching in the region 3000-3500 cm^{-1}; ^{1}H-NMR spectrum (DMSO d_6/TMS) showed signals at δ 3.83 (s, 3H, -N-C**H**$_3$), 4.93 (s, 2H, -C**H**$_2$-S-), 7.10-7.57 (complex m, 8H, **aryl protons**); MS: m/z 367 (M^++H).

7e: IR (KBr): Showed absence of –NH- stretching in the region 3000-3500 cm^{-1}; ^{1}H-NMR spectrum (DMSO d_6/TMS) showed signals at δ 3.68 (s, 3H, -N-C**H**$_3$), 4.93 (s, 2H, -C**H**$_2$-S-), 7.16-7.94 (complex m, 8H, **aryl protons**); MS: m/z 356 (M^++H).

7f: IR (KBr): Showed absence of –NH- stretching in the region 3000-3500 cm^{-1}; ^{1}H-NMR spectrum (DMSO d_6/TMS) showed signals at δ 1.89 (s, 3H, -N-CH_2-C**H**$_3$), 2.46 (s, 2H, -N-C**H**$_2$-), 4.68 (s, 2H, -C**H**$_2$-S-), 7.12-7.80 (complex m, 9H, **aryl protons**); MS: m/z 337 (M^++H).

7g: IR (KBr): Showed absence of –NH- stretching in the region 3000-3500 cm^{-1}; ^{1}H-NMR spectrum (DMSO d_6/TMS) showed signals at δ 1.90 (s, 3H, -N-CH_2-C**H**$_3$), 2.55 (s, 2H, -N-C**H**$_2$-), 4.50 (s, 2H, -C**H**$_2$-S-), 7.10-7.65 (complex m, 8H, **aryl protons**); MS: m/z 351 (M^++H).

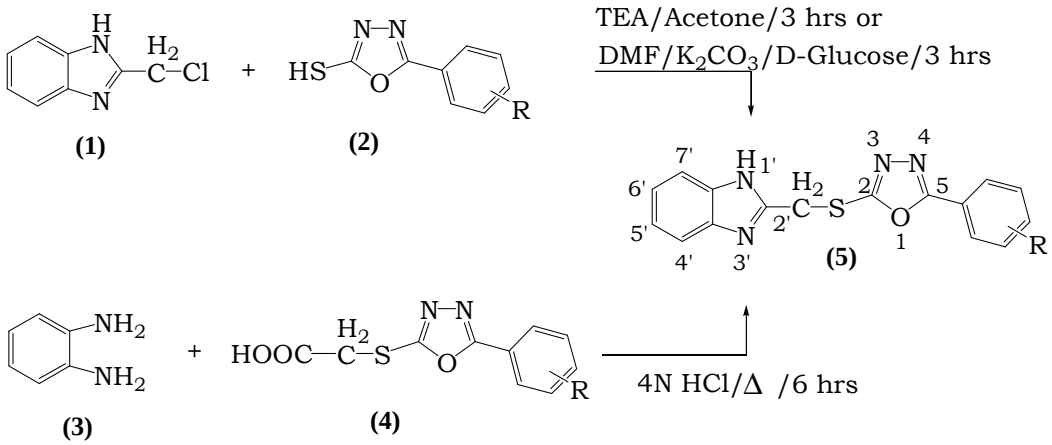
General procedure for the Synthesis of 7 from 6 and 2 (Alternate synthesis):
A mixture of **2** (1.78 g, 0.01 mol), K_2CO_3 (1.65 g, 0.012 mol), **6** (1.80 g, 0.01 mol), D-glucose (0.004 g) and DMF (50 ml) was stirred at room temperature for 2-3 h. At the end of this period, the reaction mixture was poured into ice-water. The separated product was filtered, washed with water, dried and recrystallised from methanol to obtain pure **7** (Table 1).
7a: *Yield 70%, m.p. 117-20^{0}C*
7b: *Yield 68%, m.p. 155-60^{0}C*
7c: *Yield 75%, m.p. 128-32^{0}C*
7d: *Yield 69%, m.p. 133-37^{0}C*
7e: *Yield 74%, m.p. 122-24^{0}C.*

RESULTS AND DISCUSSION

The reaction of 2-(chloromethyl)benzimidazole **(1)** with 2-mercapto-1,3,4-oxadiazole (**2a**, i.e. **2**, R=H) in acetone containing triethylamine as base at room temperature gave the previously reported[13] 2-[5-phenyl-1,3,4-oxadiazol-2-thiomethyl]-1H-benzimidazole (**5a**, i.e., **5**, R=H) in good yield. This is a lone incident and not much work seems to have been done on the synthesis of other arylsubstituted derivatives. We therefore, set out to study the reaction more intensively & extensively. We thought of carrying out this reaction using D-glucose as the phase transfer catalyst. We chose D-glucose because it has got characteristics similar to that of crown ethers and polyethylene glycol in that it acts like a cage and holds the K^+ ions of the base through complexation/coordination between lone-pairs of electrons on oxygen & K^+ ions thereby making CO_3^{-2} ions as stronger bases which can readily abstract proton from the –NH- of the reagent leading to enhancement of the reaction rate. Furthermore, glucose is readily available, reasonably cheap, non-toxic and eco-friendly in character.

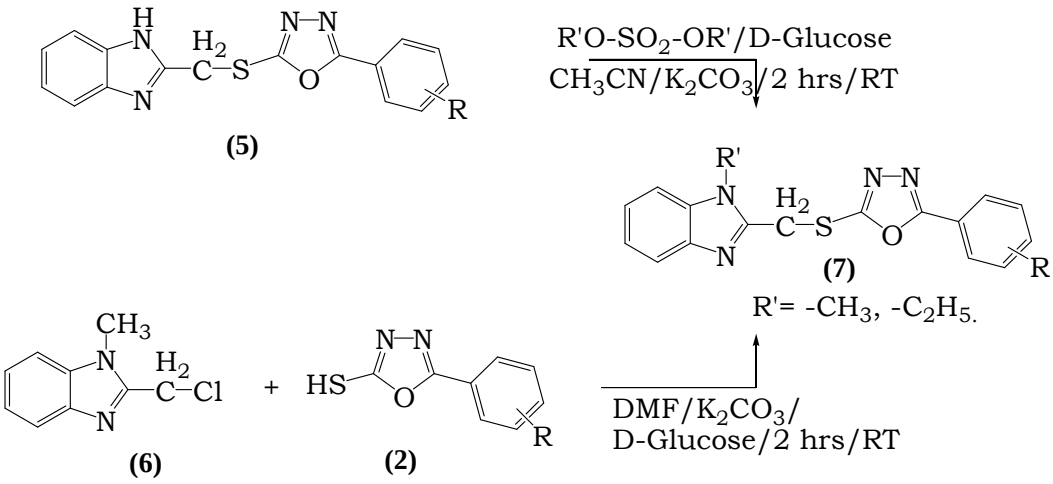
The reaction of **1** with **2a** (i.e., **2**, R=H) in DMF using potassium carbonate as base and D-glucose as phase transfer catalyst at room temperature gave **5a** (i.e., **5**, R=H). This reaction of **1** with **2a** has been found to be general one and has been extended to other **2** i.e. **2b** to **2e** and the products obtained were assigned structures **5b** to **5e** respectively, on the basis of spectral and analytical data. (For details please see Experimental Section).

The compound **5a** (i.e., **5**, R=H) could also be prepared by the condensation of *o*-phenylenediamine **(3)** with 1,3,4-oxadiazole-2-thioacetic acid **(4a)** under Phillip's conditions. This reaction of **4a** with **3** has been found to be general one and has been extended to other **4**. The products obtained, have been found to be **5** by comparison of their m.p., m.m.p., and TLC with those of the same products obtained in the earlier route **1+2a → 5a.** (**Scheme-1).**



Scheme 1. Synthetic pathway for the preparation of compounds 5(a-e)

Alkylation of **5a** (i.e., **5**, R=H) with dimethyl sulfate in acetonitrile in the presence of potassium carbonate as base and D-glucose as phase transfer catalyst gave a product which has been characterized as 2'-[5-phenyl-1,3,4-oxadiazol-2-thiomethyl]-*N*-methyl-benzimidazole **7a (**i.e., **7,** R=H**)** on the basis of its spectral and analytical data. Thus, its IR (KBr) spectrum showed the absence of any broad medium band in the region 3000-3500 cm^{-1} which is a diagnostic peak due to –NH– stretching. Its ^{1}H-NMR spectrum (DMSO d_6/TMS) showed signals at δ 3.89 (s, 3H, -N-C**H**$_3$), 4.93 (s, 2H, -C**H**$_2$-S-), 7.16-7.94 (complex m, 9H, **aryl protons**). Its normal ^{13}C-NMR spectrum (DMSO d_6/TMS) showed signals at δ 28.7 (-**C**H_2), 30.0 (-N-**C**H_3) and other signals due to **aromatic carbons** at 118.8, 121.0, 122.4, 126.4, 129.3, 132.0, 135.9, 141.8, 149.3, 162.6, 165.4 which were further confirmed from the DEPT spectrum of the compound. Its Mass spectrum when recorded in the CI method, showed the molecular ion peak at 323 corresponding to a molecular mass of 322 when recorded in the Q+1 mode.



Scheme 2. Synthetic pathway for the preparation of compounds 7(a-g)

In an yet another approach, the reaction of 2-(chloromethyl)-*N*-methylbenzimidazole **(6)** with 2-mercapto-5-phenyl-1,3,4-oxadiazoles (**2a**, i.e., **2**, R=H) in DMF using D-glucose as PTC and potassium carbonate as base at room temperature gave **7a** (i.e., **7,** R=H**)** identical with the one obtained in the route **5a** → **7a**. This reaction of **2a** (i.e., **2**, R=H) with **6** has been found to be a general one and has been extended to other derivatives of **2** i.e. **2b** to **2e** and the products obtained were assigned structure **7b** to **7e**, on the basis of spectral and analytical data. (For details please see Experimental Section) (Table 1). All the above reactions are briefly summarized in the **Scheme-2**.

Table-1: Characterization data of synthesized compounds

Compound	Substituents R	Yield (%)	M.P (Lit.) (^{o}C)
5a	H	88	168-70 (166) [9]
5b	*p*-CH_3	85	>250
5c	*p*-NO_2,	78	168-70
5d	*m*-NO_2	80	179-80
5e	*p*-Cl	83	165-66 (180) [9]
7a	H	80	118-20
7b	*p*-CH_3	79	158-63
7c	*p*-NO_2	83	128-32
7d	*m*-NO_2	79	135-37
7e	*p*-Cl	82	120-24
7f	H	80	110-12
7g	*p*-CH_3	80	120-25

CONCLUSION

A series of *N*-alkylbenzimidazole oxadiazoles **7(a-g)** were synthesised in very good yields employing D-glucose as phase transfer catalyst, which is readily available relatively cheap, perfectly non-toxic and eco-friendly in character.

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REFERENCES

[1] A. I Hashem, A. S. A Youssef, K. A. Kandeel, W. S. I. Abou-Elmagd, *Eur. J. Med. Chem.* **2007,** 42, 934.
[2] S. G. Kuecuekguezel, I. Kuecuekguezel, E. Tatar, S. Rollas, F. Sahin,. M Guelluece, E. D. Clercq, L. Kabasakal, *Eur. J. Med. Chem.* **2007,** 42, 893.
[3] A. A. Kadi, N. R. El-Brollosy, O. A. Al-Deeb, E. E. Habib, T. M. Ibrahim, A. A. El-Emam, *Eur. J. Med. Chem.* **2007,** 42, 235.
[4] F. A. Ashour, S. A. M. El-Hawash, M. A. Mahran, *Bull. Pharm. Sci., Assiut Uni*V. **1994**, 17(1), 17.
[5] Chen, Z. Li, Y. Han, *J. Agric. Food Chem.* **2000**, 48, 5312.

[6] D. H. Boschelli, D. T. Connor, D. A. Bornemeier, R. D. Dyer, J. A. Kennedy, P. J. Kuipers, G. C. Okonkwo, D. J. Schrier, and C. D. Wright. *J. Med. Chem.*, **1993,** 36, 1802.
[7] D. M. Michael, W. W. Michael, T. C. David, R. K. Catherine, J. S. Denis, D. D. Richard, *J. Med. Chem.*, **1993**, 36 (8), 1090.
[8] G. Sahin, E. Palaska, M. Ekozoghu, M. Ozalp, *Il Farmaco*, **2002**, 57, 539.
[9] E. Palaska, G. Sahin, P. Kelicen, N.T. Durlu, G. Altinok, *Il Farmaco*, **2002**, 57, 101.
[10] J. B. O'Neal, H. Rosen, P. B. Russell, A. C. Adams, A. Blumenthal, *J. Med. Chem.*, **1962**, 5 (3), 617.
[11] R. Rastogi, S. Sharma, *Synthesis*, **1983**, 861.
[12] T. C. Kuhler, M. Swanson, V. Sheherbuchin, H. Larrson, B. Mellgard, J. E. Sjostrom, *J. Med. Chem*., **1998**, 41, 1777.
[13] L. Mishra, V.K. Singh, N.K. Dubey, A.K. Mishra, *Biosci. Biotech. Biochem.*, **1993**, 57(6), 989.
[14] S. Herman, G. M. John, R. D. Allan *J. Am. Chem. Soc* **1943**, 65, 1854.
[15] J.R. Reid, N. D. Heindel, *J. Heterocyclic chem.*,**1976,** 13, 925.
[16] B. Maximo and V. W.Charles, *J.Org. Chem*. **1957**, 23, 1021.
[17] C. Anisworth *J. Am. Chem. Soc.* **1955**, 78, 4475.
[18] W. Richard, Young and H. W. Kathryn, *J. Am. Chem. Soc* **1954**, 77, 400.
[19] T. L. Rebstock, C. D. Ball, C. L. Hamner, H. M. Sell, *J. Am. Chem. Soc*., **1956**, 78, 5831.
[20] D. P. Pathak, N. Jain, P. Mishra, S. Jain, *Indian J. Het. Chem.*, **2005**, 15, 177.
[21] J. A. Vanallan, *J. Org. Chem*. **1956**, 21, 24.
[22] I. Ryuichi, K. Tsuneo, F.Toshikazu,; I. Keizo, T. Goro, *J. Heterocyclic Chem.*, **1989**, 26, 747.
[23] W. R. Roderick, C. W. Nordeen, A. M. Vonesch, R. N. Appell, *J. Med. Chem.*, **1972**, 15, 655.
[24] I.Ryuichi, K. Tsuneo, F. Toshikazu, I. Keizo, T. Goro, *J. Heterocyclic Chem.*, **1987,** 24, 31.