

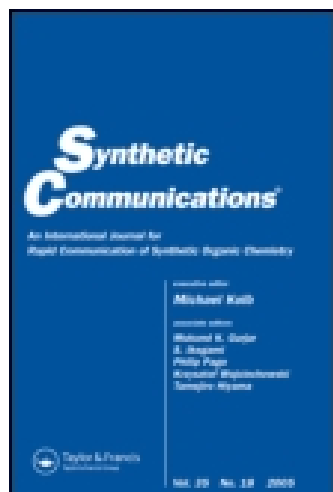
This article was downloaded by: [Universite Laval]

On: 07 July 2014, At: 23:52

Publisher: Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office:

Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/lcyc20>

Synthesis of Substituted Tricyclo[5.3.1.0^{4,9}]undecan-2,6-dione from 4,4-Disubstituted Cyclohexanone Enamines and Methacryloyl Chloride

Syeda Asghari Ahmed ^a, Kawsari Akhter ^a, Yoshisuke Tsuda ^b, M. Mahmum Hossain ^c, F. Holger Forsterling ^c & M. Giasuddin Ahmed ^a

^a Department of Chemistry, University of Dhaka, Dhaka, Bangladesh

^b Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa, Japan

^c Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin, USA

Published online: 24 Feb 2007.

To cite this article: Syeda Asghari Ahmed, Kawsari Akhter, Yoshisuke Tsuda, M. Mahmum Hossain, F. Holger Forsterling & M. Giasuddin Ahmed (2006) Synthesis of Substituted Tricyclo[5.3.1.0^{4,9}]undecan-2,6-dione from 4,4-Disubstituted Cyclohexanone Enamines and Methacryloyl Chloride, *Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry*, 36:9, 1273-1283

To link to this article: <http://dx.doi.org/10.1080/00397910500516381>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

Synthesis of Substituted Tricyclo[5.3.1.0^{4,9}]undecan-2,6-dione from 4,4-Disubstituted Cyclohexanone Enamines and Methacryloyl Chloride

M. Giasuddin Ahmed, Syeda Asghari Ahmed,
and Kawsari Akhter

Department of Chemistry, University of Dhaka, Dhaka, Bangladesh

Yoshisuke Tsuda

Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa,
Japan

M. Mahmum Hossain and F. Holger Forsterling

Department of Chemistry, University of Wisconsin—Milwaukee,
Milwaukee, Wisconsin, USA

Abstract: Morpholine enamines 4-acetyl-4-methyl-1-morpholinocyclohexene **4a**, 4-acetyl-4-phenyl-1-morpholinocyclohexene **4b**, and 4-acetyl-4-isopropenyl-1-morpholinocyclohexene **4c** react with methacryloyl chloride to give 1,7-dimethyl-4(N-morpholino) tricyclo[5.3.1.0^{4,9}]undecan-2,6-dione **9a**, 1-phenyl-7-methyl-4(N-morpholino) tricyclo[5.3.1.0^{4,9}]undecan-2,6-dione **9b**, and 1-isopropenyl-7-methyl-4(N-morpholino) tricyclo[5.3.1.0^{4,9}]undecan-2,6-dione **9c** respectively, along with the corresponding substituted adamandane-2,4-diones.

Keywords: Methacryloyl chloride, morpholine enamines, tricycloundecanediones

Received September 9, 2005

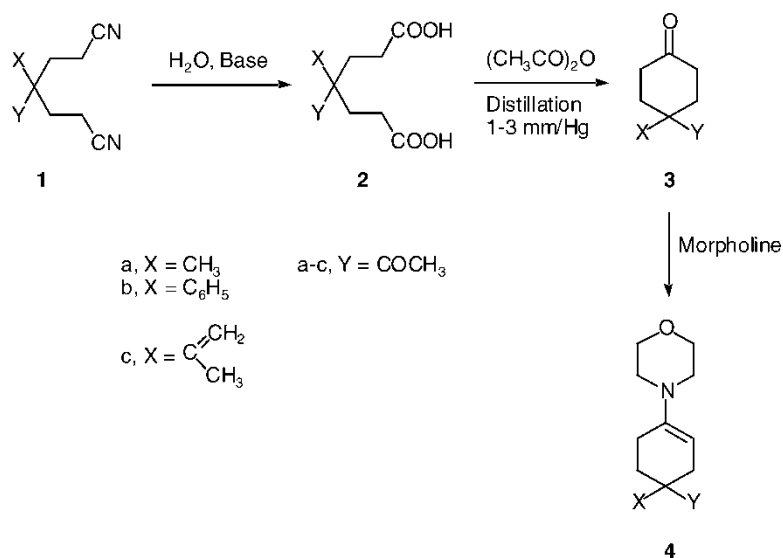
Address correspondence to M. Giasuddin Ahmed, Department of Chemistry, University of Dhaka, Dhaka 1000, Bangladesh. Fax: 880-2-8615583; E-mail: mgahmed1@yahoo.com

In continuation of our previous work^[1-4] on the synthesis of the substituted tricyclo[5.3.1.0^{4,9}]undecan-2,6-diones we now herein report the synthesis of three new substituted tricyclo[5.3.1.0^{4,9}]undecan-2,6-diones **9a**, **9b**, and **9c**. The synthesis is based on a general reaction of 4,4-disubstituted cyclohexanone enamines with methacryloyl chloride. We first prepared 4,4-disubstituted cyclohexanones **3a-c** following literature methods^[5,6] in which one of the substituents is an acetyl group (Scheme 1). The morpholine enamines **4a-c** were prepared (Scheme 1) in accordance with the general procedure reported earlier^[3,4] without using any catalyst.

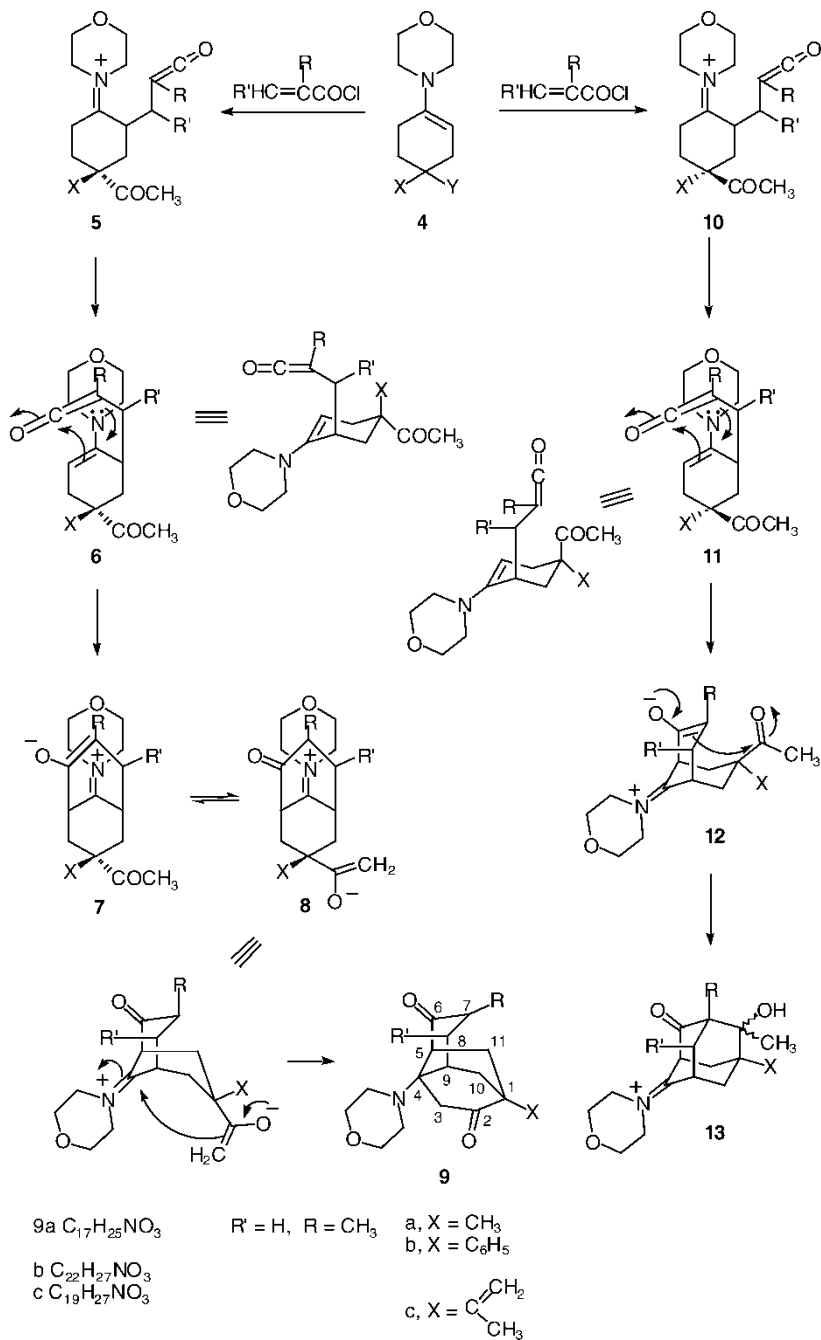
Methacryloyl chloride underwent reaction with the morpholine enamines **4a-c** to produce the compounds **9a** (25%), **9b** (25%), and **9c** (10%) respectively, in addition to the corresponding substituted isomeric adamantane-2,4-diones.^[7]

RESULTS AND DISCUSSION

The general reaction between α,β -unsaturated acid chlorides and 4,4-disubstituted cyclohexanone enamines is shown to follow the mechanistic pathways (Scheme 2) reported earlier,^[1] yielding substituted adamantane-2,4-diones and substituted tricycloundecan-2,6-diones. The formation of substituted adamantane-2,4-diones has been explained through the formation of the intermediate enolate anion **12**, which cyclizes eventually onto the



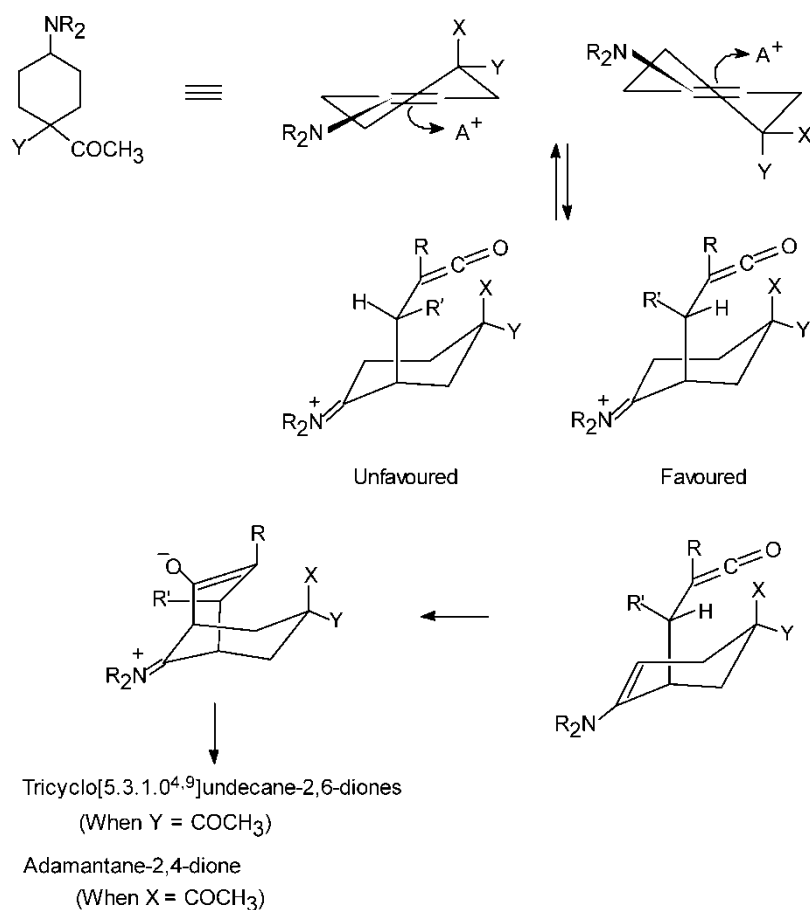
Scheme 1.



Scheme 2.

axially orientated acetyl group. When the acetyl group is in equatorial conformation it may give rise to an alternative enolate anion **8** (preferably twist form), which would lead to the formation of the tricycloundecan-2, 6-dione structures by cyclization onto the iminium carbon.

In our previous studies we found that the reactions of **4a**, **4b**, and **4c** with methacryloyl chloride yielded the corresponding adamantanediones^[7] **13a**, **13b**, and **13c** and the respective tricycloundecanediones **9a**, **9b**, and **9c**. It is evident that the substituent X is equatorial in the enolate anion **12**, producing the adamantanediones, and is axial in the enolate anion **8**, producing the tricycloundecanediones. The reactions of the same enamines also yielded a mixture of adamantanediones and tricycloundecanediones with acryloyl chloride, as reported^[1] earlier. The explanation for the formation of both such types of tricyclic compounds in reactions with



Scheme 3.

acryloyl chloride may be attributed to the steric interaction resulting from the axially orientated substituent X, or Y would be a minimum in the ketene or enolate anion where R' and R'' both are H (Scheme 3). A similar explanation may be put forward for similar results, which we obtained from such reactions with methacryloyl chloride, showing that the resulting steric interactions are still at a minimum when R' is H and R'' is CH₃.

The structures of the compounds **9a**, **9b**, and **9c** were fully established from its elemental analysis, IR spectra, ¹H and ¹³C NMR, ¹H–¹H NMR COSY, ¹³C–¹H NMR COSY, DEPT, HMBC, and mass spectral data. The coupling sites of all the protons of the compounds were located clearly from ¹H–¹H NMR COSY, and their coupling constants were determined from one-dimensional ¹H NMR spectrum. In the ¹H NMR spectra (Table 1) the equivalent CH₂–O–CH₂ methylene protons of the morpholine moiety of the compounds **9a–c** appeared as a triplet at δ 3.58–3.60 (3' and 5' protons) at the lowest field. On the other hand 2' and 6' protons, which are α to the N-atom, appeared as a multiplet, and the non-equivalence of these protons arises probably because of different spatial arrangements next to the cage structure. The methylene protons at position 3 gave two doublets (18.60–18.75 Hz) in the form of ABq, which characterizes their structural environment. The axial proton at position 3 is more deshielded than the equatorial protons because of the

Table 1. ¹H NMR spectral data of the tricycloundecandiones **9a**, **9b**, and **9c** (chemical shift in δ and coupling constants *J* in Hz)

Protons	9a	9b	9c
3-H ^a	2.24	2.42	2.26
3-H ^c	2.32	2.50	2.34
5-H	2.91	3.08	2.96
7-H	2.85	2.85	2.81
8-H ^a	1.87	1.92	1.86
8-H ^c	1.74	1.81	1.76
9-H	2.38	2.56	2.43
10-H ^a	1.77	2.17	1.84
10-H ^c	2.03	2.66	2.41
11-H ^a	1.63	2.03	1.71
11-H ^c	1.85	2.48	2.24
2', 6'-H ₂	2.43–2.56 (m)	2.50–2.63 (m)	2.42–2.55 (m)
3', 5'-H ₂	3.60	3.63	3.58
1-CH ₃	1.02	—	—
7-CH ₃	1.11	1.10	1.08
1-C ₆ H ₅	—	7.16–7.36 (m)	—
1-C-CH ₃	—	—	1.75
1-C-C-H ^c	—	—	4.72
1-C-C-H ^t	—	—	5.00

adjacent carbonyl group. But at position 3, the axial proton also receives steric shielding from the adjacent morpholine group (position 4), which is equatorial. The overall effect is that 3-H^a is more upfield by 0.08 ppm than 3-H^c. Of the alicyclic part, the most downfield proton was at bridge-head position 5 as it is flanked by a carbonyl group and a morpholino group. 8-H^a is more deshielded than 8-H^c because of the anisotropic effect of carbonyl group at position 6.

At both the positions 10 and 11 the axial protons came more upfield than the equatorial protons, 0.26–0.57 ppm in the case of 10-H^a and 0.22–0.53 ppm in the case of 11-H^a, probably because of the anisotropic effect of the X group at position 1. 7-CH₃ resonated at δ 1.08–1.11 as a doublet. The chemical shift value of 7-H at δ 2.81–2.85 is comparable to that of the axial proton at the 7-position in the reported^[1] similar tricyclo compound, 1-methyl-4-(N-morpholino)tricyclo[5.3.1.0^{4,9}]undecan-2,6-dione. This indicates the equatorial conformation of the methyl group in the compounds **9a**, **9b**, and **9c**, which is also expected for its bulky nature.

The coupling constants are shown in Table 2. The geminal couplings between 8-H^a and 8-H^c, 10-H^a and 10-H^c, and 11-H^a and 11-H^c showed the *J* values as 12.80–13.80, 11.9–13.9, and 14.5–14.75 respectively. The large *J* values of 11.9–12.15 Hz were observed for vicinal coupling between 5-H and 11-H^c. The vicinal coupling between 9-H and 10-H^c also showed a large coupling constant of 11.90–12.00 Hz (Table 3).

The ¹³C NMR of tricyclic compounds **9a**, **9b**, and **9c** were analyzed by means of ¹³C–¹H NMR COSY, DEPT, and HMBC. The two carbonyl groups at positions 2 and 6 resonated at the lowest field (Table 2). The

Table 2. Coupling constants (*J* in Hz) of the tricycloundecan-diones **9a**, **9b**, and **9c**

Protons	9a	9b	9c
3-H ^a , 3-H ^c	18.75	18.60	18.66
5-H, 11-H ^a	3.5	3.65	3.67
5-H, 11-H ^c	12.0	11.9	12.15
9-H, 10-H ^a	3.5	3.25	4.18
9-H, 10-H ^c	12.0	11.90	—
7-H, 8-H ^a	4.5	4.84	4.94
7-H, 8-H ^c	2.5	2.75	—
9-H, 8-H ^a	4.0	3.65	3.13
9-H, 8-H ^c	3.0	2.75	—
8-H ^a , 8-H ^c	13.25	12.8	13.80
10-H ^a , 10-H ^c	11.5	13.9	12.04
11-H ^c , 11-H ^a	14.5	14.75	14.50
11-H ^c , 10-H ^c	4.0	3.65	2.99
7-CH ₃ , 7-H	6.38	6.4	6.41

Table 3. ¹³C NMR spectral data of the tricycloundecandiones **9a**, **9b**, and **9c** (chemical shift in δ)

Carbons	9a	9b	9c
1-C	41.53	48.71	49.54
2-C	213.15	210.42	210.80
3-C	38.63	39.53	39.42
4-C	63.16	63.01	63.06
5-C	47.75	41.86	47.46
6-C	213.58	213.06	213.30
7-C	33.12	33.16	33.07
8-C	34.91	34.99	34.89
9-C	30.46	30.79	30.37
10-C	36.34	35.05	33.03
11-C	33.59	32.45	30.46
2', 6',-C ₂	44.83	44.95	44.85
3', 5',-C ₂	67.43	67.47	67.41
1-CH ₃	19.18	—	—
7-CH ₃	14.27	14.26	14.23
1-C ₆ H ₅	—	138.95 (C ₁) 128.27 (C ₂) 127.34 (C ₂) 127.12 (C ₁)	—
1-C-C(CH ₃)=CH ₂	—	—	144.40
1-C-C(CH ₃)=CH ₂	—	—	112.90
1-C-C(CH ₃)=CH ₂	—	—	20.66

signal at δ 213.06–213.58 was assigned to 6-C and at δ 210.42–213.15 for 2-C. 6-C of the 6-carbonyl group shifted downfield in comparison with 2-carbonyl carbon because 6-C is flanked by the α -substituent 7-CH₃ and the bridgehead carbon at position 5. In the present work, the two resonating values (for 6-C and 2-C) were confirmed with the help of HMBC. 6-Carbonyl carbon and 2-carbonyl carbon were correlated to 7-CH₃ and substitutions at the adjacent carbon's position 1, by three-bond coupling (HMBC). The methyl carbon in the case **9a** at position 1 and at position 7 resonated at the highest field (δ 19.18 and δ 14.27 respectively). 1-CH₃ is more deshielded than 7-CH₃ because of the fully substituted 1-C. The quarternary 1-C and 4-C gave less intense peaks. 4-C was deshielded tremendously because of the electron-withdrawing morpholino group. 7-C of **9a**, **9b**, and **9c** were deshielded by 2.57–2.66 ppm in comparison to that in the reported^[1] compound. This can be explained by CH₃ substitution at 7-C. The chemical shift for 8-C (δ 34.89–34.99) was also deshielded by about 9.55–9.65 ppm in the same reported^[1] tricyclic compound. This may be accounted for by the β -SCS effect because of the methyl group at the 7-position.

The δ values of 9-C and 11-C agreed very well with the reported^[11] compound. Of 7-C, 8-C, 9-C, 10-C, and 11-C, carbon at the 10-position is the most deshielded (δ 33.03–36.34). Besides other factors, the reason may be attributed to γ -anti-effect,^[8] which indicates that C_α (11-position), C_β (1-position), and C_γ (2-position doubly substituted by O) are compressed in the same plane.^[8] 3-C gave the expected downfield shift because of the adjacent (2-position) carbonyl group and fully substituted 4-position. The 5-C is more deshielded than 3-C by 8.04–9.12 ppm because of more substitution at the bridgehead. In the case of compound **9b**, because of phenyl substitution at position 1, 1-C was more deshielded (δ 48.71) in comparison to that in **9a** (δ 41.53).

Synthesis of substituted tricyclo[5.3.1.0^{4,9}]undecan-2,6-dione

EXPERIMENTAL

The ¹H NMR and ¹³C NMR spectra were recorded on Bruker 500-MHz and 300-MHz instruments at the University of Wisconsin—Milwaukee, Department of Chemistry, USA. A number of NMR spectra were also recorded on JEOL 500-MHz and 400-MHz instruments, at the Kyoto, Kanazawa, and Showa Pharmaceutical Universities in Japan. Some of NMR and mass spectra were also recorded at the H. E. J. Laboratory of Karachi University, Pakistan, and mass spectra were also recorded in the Department of Chemistry, George Mason University, USA. The infrared spectra were recorded on a IR 470 infrared spectrometer (Shimadzu) in the Department of Chemistry, University of Dhaka, Bangladesh. All ¹H and ¹³C NMR spectra were recorded in CDCl₃ if not otherwise mentioned. IR spectra were run as KBr pellets in the case of solids and solution in the case of liquids; absorptions are expressed in centimeters⁻¹. For column chromatography, silica gel 100 (supplied by E Mark) and light petroleum (60–80°C): chloroform = 10:1 were used.

Preparation of 4,4-Disubstituted Cyclohexanones

4-Acetyl-4-methyl cyclohexanone **3a**,^[6] 4-acetyl-4-phenylcyclohexanone **3b**,^[5] and 4-acetyl-4-isopropenylcyclohexanone **3c**,^[6] and their precursors **1a**,^[5] **2a**,^[5] **1b**,^[5] **2b**,^[5] **1c**,^[9] and **2c**^[10] were prepared by essentially following the literature methods.

Preparation of Enamines: General Method

A mixture of the 4,4-disubstituted cyclohexanone (17.47–32.2 mmol) and a slight excess of morpholine (17.47–32.2 mmol) in toluene (75–80 ml) was

heated to reflux under a Dean and Stark head for 12 h. On cooling, the solvent and the excess of morpholine were removed under reduced pressure, and crude enamine was used without further purification because extensive decomposition occurred on distillation. In this way the following enamines were obtained:

4-Acetyl-4-methyl-1-morpholinocyclohexene (**4a**) γ_{\max} in cm^{-1} : 1700 (C=O), 1638 (C=C).

4-Acetyl-4-phenyl-1-morpholinocyclohexene, (**4b**), γ_{\max} in cm^{-1} : 1700 (C=O), 1638 (C=C).

4-Acetyl-4-isopropenyl-1-morpholinocyclohexene (**4c**), γ_{\max} in cm^{-1} : 1700 (C=O) 1655, 1638 (C=C).

Synthesis of 1,7-Dimethyl-4(N-morpholino)

Tricyclo[5.3.1.0^{4,9}]undecan-2,6-dione **9a**, 1-Phenyl-7-methyl-4(N-morpholino) Tricyclo[5.3.1.0^{4,9}]undecan-2,6-dione **9b**, and 1-Isopropenyl-7-methyl-4(N-morpholino)

Tricyclo[5.3.1.0^{4,9}]undecan-2,6-dione **9c**: General Method

The methacryloyl chloride (21.72–35.40 mmol) in dry toluene (40–45 ml) was added dropwise to a boiling solution of the enamine (21.5–35.45 mmol) in dry toluene (130–160 ml) during 2 h. During the addition a solid was slowly precipitated from the reaction mixture. The mixture was then heated under reflux with stirring for 5 h and cooled, and the precipitated iminium salt was filtered off, washed with dry toluene, and hydrolyzed by stirring with ice-cold water (50 ml) for 10 h. The crude solid were isolated by extraction with ether (5 × 25 ml). The separated aqueous layer was further extracted with chloroform (5 × 25 ml). The crude tricyclic compound was isolated from the extracts and purified by separation from adamantanediones with the help of column chromatography (silica-gel column) and was eluted initially with light petroleum (60–80°C) followed by gradual addition of chloroform. The following results were obtained:

Methacryloyl chloride reacting with (**4a**) gave a 25% yield of **9a**, which was further purified by recrystallization from chloroform and light petroleum (40–60°C) and obtained as white crystals, mp 149–50°C; R_f in TLC 0.37 (chloroform and ethyl acetate, 5:1); IR γ_{\max} 1700 (C=O), 1665, 1595 (C=C); MS *m/z* 291 (M⁺), 263, 248, 222, 195, 166, 119, 91, 79, 41, 27. Anal. calcd. for C₁₇H₂₅NO₃: C, 70.10%; H, 8.59%; N, 4.81%. Found: C, 70.05%; H, 8.62%; N, 4.78%.

Methacryloyl chloride reacting with (**4b**) gave a 25% yield of **9b**, which was further purified by recrystallization from chloroform and light petroleum (40–60°C) and obtained as white needles, mp 197–98°C; R_f in TLC 0.36 (chloroform and ethyl acetate, 5:1); IR γ_{\max} 1705 (broad C=O), 1680

(C=C), 760, 740, 700, 670, 620, 545, 560 (C–H bending of phenyl); MS m/z 353 (M^+), 236, 311, 270, 257, 207, 193, 165, 139, 91, 86, 40, 18. Anal. calcd. for $C_{22}H_{27}NO_3$: C, 74.78%; H, 7.64%; N, 3.96%. Found: C, 74.34%; H, 7.64%; N, 3.81%.

Methacryloyl chloride reacting with (4c) gave a 10% yield of 9c, which was further purified by recrystallization from chloroform and light petroleum (40–60°C) and obtained as white needles, mp 150–51°C; Rf in TLC 0.40 (chloroform and ethyl acetate, 5 : 1); IR γ_{max} 1710 (broad C=O), 1630 (C=C). MS m/z 317 (M^+), 289, 274, 260, 246, 234, 218, 208, 193, 180, 166, 152, 134, 131, 117, 105. Anal. calcd. for $C_{19}H_{27}NO_3$: C, 71.92%; H, 8.52%; N, 4.42%. Found: C, 70.64%; H, 8.42%; N, 4.31%.

ACKNOWLEDGMENT

Dr. Kudrat-e-Khoda Doctoral Fellowship (October 1999–March 2003) to Kawsari Akhter by BCSIR Laboratories, Dhaka, Bangladesh, is acknowledged.

REFERENCES

1. Ahmed, M. G.; Moeiz, S. M. I.; Ahmed, S. A.; Kiuchi, F.; Tsuda, Y. Synthesis of substituted tricyclo[5.3.1.0^{4,9}]undecane-2,6-dione. *Tetrahedron* **2001**, (57), 3143–3150.
2. Ahmed, M. G.; Moeiz, S. M. I.; Ahmed, S. A.; Kiuchi, F.; Tsuda, Y.; Sampson, P. J. Synthesis of some substituted 2,4-adamantanedione from 4,4-disubstituted cyclohexanone enamines and α,β -unsaturated acid chlorides. *J. Chem. Res. Syn.*, 316–317; Miniprint, 1439–1470.
3. Huque, A. K. M. F.; Mosihuzzaman, M.; Ahmed, S. A.; Ahmed, M. G.; Andersson, R. Synthesis of some substituted adamantane-2,4-diones. *J. Chem. Res. Synop.*, 214–215; Miniprint, 1701–1710.
4. Ahmed, M. G.; Huque, A. K. M. F.; Ahmed, S. A.; Mosihuzzaman, M.; Andersson, R. Reaction of α,β -unsaturated acid chlorides with 4,4-disubstituted cyclohexanone enamines. *J. Chem. Res. Synop.*, 362–363; Miniprint, 2815–2835.
5. Bruson, H. A.; Riener, T. W. Chemistry of acrylonitrile: II, reaction with ketones. *J. Am. Chem. Soc.* **1942**, *64*, 2850–2858.
6. Chapman, N. B.; Sotheeswaran, S.; Toyne, K. J. Preparation of 4-substituted 1-methoxycarbonylbicyclo[2.2.2]octanes, 4-substituted 1-phenylbicyclo[2.2.2]octanes, 4-substituted 1-p-nitrophenylbicyclo[2.2.2]octanes and 1,4-disubstituted bicyclo[2.2.2]octanes. *J. Org. Chem.* **1970**, *35*, 917–923.
7. Ahmed, M. G.; Ahmed, S. A.; Akhter, K.; Moeiz, S. M. I.; Tsuda, Y.; Kiuchi, F.; Hossain, M. M.; Forsterling, F. H. Synthesis of some substituted adamantane-2,4-diones from 4,4-disubstituted cyclohexanone enamines and methacryloyl chloride. *J. Chem. Res. Synop.* **2005**, in press.

8. Duddeck, H.; Klein, H. ¹³C nuclear magnetic spectra—VI, stereochemical dependence of γ_{anti} heterosubstituent effects on ¹³C chemical shifts of bridgehead substituted molecules. *Tetrahedron* **1977**, *33*, 1971–1977.
9. Bruson, H. A.; Riener, T. W. Chemistry of acrylonitrile: III, cyanomethylation of α,β -unsaturated compounds. *J. Chem. Soc.* **1943**, *65*, 18–23.
10. Colonge, J.; Vuillemet, R. The bicyclo[2.2.2]octane series. *Bull. Soc. Chim. Fr.* **1961**, 2235–2238.